Electronic identifier: 15173

Date of electronic submission: 20/07/2015

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A PILOT STUDY TO EXAMINE THE FEASIBILITY AND ACCEPTABILITY OF ASSESSING THE EFFECT OF TOPICAL OILS ON TERM BABIES’ SKIN BARRIER FUNCTION:
THE OBSeRvE (Oil in Baby SkincaRE) STUDY

A thesis submitted to The University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

2015

ALISON COOKE

School of Nursing, Midwifery and Social Work
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<td>NIHR</td>
<td>National Institute for Health Research</td>
<td></td>
</tr>
<tr>
<td>NMF</td>
<td>Natural moisturising factor</td>
<td></td>
</tr>
<tr>
<td>NSCS</td>
<td>Neonatal Skin Condition Score</td>
<td></td>
</tr>
<tr>
<td>OBSeRvE</td>
<td>Oil in Baby SkincaRE study acronym</td>
<td></td>
</tr>
<tr>
<td>RCPCH</td>
<td>Royal College of Paediatrics and Child Health</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
<td></td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
<td></td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
<td></td>
</tr>
<tr>
<td>TEWL</td>
<td>Trans-epidermal water loss</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
<td></td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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Abstract

Background: The differential effects of using topical oils for the prevention or treatment of baby dry skin on skin barrier function may contribute to the development of childhood atopic eczema. Prevalence of atopic eczema has increased from 5% of children aged 2 to 15 years in the 1940s, to approaching 30% more recently. This increase cannot be attributed to genetic changes. It is likely that increases stem from environmental factors, including the increased use of some inappropriately formulated commercial and natural baby skincare products. Midwives, health visitors and other maternity service health professionals, in the UK, routinely recommend the use of olive oil and sunflower oil for baby dry skin or massage, but the effect of these oils on newborn baby skin has not been studied.

Aim: The aim of this research was to assess the feasibility and acceptability of testing the hypothesis that the regular application of sunflower oil, when compared to no oil or olive oil, had an effect on skin barrier function of newborn term babies.

Study Design: A pilot, assessor-blinded, single centre, three-arm, randomised controlled trial, with nested qualitative component, underpinned by post-positivism.

Methods: Quantitative methods were used to establish proof of concept that the use of topical oils had some effect on newborn baby skin barrier function, and to assess the feasibility of trial processes and parameters. Qualitative methods were used to explore the acceptability to parents of having a newborn baby participating in a randomised controlled trial, and trial design and procedures. The study was conducted in St. Mary’s hospital, a large teaching hospital in North West England. Data were collected between September 2013 and August 2014.

The randomised controlled trial included 115 babies who were randomised to three groups: sunflower oil, olive oil and no oil, using a computer-generated varied size block randomisation with concealed allocation. Parents of babies randomised to the oil groups were blinded to which oil they were allocated. Data were collected using standardised case report forms for demographic and clinical observation data, weekly telephone questionnaires and a follow-up questionnaire, informed by previous baby skincare trials.

The qualitative study encompassed semi-structured interviews, conducted within six months of birth. The sample was a subset of the trial participants, purposively sampled to incorporate a mix of treatment groups and positive and negative experiences derived from the follow-up questionnaire. Data also included two open-text questions from the follow-up questionnaire.

Quantitative data were managed using IBM SPSS Statistics versions 20 and 22 and analysed descriptively. Qualitative data were managed in NVivo 10 and analysed using Framework Analysis.

Results: The pilot study found that a definitive randomised controlled trial is not the optimal next step. A longitudinal observational study and further mechanistic work is recommended. Recruitment was challenging and loss to follow-up was higher than anticipated. Protocol adherence was reasonable and the study was acceptable to parents. Some statistically significant results were obtained, which must be interpreted with caution as the study was not powered to detect such a difference. These results showed that both oils may impede the development of the skin barrier function from birth; clinical importance of the results is not known.

Conclusion: A longitudinal observational study is required, which maps the diagnosis of atopic eczema with environmental factors such as the use of baby skincare products from birth. Mechanistic work is also required to consider the optimal skincare formulation. As any intervention should do more good than harm, it would be wrong to support the recommendation of topical olive oil or sunflower oil for newborn baby dry skin or massage, based on the study data.
DECLARATION

There is no portion of the work referred to in the thesis that has been submitted in support of an application for another degree or qualification of this or any other University or other institute of learning.

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Acknowledgements

Firstly, I would like to thank my supervisors Professor Dame Tina Lavender, Professor Michael J. Cork and Dr Suresh Victor, for sharing their wealth of expertise and knowledge, providing advice and support, and being willing to be part of my guiding team throughout my doctoral study.

Secondly, I would like to thank Dr Malcolm Campbell for his overwhelming patience in providing statistical support in addition to his timely supportive words, and also Dr Simon Danby for his expertise, enthusiasm and guidance in skin barrier measurements.

Thirdly, I wish to thank all of the parents and babies who agreed to take part in the OBSeRvE study. Their desire to participate in research for the benefit of others is truly inspirational. I could not have done this without you.

Finally, I thank my parents: Angela, Paul and Pauline for being there to help whenever I have needed it, and my colleague and friend Angela for being a voice of reason when it was hard going.

I dedicate this work to my family: my husband David, and my children Daniel, Laura, Chloe and Matthew, who have given me the strength and support to succeed. I know what we have been through to get this far. I am so proud of you all and truly appreciate all of your sacrifices.
The Author

The author completed her Bachelor of Midwifery degree with First Class Honours in March 2006 at The University of Manchester, and started work as a rotational midwife in a local District General Hospital. In February 2009, she was successful in securing a part-time position as a Research Midwife at the main tertiary hospital working with the Professor of Midwifery. During this time she also continued to work part-time in clinical practice. In September 2009, she was awarded a National Institute for Health Research Masters in Clinical Research fully-funded studentship and was awarded her Masters degree in September 2010. This degree enabled her to conduct a qualitative phenomenological study of women’s experiences of delayed childbearing. Leading this discrete piece of research encouraged her to apply for an NIHR Doctoral Research Fellowship which she was awarded in 2012. She has a number of research interests including advanced maternal age, obesity, intrapartum care, antenatal education and baby skincare. It was her experience during her clinical positions in the community and as a Parent Education midwife that led to her desire to address the research question for this doctoral study.

Funding

This thesis is independent research from a Doctoral Research Fellowship (DRF-2012-05-160) supported by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the National Health Service, the NIHR or the Department of Health.
CHAPTER ONE: INTRODUCTION

1.1 Introduction

This chapter will be presented in two parts. Part One will provide an introduction to the context of the study, including a description of the setting and an outline of the thesis. Part Two will present an overview of the background to the study including the physiology of the skin, current clinical practice and the rationale for the doctoral study.

CHAPTER ONE PART ONE

1.2 Context overview

1.2.1 Overview of the topic

Topical skincare products are those which are applied on to the surface of the skin. Topical oils have been used in skincare regimens for centuries, and can be documented as early as 2760BC (Mitzel-Wilkinson 2000). The use of topical oils has become a traditional recommendation by midwives and other maternity service health professionals for the prevention or treatment of baby dry skin or for baby massage (Cooke et al. 2011; Walker et al. 2005). This is a global phenomenon; mustard and coconut oils are popular in Eastern cultures (Mullany et al. 2005; Sankaranarayanan et al. 2005; Darmstadt and Saha 2002) compared to olive and sunflower oils in the UK (Cooke et al. 2011; appendix 1). The differential effects of using topical oils for the prevention or treatment of baby dry skin on skin barrier function may contribute to the development of childhood atopic eczema (Danby et al. 2013). Certain compositions of oil have been shown to affect the stratum corneum. Olive oil, with a high ratio of oleic acid to linoleic acid, disrupts the lipid structure of the skin barrier (Danby et al. 2013; Jiang and Zhou 2003; Darmstadt et al. 2002). Sunflower oil, with a high ratio of linoleic acid to oleic acid, has been shown to benefit the skin barrier (Danby et al. 2013; Darmstadt et al. 2002). A damaged skin barrier is a characteristic of atopic eczema. Prevalence of atopic eczema has increased from 5% of children aged 2 to 15 years in the 1940s (Taylor et al. 1984) to approaching 30% more recently (Gupta et al. 2004). It is not possible to attribute this increase to genetic changes in the skin. Conversely, environmental factors have changed over the years, including the increased availability and use of some inappropriately formulated baby skincare products. Furthermore, there is a common but unfounded belief that what is ‘natural’ is also ‘safe’ (Bedwell and Lavender 2012), resulting in the widespread use of untested vegetable oils on newborn skin. It is unestablished whether there is a link between the use of topical products on newborn skin and the development of atopic eczema, but the potential for this link exists. The question of whether there is such a link led to the hypothesis for this doctoral study: that the regular application of topical sunflower oil, when compared to no oil or topical olive oil, had an effect on the skin barrier function of newborn term babies.
A pilot, assessor-blinded, randomised controlled trial was designed and implemented to assess the feasibility of conducting a definitive trial to investigate the impact of topical oil use on the skin of newborn term babies. Aims were to provide proof of concept that topical oils have some effect on skin barrier function, and to generate data to inform the optimal definitive trial design.

1.2.2 Setting

During 2013, England had 698,512 live births (Office of National Statistics 2014b). The North West of England has the highest rate of births after London and the South East (table 1.1). Greater Manchester has the largest number of births for the North West (Office of National Statistics 2014b). Most births take place in the hospital setting. The rate for home births remains low at 2.3% nationally, but even lower in the North West at 2.0% (Office of National Statistics 2014a).

<table>
<thead>
<tr>
<th>Usual Residence of Mother</th>
<th>Total Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORTH EAST</td>
<td>28,961</td>
</tr>
<tr>
<td>NORTH WEST</td>
<td>86,372 (of which Greater Manchester 37,045)</td>
</tr>
<tr>
<td>YORKSHIRE AND HUMBER</td>
<td>64,560</td>
</tr>
<tr>
<td>EAST MIDLANDS</td>
<td>52,895</td>
</tr>
<tr>
<td>WEST MIDLANDS</td>
<td>71,188</td>
</tr>
<tr>
<td>EAST</td>
<td>71,309</td>
</tr>
<tr>
<td>LONDON</td>
<td>128,332</td>
</tr>
<tr>
<td>SOUTH EAST</td>
<td>102,190</td>
</tr>
<tr>
<td>SOUTH WEST</td>
<td>58,710</td>
</tr>
<tr>
<td>ENGLAND</td>
<td>698,512</td>
</tr>
</tbody>
</table>

Table 1.1: Birth Summary Table: England and Wales, 2013 (Office of National Statistics 2014b)

This doctoral study was conducted in a large regional teaching hospital in North West England. St. Mary's Hospital in Manchester has approximately 8000 births per annum (September 2013 to August 2014), of which approximately 7250 babies are born full term (Central Manchester NHS Foundation Trust 2014).

This setting was chosen because Greater Manchester is an ethnically diverse county with a high number of full term births. In the study recruitment year (2013/2014), of mothers who gave birth at St. Mary's: 48% were White British, 15% were of Asian origin, 10% were of Afro-Caribbean origin and 1% were of oriental origin (Central Manchester NHS Foundation Trust 2014). Others were of mixed origin or had not disclosed their ethnic group.

As this was a pilot study, a single centre setting was chosen. If the pilot were to proceed to a definitive trial, a multi-centre design would allow for recruitment of a much larger
sample size, and findings which are more precise and more generalisable to a larger population (Gardner and Altman 2000).

1.3 Outline of the Thesis

The thesis comprises eight chapters, of which an outline of each is presented here.

**Chapter one** introduces the study topic in two parts. Part one presents the background and setting for the project. The structure of the thesis is also detailed. Part two continues with an overview of the dermatological aspect of the study including physiology of the skin, the differences between newborn and adult skin, dry skin and atopic eczema. This part also outlines current clinical practice, the rationale for, and the originality of, the doctoral study.

**Chapter two** presents a structured literature review using a comprehensive systematic approach. This chapter is detailed in two parts. The first part provides a detailed description of the literature search and the critical appraisal process. The literature search is fully explained including the formulation of the research questions for both quantitative and qualitative research, the search strategies and tools used, the inclusion and exclusion criteria, the databases searched and what steps were taken to ensure completeness of the evidence base. The tools used for the critical appraisal process and the rationale behind the choice of these tools are then addressed. The second part of this chapter provides the literature review. The review is presented in sections commencing with the broader issues of bathing and cleansing, baby massage, cultural influence and parental and health professional views and experiences. The review then focuses on topical applications. This section considers animal studies, adult studies, preterm baby studies focusing on those investigating oils alone, those investigating emollients and those considering both, and finally looking in detail at those studies investigating topical applications for term babies.

The underpinning methodology is presented in **chapter three**, in three parts. Part one addresses the purpose of the research, and defines the aims and objectives, the research questions and the research hypothesis. Part two presents the theoretical perspective including a discussion of how the methodological choices were undertaken and the paradigmatic stance of the study. This part of the chapter also presents a discussion of positivism and why this was rejected in favour of post-positivism as the underpinning philosophical perspective of the research. Part three demonstrates the methodological considerations of the research design for the quantitative and qualitative components, which support the methods discussed in the next chapter.

**Chapter four** continues with a presentation of the methods used for the doctoral study, in two parts. Part one considers the quantitative methods including the study design, setting,
sample including sample size consideration, outcome measurements, recruitment, randomisation, interventions and data collection and data analysis. Part two proceeds to consider the same aspects for the qualitative component.

The ethical considerations of the research are presented in chapter five. This chapter discusses the study design including protecting participants from harm, informed consent, confidentiality and anonymity, safety monitoring and reporting, and issues affecting the setting where the study takes place.

**Chapter six** presents the results of the study. This chapter is separated in to three sections. The first comprises a full report of the results of the pilot randomised controlled trial biological data. The second part presents a full report of the results of the questionnaire data. Part three reports the data resulting from the nested qualitative component. The flow of participants through the study is highlighted in a CONSORT diagram. The baseline characteristics of the sample are presented. The results are presented in full detail including the primary outcome data analysis for lipid lamellae structure and trans-epidermal water loss, and the secondary outcome data analysis for stratum corneum hydration, skin surface pH and erythema / clinical observation of the skin. The results of the analysis are presented in text and tabular format. Questionnaire data is also presented including alternative product use, treatment compliance and health professional consultations or medication prescriptions. The final part of the chapter presents the results of the qualitative data analysis in full. This chapter concludes with a statement of the main findings in preparation for the discussion of these results in chapter seven.

**Chapter seven** provides a discussion of the results, integrating these findings with the existing evidence base. The original aims and objectives of the study are discussed in the light of the results. Proof of concept is discussed, the optimal primary outcome measure is considered, and the optimal study design is addressed with regard to feasibility. The strengths and limitations of the study are explored, recommendations for future research and implications for clinical practice are presented.

The final chapter, **chapter eight**, provides a conclusion to the thesis, incorporating a personal reflection by the author.
1.4 Baby skin

1.4.1 Physiology of the skin

Human skin is the largest organ of the body. It separates and protects the internal organs from the environment, acting as a barrier to infiltration from external irritants, allergens and pathogens, and as protection from excessive water loss (Lewis-Jones 2012). The skin has three layers: the epidermis, the dermis and the hypodermis (subcutaneous layer) which are illustrated in figure 1.1.

![Figure 1.1: The structure of the skin. The stratum corneum (outermost layer) is crucial to skin barrier function. If this layer is damaged, water loss can increase and external irritants can penetrate to the deeper layers of the skin, as in atopic eczema (synonym atopic dermatitis). Diagram from www.shutterstock.co.uk (2013b). ©License for use granted.](image)

The epidermis (figure 1.2) is made up of layers of keratinocytes closely packed together. These keratinocytes are at different stages of differentiation. The process of differentiation involves the formation of new keratinocytes in the stratum basale, which travel upwards through the skin layers until they become corneocytes as they pass through the stratum compactum (Candi et al. 2005). Once the corneocytes reach the surface of the skin, they are shed in a normal physiological process termed desquamation (figures 1.1 and 1.2).
1.4.2 Skin barrier function

Skin barrier function can be affected by genetic and environmental factors. One method of understanding how the skin barrier works is by using a ‘brick wall’ analogy (Cork et al. 2009; figure 1.3). Panel A in figure 1.3 represents a well-functioning skin barrier, where water loss is minimised and the skin barrier prevents penetration of external agents. The ‘bricks’ represent the corneocytes. They are held together by ‘iron rods’ which represent the corneodesmosomal junctions (supporting structure of the stratum corneum), and surrounded by mortar, which represents the lipid lamellae.

Figure 1.3: The ‘brick wall’ analogy of the skin barrier. Panel A represents a functioning skin barrier with defensive properties against invasion by external irritants and protection from water loss. Panel B represents a damaged skin barrier resulting in penetration of external irritants and excessive water loss. Diagram from Cork et al. (2009). ©Permission for use granted.
The ‘rusting’ or breakdown of the iron rods at the outermost layer allows the normal process of desquamation to occur, where corneocytes are shed naturally from the skin. However, in panel B, breakdown of the skin is represented by a broken wall with excessive crumbling mortar, illustrating the disorder or increased fluidity of the lipid lamellae. This damage enables penetration by external bacteria, irritants and allergens, and loss of water from the epidermis (trans-epidermal water loss [TEWL]).

1.4.3 Differences between adult and baby skin

Extra care of baby skin is important due to differences in the biological composition between baby skin and adult skin. Skin starts to develop in-utero at approximately three weeks of gestation; the epidermis develops from surface ectoderm and consists of one layer of cells (Ackerman 1985). At term birth (≥37⁺⁰ weeks gestation) the skin is sufficiently developed to withstand extrauterine life; however it continues to change during the first twelve months after birth (Stamatas et al. 2010). Biophysical and biological properties such as corneocytes size, stratum corneum hydration and pH, lipid composition and structure, natural moisturising factor (NMF) and water composition continue to be in a state of transition during the early years of life (Fluhr et al. 2011; Stamatas et al. 2011; Nikolovski et al. 2008). Baby skin is more vulnerable than adult skin due to several differences. The stratum corneum is 30% thinner and the epidermis is 20% thinner in babies (Stamatas et al. 2010), which causes increased permeability and dryness. The neonatal body surface to body weight ratio is higher for babies than for adults, which results in an increased vulnerability to the use of topical treatments (Nikolovski et al. 2008). The differences in skin composition include less lipids, melanin and moisturising factors than adult skin, causing increased trans-epidermal water loss and reduced skin surface hydration in babies (Chiou and Blume-Peytavi 2004; Nakagawa et al. 2004). Baby skin also has a higher surface pH to adult skin (Yosipovitch et al. 2000), which results in an increase in protease activity in the breakdown of corneodesmosomes (the ‘iron rods’ of the stratum corneum; see figure 1.3), and hinders enzyme lipid processing (Danby and Cork 2011; Hachem et al. 2003). Given that babies have a propensity for reduced skin barrier function, it is important that careful consideration is given to what topical products are used on baby skin to ensure that the developing epidermal barrier is not adversely altered or affected. Reduced skin barrier function and the development of atopic eczema are associated with alteration in the lipid composition and structure of the stratum corneum, a principal component of the epidermal barrier (Higgs-Bayliss et al. 2014; Janssens et al. 2012; 2011). Baby skincare products should be proven to enhance the integrity, barrier and / or the immune system of baby skin before they are recommended to new parents to use on their newborn babies.
1.4.4 Differences between term and preterm baby skin

Babies are classed as preterm if they are born before 37 weeks of gestation. Preterm skin is thinner than for term babies, and is consequently more transparent (Lund and Kuller 2007). The stratum corneum is not visible in-utero until 34 weeks of gestation (Kalia et al. 1998; Evans and Rutter 1986). Although the stratum corneum consists of ten to twenty layers in term babies and adults, it has only two to three layers in preterm babies of less than 30 weeks gestation (Lund and Kuller 2007). The development of the skin barrier is more rapid after birth for preterm babies, and the stratum corneum can be equivalent to that of a term baby within two weeks of extrauterine life (Evans and Rutter 1986). This more rapid development is thought to result from the effect of the transition from wet to dry environment at birth. However other studies have reported that for babies born before 27 weeks gestation, this process is much slower (Agren et al. 1998; Kalia et al. 1998).

1.4.5 Vernix caseosa

Vernix caseosa is defined as a thick white greasy substance that ‘varnishes’ the baby skin at birth, functioning as a naturally occurring barrier film (Rissmann et al. 2006; Hoath et al. 2001; Holbrook and Hoff 1984). Vernix is composed of approximately 80% water and other lipid and protein elements (Hoeger and Enzmann 2002; Hoath et al. 2001). The layer of vernix often present at birth is formed in-utero. It forms as a result of sebaceous lipid synthesis and secretion, combined with in-utero desquamation of maturing fetal corneocytes (Hoath et al. 2001). The structure of vernix is therefore very similar to that of the stratum corneum (Rissmann et al. 2006).

The process of vernix formation begins at around week 24 of pregnancy gestation (Hardman et al. 1999) and production increases during the last trimester of pregnancy. Any baby born before 28 weeks of gestation has an immature epidermal barrier function and is likely to lack a sufficient coating of vernix. Largest amounts of vernix (approximately 70% coverage) are evident between 33 and 37 weeks of gestation. Babies have approximately 35% bodily coverage if born between 37 and 41 weeks of gestation, but only 10% coverage if born between 41 and 42 weeks of gestation (Visscher et al. 2005).

Preterm babies have a high trans-epidermal water loss. At birth, babies are typically dried to prevent further loss of water through evaporation. Any thin coating of vernix is therefore wiped away (Visscher et al. 2005). There is some suggestion that the proteins in vernix create an anti-microbial defence which may explain why preterm babies are more susceptible to nosocomial infections (Hoath et al. 2001).

There is a likelihood that vernix has some moisturising properties due to its high water content. It could therefore be expected that preterm babies born without a protective layer of vernix will have very dry skin. This could also explain why babies born after 40 weeks of gestation also suffer from very dry skin, as it is unusual to see a baby covered in vernix.
born at late gestation (Visscher et al. 2005). This effect is magnified by the fact that the stratum corneum in healthy term babies has a propensity for dryness in any case. It is normal for babies to have dry skin (Saijo and Tagami 1991), but it is not known whether this process is secondary to the removal of vernix (Visscher et al. 2005).

Vernix is reported to be multi-functional; a protective barrier to bacteria (Tollin et al. 2005), a protective water-proofing barrier against the amniotic fluid (Youssef et al. 2001), and a natural moisturiser (Bautista et al. 2000). It is thought to be beneficial to leave vernix in place after birth and allow it to absorb or shed gradually (Tansirikongkol et al. 2007; Visscher et al. 2005).

1.4.6 Dry skin

Madison defines dry skin as “a cutaneous reaction pattern reflecting abnormal desquamation of diverse etiologies” (2003; p236). In normal skin, corneocytes are shed from the skin in such small quantities that they are rarely visible to the naked eye; however in dry skin the skin appearance becomes rough and flaky as this process is disturbed. Neonatal dry skin is a normal process of adaptation to the extrauterine environment following birth, possibly occurring due to the change in environmental conditions from wet amniotic fluid in-utero, to the dry extrauterine conditions. Research has shown that trans-epidermal water loss is high in the first few hours after birth, suggesting a process of ‘drying out’ (Rutter and Hull 1979). High trans-epidermal water loss persists throughout the first year of life (Nikolovski et al. 2008). Neonatal dry skin may continue in the first few months of a baby’s life (Saijo and Tagami 1991). Midwives and other maternity service health professionals commonly recommend the use of topical oils for the prevention and treatment of baby dry skin (Cooke et al. 2011).

1.4.7 Atopic eczema

Atopic eczema (synonym atopic dermatitis) is a disease which results from gene environment interactions leading to the breakdown of the skin barrier, cutaneous inflammation and allergy (Danby and Cork 2011; Bieber 2008). It is characterised by dry and scaly skin, redness, blistering and itching (figure 1.4). In one study in the United Kingdom (UK) atopic eczema was found to affect approximately 30% of children aged 2 to 15 years (Gupta et al. 2004). Affected children are also more at risk of developing asthma and allergic rhinitis (Gustafsson et al. 2000); this progression has been termed the ‘atopic march’. Approximately 60% of sufferers are diagnosed with atopic eczema in the first year after birth, and 45% in the first six months (Bieber 2008). Prevalence has increased from approximately 5% of children in the 1940s (Taylor et al. 1984). This substantial increase in prevalence cannot be attributed to genetic changes; however the way that we care for baby skin has been influenced by multiple environmental factors including the increased availability and use of skincare products, harsh detergents and oils (Danby and Cork
2011; Cork et al. 2009). Atopic eczema is associated with a defective skin barrier function. There may be a link between early use of particular types and formulations of oils on baby skin and the development of atopic eczema, and this requires further research. Only topical products that are proven to have beneficial effects on the skin barrier should be used on newborn babies.

Figure 1.4: Atopic eczema, characterised by dry and scaly skin, redness and blistering. Photograph from Cork (1992). ©Permission for use granted.

1.4.8 The atopic march

The atopic march is a term used to emphasise the development of allergic disease ‘marching’ from atopic eczema in infancy to asthma and allergic rhinitis in later childhood (Hogan et al. 2012). It is estimated that 20% to 60% of children with atopic eczema will develop asthma, and up to 66% will develop allergic rhinitis (von Kobyletzki et al. 2012; Spergel 2010; Kapoor et al. 2008; Spergel and Paller 2003; Gustafsson et al. 2000).

Several factors contribute to the atopic march hypothesis: genetic association, environmental association and the direct effect of eczema on the development of asthma (Lowe et al. 2008). Of these factors, the environmental association is the least understood. Many experts believe that if atopic eczema can be prevented then the prevalence of allergic disease can be reduced, and the atopic march can be interrupted or halted altogether (Hogan et al. 2012). The main focus of attention is on skin barrier function, as a defective skin barrier is one of the major contributors to the development and exacerbation of atopic eczema.

1.5 Baby skincare practice

1.5.1 Guideline recommendations

There is no national guidance on baby skincare. The Postnatal Care clinical guidelines from the UK National Institute for Health and Care Excellence (2014) have only two entries for skin health (figure 1.5). The first entry recommends a written record of observation of the skin during examination of the baby, and the second mentions cleansing products only. There is no national guidance for the use of topical oils.
In the United States (USA), there are guidelines for preterm babies that include skin assessment (Lund et al. 2001), including a Neonatal Skin Condition Score (NSCS) tool which has been adopted for use in other research and clinical settings (table 1.2).

<table>
<thead>
<tr>
<th>Dryness</th>
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<tbody>
<tr>
<td>1 = normal, no sign of dry skin</td>
<td></td>
</tr>
<tr>
<td>2 = dry skin, visible scaling</td>
<td></td>
</tr>
<tr>
<td>3 = very dry skin, cracking / fissures</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Erythema</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = no evidence erythema</td>
<td></td>
</tr>
<tr>
<td>2 = visible erythema &lt;50% body surface</td>
<td></td>
</tr>
<tr>
<td>3 = visible erythema &gt;50% body surface</td>
<td></td>
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<table>
<thead>
<tr>
<th>Breakdown / excoriation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = none evident</td>
<td></td>
</tr>
<tr>
<td>2 = small localized areas</td>
<td></td>
</tr>
<tr>
<td>3 = extensive</td>
<td></td>
</tr>
</tbody>
</table>

Note: Perfect score = 3; worst score = 9

Table 1.2: The Neonatal Skin Condition Score (NSCS) (Lund et al. 2001)

1.5.2 Current clinical practice and products

The recommendation to parents to use oils, mainly for the treatment of baby dry skin (figure 1.6), and most commonly olive oil (figure 1.7), has become traditional practice (Cooke et al. 2011; Walker et al. 2005). A survey in the North West of England (Walker et al. 2005) found that seventeen different products were recommended to parents for baby skincare. The most common was olive oil, recommended by 75% of respondents, closely followed by commercial baby oil (71.4%). This practice continues as highlighted in a more recent online national survey of UK maternity and neonatal units (Cooke et al. 2011; appendix 1). The aim of the survey was to establish what oils were used or recommended by maternity service health professionals in the UK, and for what reasons. The survey had a low overall response rate (31%) but this is suggested to be within an expected range for online surveys (Hamilton 2009). The survey found that 52% of responding units recommended the use of topical oil mainly to treat dry skin (figure 1.6) and of those, 81.6% recommended olive oil followed by 20.4% recommending sunflower oil (figure 1.7). Walker’s survey had a high response rate (80%) and the findings can therefore be generalised to North West England. Cooke’s survey highlighted that olive oil is still the most popular recommendation for baby dry skin amongst maternity service health professionals nationally. However unlike Walker’s survey, commercial baby oil was not
recommended as frequently (12.2%). There is no obvious reason for this substantial reduction; it may be surmised that in recent years midwives have become more research-aware, and are reluctant to recommend commercial products for which there is no evidence base. There is a dearth of evidence to support recommending vegetable oils; however, there is a readiness to believe that what is ‘natural’ is also ‘safe’ (Bedwell and Lavender 2012; Lavender et al. 2009). Societal interest in ‘natural’ products has grown (Allemann and Baumann 2009), especially for parents of newborn babies (Cottingham and Winkler 2007).

Previous studies have shown that parents want to use skincare products to make their baby look and smell nice (Furber et al. 2012; Lavender et al. 2009). Parents can become anxious about their baby’s skin condition (Adalat et al. 2007), and will often follow the advice given to them by health professionals regarding their baby’s care (Lavender et al. 2009). However, the use of oils as skincare products is not regulated. The potential consequences of this are of concern. It is necessary to provide an evidence base from which health professionals can offer the best advice for baby skincare, in order to avoid harmful practices.
1.6 Rationale for the study

Midwives, health visitors and other maternity service health professionals routinely recommend topical oils to new parents for use on their newborn baby’s skin. There is insufficient evidence to support this practice. It is not known whether these oils are good for or harmful to baby skin. There is a need for further research to consider the effects of commonly recommended topical oils on newborn baby skin, as the use of oils which are harmful to skin barrier function may be a contributing factor in the development of atopic eczema. Around 45% of atopic eczema cases present in the first six months after birth (Bieber 2008) when maternity service health professionals have most influence with parents. Robust evidence is required so that the correct clinical advice can be given to new parents. The proposed study begins to address this gap in evidence.

1.7 Originality

This doctoral work incorporates the first study the researcher is aware of which assesses the impact of topical olive oil and topical sunflower oil, the two most commonly recommended oils in the UK, on newborn term baby skin. It also assesses the feasibility of a novel and ethical outcome measure: Attenuated Total Reflectance Fourier Transform Infra-Red spectroscopy (ATR-FTIR), for a baby population that can detect changes in the skin profile before they become visible clinically. The study has provided a substantial dataset of newborn biophysical skin measurements for babies using topical olive oil, sunflower oil or no oil. The researcher is also currently finalising a first Cochrane systematic review of topical oils for prevention or treatment of dry skin in term babies.

1.8 Conclusion

This chapter has provided an overview of the physiology of the skin and current skincare practices, together with explanations of the various conditions which may affect newborn babies such as dry skin. Atopic eczema and the ‘atopic march’ have been discussed, as development may be associated with early skincare practices. The next chapter considers the evidence base for baby skincare from birth.
CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction to the literature review chapter

Part one of this chapter provides a discussion of the types of review which have been considered, followed by an explanation of the systematic search strategy and critical appraisal process. A structured literature review of the evidence is presented in part two. In view of the dearth of evidence for topical oil and emollient use in term babies, the literature for animals, adults and preterm babies is also presented. The chapter concludes with a rationale for the proposed doctoral study.

PART ONE: LITERATURE SEARCH AND CRITICAL APPRAISAL PROCESS

2.2 Background

Fink (2005; p3) defines a literature review as a "systematic, explicit, and reproducible method for identifying, evaluating, and synthesising the existing body of completed and recorded work produced by researchers, scholars, and practitioners". The popular use of the word ‘systematic’ in the term ‘systematic review’ is often misleading. All literature reviews are required to be conducted systematically at some level, but they differ in the extent to which they are systematic and therefore should be described in such a way to reflect this (Booth et al. 2012).

There are two main types of literature review: the narrative review and the systematic review. Narrative reviews, which summarise primary evidence (Greenhalgh 2006), are often provided by leading experts in the topic area. They are less structured than systematic reviews and their subjectivity may make them susceptible to bias. Systematic reviews and meta-analyses are at the top of the hierarchy of evidence (National Institute for Health and Care Excellence 2005; Clarke and Stewart 1994). Systematic review methods can be applied to almost any study design and aim to be systematic, explicit, and reproducible (Tricco et al. 2011). A systematic review has a specific research question to answer, with pre-defined eligibility criteria. The reviewer uses explicit methods to identify, critically appraise and synthesise evidence to minimise bias and produce reliable findings (Higgins and Green 2009).

The aim of this phase of the doctoral study was to perform the following two literature reviews:

1. Cochrane systematic review of randomised controlled trials (RCTs) which consider the use of topical oils and emollients for prevention or treatment of term baby dry skin (protocol appendix 2).
2. Structured review of the remaining empirical evidence in this area using a systematic approach, including all non-randomised experimental, observational and qualitative studies (protocol appendix 3).
2.3 Cochrane systematic review

Cochrane reviews are recognised globally as the highest standard available in evidence-based healthcare. A Cochrane review is a rigorous and transparent way of answering questions such as: ‘does one treatment work better than another?’ Each review has a specific research question to answer and reviews are updated regularly to ensure that treatment decisions are based on the most current evidence available. The Cochrane title "Topical oils for prevention or treatment of dry skin in term infants" was registered by the researcher with the Cochrane Neonatal Review Group, and asks the question: “What is the effect of using topical oils, in comparison to other oils, emollients or no oil, for the prevention or treatment of dry skin in term infants?” (appendix 2).

The Cochrane systematic review is currently ongoing. The remainder of this chapter focuses on presenting the methods and findings of the structured literature review conducted for the doctorate. The review uses a systematic approach to the literature search and critical appraisal. The studies included in the Cochrane review have been included in this review for completeness of evidence to support the doctoral study.

2.4 Structured literature review

2.4.1 Quantitative review

This review addresses the research question: “What is the effect of using topical oils, emollients or no oil, for the prevention or treatment of dry skin in term babies?” The types of studies in the review include quantitative empirical randomised and non-randomised experimental and observational study designs.

2.4.2 Qualitative review

This review explores the research question: “What are parents’ and health professionals’ experiences of using topical oils and emollients for the prevention or treatment of dry skin in term babies?” All types of qualitative empirical studies were included, such as, but not limited to, grounded theory, phenomenology, ethnography, action research and feminist research.

2.4.3 Preliminary scoping exercise

A scoping exercise was conducted in January 2012 in order to provide an initial literature review for the PhD funding application. The scoping literature search was repeated at the end of 2012 to determine an optimal literature search strategy. This scoping literature search included basic search terms of infant, baby, newborn, neonate, oil, emollient and dry skin. The broad search results were then reviewed to define the search terms further, and include search terms that had not been previously determined. The scoping search
also helped to determine which databases to use and how to combine Boolean operators to create the best search strategy.

The preliminary scoping literature search highlighted that there was little evidence that fulfilled the main eligibility criteria of topical oil use with term babies. Therefore, to provide a holistic overview of the topic area and to enhance breadth of knowledge, the literature search was broadened to incorporate preterm baby, animal and adult studies, bathing and cleansing and baby massage. This provided a broader context for the proposed study, and a wider background of evidence on which to draw for the study design.

Part two of this chapter presents the structured literature review, providing a balance between the subjectivity of a traditional narrative review and the objectivity of a systematic review. The underlying concepts of the systematic review are followed for the literature search and critical appraisal processes. This aims to ensure that the review maintains the thorough and methodical principles of systematic review so that transparency and robustness are evident.

2.5 Structured literature review question

The systematic review questions remained the focus of this structured review (see 2.4.1 and 2.4.2). With consideration to the dearth of evidence in this area provided by the scoping exercise, the review was extended to look at other areas of skincare such as bathing, cleansing and massage. The evidence from studies involving adults, animals and preterm babies was also explored.

2.6 Eligibility criteria

2.6.1 Type of participants

Quantitative: Newborn term babies ($\geq 37^{+0}$ weeks of pregnancy gestation) using topical skincare products within the first 28 days after birth were included. Studies investigating animals, adults and preterm babies were also reviewed for breadth of knowledge.

Qualitative: Parents and health professionals using topical skincare products on term babies within the first 28 days after birth were included.

2.6.2 Type of studies

Quantitative: Empirical randomised and non-randomised experimental and observational study designs were eligible, including randomised and non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies.
Qualitative: Empirical studies that focus on qualitative data including, but not limited to, methodologies such as grounded theory, phenomenology, ethnography, action research and feminist research were eligible.

2.6.3 Type of interventions / outcomes

The main focus of the review was the intervention of using topical oils and emollients for newborn term baby skincare (quantitative), and parent experiences of this practice (qualitative).

With regard to outcomes, the review focused on skin barrier function measured by trans-epidermal water loss, stratum corneum hydration and pH, erythema, clinical observations and skin assessment scores. Infection, atopic eczema and maternal satisfaction were also considered.

Papers were excluded if they were not empirical research, or if they investigated diagnosis or treatment of diseased skin, maternal or neonatal oral oil treatments, maternal treatment in pregnancy, or outcomes such as fetal growth, neurobehaviour or blood profiling.

2.7 Literature search

It is vital to be confident in the literature search, especially for systematic reviews, as the credibility of the review is founded on the sound retrieval of relevant papers (Cooper 1998). Effective retrieval of papers relies on the balance of identifying the correct search terms, and the clarity of context within the title and abstract of the paper being retrieved. Unfortunately assignment of database indexing terms is dependent upon the indexer’s interpretation of the paper, which can affect the success of the literature search (Evans 2002). If a title and abstract does not clearly represent the type and topic of research it is unlikely that an indexer will correctly index the paper. This will have a consequent impact on retrieval in a database literature search. In order to execute a successful search strategy it is important to have a focused research question and identify the appropriate resources to search (Harvard 2007), which includes methods to retrieve those papers incorrectly indexed in a database.

The search strategy for this doctoral study was informed by the need to identify any existing evidence which investigated the use of topical oils and emollients with babies, particularly in connection with skin barrier function. In addition, it was necessary to search for background information on other associated skincare research which could inform the design of the proposed study. As the scoping literature search had indicated that the evidence base for topical oil use in term babies was likely to be sparse, it was envisaged that this background information would include the use of other skincare products in babies and also the use of topical oils in other populations such as adults and animals.
The search strategy used a three step approach. Firstly, searches were conducted in the following databases:

- CINAHL plus – Cumulative Index to Nursing and Allied Health Literature (1937 to January 2015)
- MEDLINE (1946 to January 2015)
- EMBASE (1974 to January 2015)
- British Nursing Index (1994 to January 2015)
- Maternity and Infant Care (1971 to January 2015)
- AMED - Allied and Complementary Medicine Database (1985 to January 2015)
- SIGLE - System for Information on Grey Literature in Europe (via OpenGrey 1980 to January 2015)
- CENTRAL - Cochrane Central Register of Controlled Trials (1996 to January 2015)

Secondly, the reference lists of all papers retrieved were examined. Published literature reviews were obtained to examine reference lists.

Finally, subject-specific journals were explored using the basic search terms (shown below) to determine any obscure titles, and prolific authors and major pharmaceutical and cosmetic companies were contacted, to access any unpublished research (appendix 4).

The use of complementary search methods, such as the follow-up of references and citation searching used in steps two and three of the strategy, were important to compensate for any deficiencies in the search terms used (Papaioannou et al. 2010; Grayson and Gomersall 2003).

Initial search terms for the preliminary searches were structured according to the PICO framework (Booth et al. 2000) and included:

- P: Infant OR baby OR neonate OR newborn
- I : Oil
- C: Emollient
- O: Dry skin

Results were explored and the final search strategy was refined and implemented as illustrated in figure 2.1.
The PICO (Population/problem, Intervention/exposure, Comparison, and Outcome) tool has developed into a fundamental tool which is routinely used in evidence-based practice and systematic reviews. The tool assists researchers to develop a focused research question, to identify the best search terms, and to formulate the optimal search strategy to systematically retrieve papers which can answer the research question (Schardt et al. 2007; Villanueva et al. 2001; Booth et al. 2000). The PICO search strategy tool is widely used by researchers when reviewing evidence and formulating focused research questions, and has been adopted by the Cochrane Collaboration (O’Connor et al. 2009). Unfortunately it is not as useful when devising a search strategy for qualitative evidence, as the PICO components of intervention, comparison and outcome do not resonate with the qualitative approach. For the qualitative search strategy, the SPIDER search strategy tool was preferred (Cooke et al. 2012). This tool is a development and extension of the PICO search strategy tool and has been refined to more sensitively address the qualitative concepts of sample (S), phenomenon of interest (P, I), design (D), evaluation (E) and research type (R). The SPIDER research team used the Boolean operator ‘AND’ to combine the final concept of research type (R), however due to indexing issues this had the effect of excluding two relevant papers. The SPIDER team recommended using ‘OR R’ in place of ‘AND R’. Although it increased the number of hits, the change was successful in retrieving all of the relevant papers, one of which PICO did not find (Cooke et al. 2012). The researcher has therefore used ‘OR R’ as recommended to ensure that all papers have been successfully retrieved (see figure 2.2). The qualitative search strategy did not generate any additional qualitative studies but confirmed that, as far as possible, none had been missed.

Figure 2.1: PICO quantitative search strategy: [P] AND [I OR C] AND [O]

<table>
<thead>
<tr>
<th>P</th>
<th>infant* OR bab* OR neonat* OR newborn*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>oil* OR plant oils OR oleic acid OR linoleic OR oleic</td>
</tr>
<tr>
<td>C</td>
<td>emollients</td>
</tr>
<tr>
<td>O</td>
<td>skin barrier function OR epidermal barrier function OR skin score* OR atopic march OR dry skin OR atopic eczema OR atopic dermatitis</td>
</tr>
</tbody>
</table>
The scoping search process was conducted in January 2012 in preparation for the doctoral funding application. Zetoc alerts were set up at this point to maintain awareness of new evidence being published in the field. The scoping search was repeated at the end of 2012 to define the final search strategy. The research team discussed and agreed the search strategy in January 2013. The first systematic search was conducted in April 2013 and the final update was in January 2015. There was no restriction on start date, language or geographical location, as the scoping search had highlighted the dearth of evidence available in this topic area so it was important to capture any papers that existed. The aim was to collect all of the evidence for this topic area.

All of the search results from the final searches in January 2015 were combined and provided a yield of 14,469 papers (appendix 5). The broad search meant high specificity which consequently yielded a high number of hits. A narrow, focused search for high sensitivity would have been preferable, but when this was attempted many relevant papers were excluded. This was probably due in part to unclear titles resulting in problems with indexing within the databases. It was also impossible to exclude oral treatment and treatment in pregnancy studies in the search strategy without also excluding some topical treatment papers. The large number of hits were reviewed by title and abstract according to the review eligibility criteria, which eliminated 14,400 papers for irrelevance, such as emphasis on oral (parenteral) nutrition, treatment in pregnancy not infancy, duplication or not being empirical research (such as reviews, letters or commentaries). The full texts for 69 papers were considered and a further 12 papers were rejected (reviews/protocol n=3; letters/commentaries n=6; oral treatment n=1; no treatment n=1; not newborn n=1).

Journal searches and exploration of the reference lists for the remaining 57 papers retrieved a further 28 papers. On deeper investigation of these 85 papers, 36 were excluded due to irrelevant outcomes (n=22), reviews (n=2), treatment/no treatment emphasis (n=9) or caring for a child with atopic eczema (n=3). A total of 49 papers were
selected for critical appraisal and quality assessment (quantitative n=46; qualitative n=3).
The literature search flow chart is illustrated in figure 2.3.

2.8 Critical appraisal methods

The appraisal tools originally chosen to use with the quantitative literature were those
developed by the Critical Appraisal Skills Programme (2010; appendix 6). These tools are
specific to the type of study design. However, it became evident that using different tools
for different study designs was quite onerous and lacked consistency. A validated quality
appraisal tool which could be used across all types of study design was required. The
critical appraisal tool developed by the Effective Public Health Practice Project (2013;
appendix 7) was found to fulfil this requirement, which enabled a more consistent
approach. After quality appraisal, a total of 48 papers were selected for inclusion in the
quantitative review. The study characteristics for these included papers are illustrated in
appendix 8.

For critical appraisal of the qualitative studies, the author has experience of using the
quality assessment tool developed by Walsh and Downe (2006; appendix 9). This tool
was chosen for use in this review as it amalgamates the most useful parts of existing
validated tools. Qualitative studies were graded for quality using the grading system
developed by Downe et al. (2009; appendix 10) based on the work by Lincoln and Guba
(1985). After quality appraisal, a total of 2 papers were selected for inclusion in the
qualitative review. A third qualitative paper was rejected due to poor methodological
quality (appendix 8).
14,469 (titles and abstracts)

After removal of:
- Duplicates
- Parenteral (oral) studies
- Treatment in pregnancy studies
- Non-empirical papers (reviews, letters, commentaries)

69 papers (full text)

After removal of:
- Reviews/Protocol (n=3)
- Letters / Commentaries (n=6)
- Oral treatment study (n=1)
- No treatment study (n=1)
- Not newborn population (n=1)

57 papers

After journal searches and reference list examination:
- 28 additional papers

85 papers (full text and reference lists examined)

After removal of:
- Studies with irrelevant outcomes (n=22)
- Reviews (n=2)
- Studies with emphasis on treatment / no treatment (n=9)
- Studies with emphasis on caring for a child with atopic eczema (n=3)

49 papers

After application of quality criteria

48 papers (quantitative n=46; qualitative n=2)

Figure 2.3: Literature search flowchart
PART TWO: LITERATURE REVIEW

2.9 Findings of the literature review

After determining all of the available evidence by implementing inclusion and exclusion criteria and quality appraisal, 46 quantitative papers were reviewed in the topic areas of bathing and cleansing, baby massage, cultural influence, and topical applications. Quantitative papers were globally represented (Asia: 13; Europe: 11; USA: 10; UK: 9; UK/USA: 1; Egypt: 1; Australia: 1). Two UK qualitative studies are discussed in section 2.9.4. One study is incorporated twice within the review discussion (Ahmed et al. 2007) as the survey falls within section 2.9.3 and the RCT within section 2.9.5.3.iii. A table illustrating the key characteristics of all of the included studies is provided in appendix 8. These studies are now critically discussed in detail in this part of the chapter.

2.9.1 Bathing and cleansing

Eight papers which considered products for bathing and cleansing term babies were included (appendix 8). Six of the papers reported the findings of randomised controlled trials (RCTs) (Lavender et al. 2013; 2012; 2011; Garcia-Bartels et al. 2012; 2009; Visscher et al. 2009). One paper (Furber et al. 2012) reported the qualitative data and questionnaire data from one of the RCT samples (Lavender et al. 2012). One study was in abstract form only (Galzote et al. 2007) so quality assessment was limited. The quality of the other seven studies was high. Settings included UK (n=4), Europe (n=2), USA (n=1), and Asia (n=1).

For some time, it has been recommended to parents that using water only for baby bathing and cleansing is best. This opinion may have arisen from the advice of one midwife (Trotter 2002), who suggested that babies had less skin problems if water alone was used in their skincare regimens. Trotter’s advice was based on a small ‘study’ of her own four children, where the older two children had used wash products and the younger two used water alone. As the younger two did not experience any rashes, and the older two did, she concluded that the wash products were harmful and recommended water alone. This practice was replicated across the UK. Alternative research suggests that water may be harmful to baby skin as it is rapidly absorbed and can increase the space between cells disrupting skin barrier function (Nikolovski et al. 2008). Water has a high pH (approximately 7.2) and contains calcium salts which damage skin barrier. It is also a poor cleanser which results in substances which are damaging to the skin barrier being left in contact with the skin.

In response to the lack of research in baby skincare, a programme of research was conducted by a multi-professional team of UK researchers. Pilot (n=100; Lavender et al. 2011) and definitive (n=307; Lavender et al. 2013) RCTs of wash product versus water...
and an RCT (Lavender et al. 2012) and mixed-methods study (Furber et al. 2012) of wipes versus water for napkin area skincare were conducted (n=280). The wipes trial (Furber et al. 2012; Lavender et al. 2012) had a high completion rate (90.7%). The pilot wash study (Lavender et al. 2011) initially had a very high loss to follow-up of 58%, but this reduced to 31% at four weeks and 29% at eight weeks when the follow-up assessment was completed at home rather than in the hospital. In the definitive wash study (Lavender et al. 2013), completion rate was 78.8%. Although this research programme was industry-funded, the studies were investigator-led which meant that the trial management team conducted the trial independently of the funder. The trial management team made all of the decisions for trial design, implementation, data analysis, interpretation and dissemination. The investigator could publish the results whether they were negative or positive to the funder. Only the trial management team and the data monitoring committee had access to the data. These adequately powered, robust clinical trials found that the specific formulation products tested for bathing and cleansing were equivalent to using water alone for trans-epidermal water loss, stratum corneum hydration and pH, and clinical observations. These were the first studies to provide evidence that could reassure parents in their choice to use the tested formulation skincare products or water alone to care for their baby’s skin, and supported the findings of previous smaller RCTs (Garcia-Bartels et al. 2012; 2009; Visscher et al. 2009; Galzote et al. 2007).

2.9.2 Baby massage

Five RCTs (Fallah et al. 2013; Kumar et al. 2013; Çetinkaya and Başbakkal 2012; Mirmohammadali et al. 2011; Sankaranarayanan et al. 2005) investigating baby massage were considered; however none of the trials assessed skin barrier function. Outcomes included crying and sleep time, weight gain and neurological development. None of the studies were therefore included in the review, but are recorded here to highlight the global practice of using topical oils for baby massage. A review of the evidence has been published by the researcher (Cooke 2015; appendix 11).

2.9.3 Cultural influence

Four studies were reviewed (Karas et al 2012; Ahmed et al 2007; Fikree et al 2005; Darmstadt and Saha 2002). All were large scale questionnaire studies (n=352–23,356). All studies investigated newborn care practices and originated in Asia (Bangladesh, Pakistan and India). The strength of the studies is their size.

Across the globe, different countries use different topical oils on baby skin. There is very little evidence with regard to global epidemiology or practice of oil and emollient use in baby skincare. In Asian countries, massage with mustard oil is common (Karas et al. 2012; Ahmed et al. 2007; Fikree et al. 2005; Darmstadt and Saha 2002). Darmstadt and
Saha found that 96% of carers practised baby massage with oil, starting in the first three days of life. Fikree et al. (2005) found that daily massage of babies was universally practiced. In the largest study (Karas et al. 2012), massage was also near universal. Ahmed et al (2007) found that the majority of baby massage practices commenced within one hour of birth (61%) using mustard oil (88%) which was applied all over the baby’s body (89%). The reasons that parents gave for performing baby massage using a topical oil were to keep the baby warm (22%), to prevent infection (18%), to improve the general health of the baby (8%) and to improve skin condition (6%).

It is important that any future skincare studies include a diverse range of black and minority ethnic participants, to ensure that a range of cultures are taken into account. Useful findings should be disseminated on a global scale so that areas where traditional practices may be harmful can be informed.

2.9.4 Parental and health professional views and experiences of baby skincare

Critical appraisal was conducted on three qualitative studies which ranged in quality from grade A to D (Downe et al. 2009). Two UK studies considered bathing and cleansing practices (Furber et al. 2012; Lavender et al. 2009). These were of high quality and taken forward for review (appendix 8). One study considered baby massage in Nepal (Mullany et al. 2005) and was methodologically limited. The analytical approach was not defined and the results appeared to be listed rather than themed, without the support of verbatim quotes. This study was therefore excluded.

In both UK studies, new mothers were recruited by purposive sampling shortly after childbirth. Data from interviews (Furber et al. 2012; Lavender et al. 2009) and diaries (Furber et al. 2012) were thematically analysed. Although data for these studies were collected two years apart, living with the argument that ‘water is best’ continued. Lavender’s study found that mothers and health professionals felt that they needed to ‘toe the party line’ with regard to using water alone for bathing and cleansing.

“Yeah when the midwives were in the hospital I did [use water and cotton wool] because I knew they’d shout at you” (Lavender et al. 2009; p116)

In Furber’s later study, mothers were ‘living with the rhetoric’ that water was best but felt reassured that they could use the commercial product being tested.

“Had friend round today (midwife) and she was surprised that I was using baby wipes and not cotton wool. I explained there were no concerns on my part and baby wasn’t affected by using the baby wipes” (Furber et al. 2012; pE23)
Lavender’s study found that the majority of health professionals were promoting the use of oil for dry skin or massage, as they felt that traditional natural products were safer than commercial formulations.

2.9.5   Topical applications

2.9.5.1   Animal studies

Two studies investigating the effects of oil on the skin barrier function of mice were considered. These were functional mechanistic studies of unknown sample size (appendix 8).

These studies found that certain compositions of olive oil may adversely affect skin barrier function (Jiang and Zhou 2003; Darmstadt et al. 2002). Olive oil with a high ratio of oleic acid to linoleic acid disrupted the lipid structure of the stratum corneum. Sunflower oil with a high ratio of linoleic acid to oleic acid was shown in the same population to promote skin barrier repair (Darmstadt et al. 2002).

The studies had slightly different methods. Darmstadt used tape-stripping to damage the skin barrier and then monitored the rate of recovery; Jiang and Zhou treated the skin with 10% oleic acid/propylene glycol and examined the effect on skin barrier function. Darmstadt found that olive oil, mustard oil and soybean oil all delayed recovery compared to an accelerated recovery if sunflower oil was applied. Jiang and Zhou reported a marked alteration of the structure of the stratum corneum and epidermal permeability due to a disturbance of the lipid lamellae. Both studies demonstrated the adverse effects of oleic acid on skin barrier.

Any results in animal studies that are interpreted for a human model must be considered with prudence; however the hairless mouse model is regularly used and accepted as a precursor to clinical studies in humans. The stratum corneum is almost identical in mice and humans (Schurer and Elias 1991), although much thinner. Caution must be exercised as results are not always the same (Welzel et al. 1996).

2.9.5.2   Adult studies

Six studies considered the effects of using oils (n=3) and emollients (n=3) in adults (appendix 8). These studies were functional mechanistic studies (n=6-30). Three studied healthy volunteers (Patzelt et al. 2012; Mohammed et al. 2011; Naik et al. 1995). The other studies included volunteers with a history of atopic eczema or dry skin (Danby et al. 2013; 2011; Nebus et al. 2010). The two larger studies (Danby et al. 2013; Nebus et al. 2010) were randomised and therefore of higher quality as every participant had the same chance of receiving each treatment. Although all of the adult studies are small mechanistic
studies not generalizable to the wider population, they do add to our knowledge of the potential effect of oils on the skin.

It cannot be assumed that research in adults would produce a similar result in babies or children. Skin is on a spectrum with perfect adult skin at one end and baby skin with severe eczema at the other (Cork et al. 2005). Children are not small adults (Medical Research Council 2004). It is likely that any results seen in adults will be worse in babies, and developing effective treatments for children will often necessitate testing on children (Yeung 2007). Danby et al. (2013) drew on their functional mechanistic study of adult volunteers (n=19) to make clinical comparisons to baby skincare. In Danby’s study the topical application of olive oil for four weeks affected the integrity of the stratum corneum irrespective of whether the participant had a history of atopic eczema or not, although for the healthy volunteers the effect was limited to the deeper layers of stratum corneum following tape-stripping. Trans-epidermal water loss post tape-stripping was greater in the participants with a history of atopic eczema, indicating a higher susceptibility to the damaging effects of olive oil in those with a compromised skin barrier. The use of sunflower oil for the same duration preserved stratum corneum integrity and increased stratum corneum hydration. Danby concluded that olive oil should not be used in baby skincare or baby massage, and that it should not be assumed that ‘natural’ products are safe. Naik’s study (1995), did not measure trans-epidermal water loss or skin hydration, but measured effects using infrared spectroscopy to look at the distribution profile of oleic acid across the stratum corneum. The study found that oleic acid decreased lipid viscosity in the superficial layers of the stratum corneum. This caused increased permeability and therefore supports the finding of increased trans-epidermal water loss post tape-stripping after use of oleic acid in Danby’s study (2013). These findings also resonate with the animal research studies.

One mechanistic study (n=6) considered commonly used oils from across the globe, such as jojoba, soybean, avocado and almond oil (Patzelt et al. 2012). The authors investigated the penetration behaviour of the oils, assessed by laser scanning microscopy. This study, like Naik’s study, found that the oil penetration was confined to the upper levels of the stratum corneum, where the skin barrier function is focused. The participants were all healthy volunteers, as in Naik’s study, and therefore those with damaged skin could have different results. Olive oil and sunflower oil were not tested in Patzelt’s study, where almond oil and soybean oil were found to penetrate the deepest in two participants described as having “dry skin”.

Two studies investigated the use of the emollient Aqueous cream. Danby et al. (2011) looked at the effect of this emollient in 26 volunteers (13 with history of atopic eczema but asymptomatic for six months, and 13 with current atopic eczema). Another study had 6 healthy adult volunteers (Mohammed et al. 2011). In both studies, participants used
Aqueous cream for 28 days. Aqueous cream contains approximately 1% sodium lauryl sulphate (SLS) which is now known to be an extreme irritant to skin. It is a commonly prescribed ‘leave on’ emollient for itchy skin conditions (Mohammed et al. 2011), even though it was not designed to be used in this way (British National Formulary 2013). Both studies found that Aqueous cream should not be prescribed as a ‘leave on’ emollient as it causes damage to the skin. One final study (Nebus et al. 2010) was only available in abstract form and therefore appraisal is limited. It considered a colloidal oatmeal lotion for dry skin in a 9-day study. The lotion showed a significant improvement in itching, trans-epidermal water loss, and dryness.

2.9.5.3 Preterm baby studies

Seventeen papers were included (appendix 8); sixteen RCTs and one small observational study. Five papers investigated oils only, eight papers investigated emollients only, and four papers investigated both oil and emollients (all papers derived from one study).

There has been a plethora of research investigating the use of oils and emollients in preterm babies. The RCTs have provided valuable results to include in Cochrane reviews (Conner et al. 2009; Seliem et al. 2009), with infection as the primary outcome. Infection is one of the leading causes of neonatal morbidity and mortality in low resource countries (Darmstadt et al. 2002). The vulnerability of an under-developed preterm stratum corneum (Conner et al. 2009), the lack of protective vernix (Yoshio et al. 2003), the use of potentially harmful topical products, combined with poor hygiene conditions, provides the potential for increased infection rates.

This section has been divided into three to review this evidence: studies investigating topical oils only, topical emollients only or topical oils with topical emollients.

2.9.5.3.i Topical oils

Five RCTs considered the use of topical oil for preterm skincare (appendix 8). One study was only provided in abstract form and quality assessment was therefore limited (Hu and Zhang 2014). Different oils were investigated so it was difficult to compare all of the studies together. Darmstadt et al. (2004) conducted an RCT of 103 babies (<34 weeks gestation) in India comparing sunflower seed oil with no oil. The main outcomes were skin scores, sepsis and mortality. The study suffered from declining numbers for follow-up due to the high rate of mortality which can be expected in this high-risk population. Even so, significant improvement in skin condition was found in the treatment group together with a significant reduction in infection. Another study found no difference across groups for infection (n=428; Hu and Zhang 2014). However, Hu and Zhang’s study did find that the use of sunflower seed oil resulted in significantly less dermatitis than commercial baby oil (Johnson & Johnson Consumer Companies, Inc) and that both oils resulted in significantly
less dermatitis than using no oil. In contrast, Kanti et al (2014), a small RCT (n=22) comparing sunflower seed oil against no treatment, found that sunflower seed oil may impede skin barrier development. The use of sunflower seed oil in Darmstadt’s (2008; 2005) work had a substantially significant improvement in infection rates (41% less likely to develop infection) and mortality rates (26% reduction in mortality). It is possible that the positive effect found by Darmstadt was due to the antimicrobial effect of sunflower seed oil which would explain the beneficial effect on infection and mortality rates.

A small RCT in Greece (Xatzopoulou et al. 2010) of 35 very low birthweight preterm babies compared the use of olive oil to no treatment. The outcomes under consideration in this study were infection and mortality. No differences between groups were found and the authors conclude that olive oil appears to be well tolerated by preterm babies. It would have been useful to include skin condition as an outcome. Another RCT conducted in France (Vaivre-Douret et al. 2008) included preterm babies (31 - 34 weeks gestation) and compared sweet almond oil, ISI04 blended oil or placebo with no treatment. The main outcomes were weight, growth, neurological and psychomotor development. Stratum corneum hydration and clinical observations were also reported. Unfortunately statistics for hydration and clinical observations were not provided and the authors were approached for this information (not received at time of submission). The study found significantly improved moisturisation in both oil groups, and quicker recovery of dermatological conditions in the ISI04 blended oil group. These results are limited for this review as the sample size was powered on the primary outcome of weight gain, not skin condition.

2.9.5.3.ii Topical emollients

Eight studies compared various emollients, seven of which were RCTs and one a small observational study (appendix 8). The observational study (Rutter and Hull 1981) observed the effects of a paraffin mixture (80% soft and 20% hard paraffin BP) on preterm babies (n=3 [number not absolutely clear]; 26 - 32 weeks gestation) and found decreased trans-epidermal water loss maintained six hours later. Five of the RCTs included Aquaphor™ as a treatment group (Erdemir et al. 2015; Brandon et al. 2010; Edwards et al. 2004; Pabst et al. 1999; Nopper et al. 1996) with babies between 26 and 33 weeks gestation. None of these five studies had identical outcomes. Brandon et al. found no difference in trans-epidermal water loss between Aquaphor™ and No-Sting Skin Protectant. The use of Aquaphor™ had the highest (worse) skin condition score but both treatments were within normal range. Nopper et al. found that the use of Aquaphor™ resulted in significantly reduced trans-epidermal water loss and better skin condition compared to the control group. However the control group were able to use a water-in-oil ointment (Eucerin®) as required and this may have had an effect on the results. Edwards
et al. conducted a large multi-centre RCT of 1,191 preterm babies. The trial compared Aquaphor™ to no treatment but reported that 34% of babies in the control group also received ointment therapy for an average of 4.1 days due to a misinterpretation of the protocol, which may have affected the results. The study found that babies in the treatment group had significantly better skin condition and less skin injury than controls. One study of 197 preterm babies investigated neonatal sepsis as an outcome when Aquaphor™ was compared to no treatment (Erdemir et al 2015). The study found no difference between groups. The final RCT investigating Aquaphor™ against usual skincare was a small study of 19 babies (Pabst et al. 1999). At follow-up, only 16 babies remained although the reason for this loss is unclear. Again Aquaphor™ was found to improve skin condition.

Of the two other RCTs, one investigated Bepanthen® ointment against a lanolin (70%)/olive oil (30%) cream against no treatment (Kiechl-Kohlendorfer et al. 2008) and the other compared routine skin care to Eucerin® (water-in-oil) cream (Lane and Drost 1993). In the first study, there is a discrepancy in the reporting of numbers lost to follow-up; approximately 25% are unaccounted for. Babies treated with the cream had significantly less dermatitis, and both treatment groups had better outcomes than the control group. In this study the olive oil cream had the best outcome; however, the olive oil is diluted by the volume of lanolin in the composition of the cream. The study by Lane and Drost also found that the treatment group (Eucerin®) had less dermatitis. This study had more than 50% loss to follow-up for which the reason is not reported. The result should therefore be interpreted with caution. Both of these studies could be affected by attrition bias, where the loss to follow-up results in incomplete outcome data and consequently, systematic differences between the groups (Higgins and Green 2009). Lane and Drost is a seminal piece of work and the skin scoring assessment tool (table 2.1), which was introduced in this study, has been used by many researchers since.

2.9.5.3.iii Topical oils versus emollients

Although there were four papers (appendix 8) that compared oils and emollients, all papers resulted from the same RCT (Darmstadt et al. 2008; 2007; 2005; Ahmed et al. 2007) but reported different outcomes.

Ahmed’s study investigated the massage practices of 497 RCT participants. The RCT compared sunflower seed oil, Aquaphor™ or no treatment in preterm babies (<33 weeks gestation). All participants completed the baseline survey; however only 121 completed the follow-up questionnaire. Although most of these were lost due to the high mortality rate (n=281), the reason lost was not reported for 39 of the initial participants. This study may have benefitted from a qualitative element to explore more deeply the views and experiences of parents. Of interest in the results of this study was the reporting of oils
commonly used by parents on their babies in Bangladesh. Mustard oil was most commonly administered (88%), shown in an animal study to be harmful to skin (Darmstadt et al. 2002). After the study, many parents preferred Aquaphor™ (42%) and perceived that sunflower seed oil and Aquaphor™ were superior to mustard oil. However 29% of parents reported that they would continue to use mustard oil, which indicates the strong tradition of using this oil in this population.

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<tr>
<td>0</td>
<td>Normal, no sign of dry skin</td>
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<tr>
<td>1</td>
<td>Dry skin with few visible scales</td>
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<tr>
<td>2</td>
<td>Dry skin with moderate visible scales</td>
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<tr>
<td>3</td>
<td>Dry skin with many visible scales</td>
</tr>
<tr>
<td>4</td>
<td>Dry skin with thicker, darker scales and areas of mild erythema</td>
</tr>
<tr>
<td>5</td>
<td>Dry skin with thicker, darker scales, increased areas of mild erythema, and skin has a rough texture</td>
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<tr>
<td>6</td>
<td>Dry skin with thicker, darker scales, increased areas of mild erythema, skin has a rough texture, and superficial fissures are seen</td>
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<tr>
<td>7</td>
<td>Dry skin with thicker, darker scales, increased areas of mild erythema, and skin has a rough texture with deeper fissures</td>
</tr>
<tr>
<td>8</td>
<td>Dry, crusted skin on erythematous base with dark scales, fissures, and occasional areas of erythematous, crusting, oozing skin</td>
</tr>
<tr>
<td>9</td>
<td>Erythematous, crusting, oozing skin involving the entire area</td>
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Table 2.1: Skin Condition Grading Scale (Lane and Drost 1993)

Darmstadt’s papers report various outcomes of the same RCT as Ahmed: infection (2005), mortality (2008), skin scores and skin blood cultures (2007). This was a robust study with intention-to-treat analysis and a high rate of adherence to the treatment regimen. Babies treated with sunflower oil were 41% less likely to develop nosocomial infections, had a 26% reduction in mortality rates against controls, and a better skin condition score compared to the control group. The alternative treatment (Aquaphor™) also resulted in a 32% reduction in mortality and equally better skin condition score than control group. Topical administration of sunflower oil reduced the passage of pathogens from the skin surface into the bloodstream, implying antimicrobial properties.

2.9.5.4 Term baby studies

Ten papers investigated the use of oils and emollients in term babies (appendix 8). Only one considered olive oil (Erenel et al. 2010). Six papers were RCTs; two of which comprised one study reported in abstract form (Simpson et al. 2012) and then in full (Simpson et al. 2014).

One RCT (Garcia-Bartels et al. 2010) compared methods of bathing term babies, with two groups incorporating the use of an emollient after bathing. These two groups showed
significantly lower trans-epidermal water loss and higher stratum corneum hydration. This was a single-centre study in Germany (n=64). The randomisation process and power calculation were not given so it is unclear if this was robust, and if the results are inferential, for example it is not reported if allocation was concealed. This makes it difficult to determine if there was selection bias (Altman and Schultz 2001). The data collection methods were valid and reliable, and there was no loss to follow-up. It is not reported whether assessor-blinding was incorporated in the methods which may be a source of observer bias (Schultz and Grimes 2002). It is unclear whether parents may have used other products during the treatment period which may have contaminated the results. The cream used was Body Cream Penaten® and although the study was partly funded by the manufacturer of this product, it was investigator-led with the funders having no influence over study design, conduct, analysis, interpretation or dissemination.

The BEEP pilot study (n=124; Simpson et al. 2012), published in abstract form, reported a pattern in the emollient group towards improved skin barrier function where this outcome was measured in a subset of babies (n=32), but no significant differences were found between the intervention and control groups. The BEEP pilot study is an on-going multi-centre study, involving four centres in the UK and one in the USA. It aims to assess the feasibility of a daily full body emollient therapy to prevent onset of atopic eczema in those at risk of developing the condition. The pilot study had an 87% completion rate; allocation concealment was maintained to minimise selection bias (Schultz and Grimes 2002); assessors were blinded to treatment allocation reducing observer bias (Altman and Schultz 2001); and although the study consisted of a small pilot sample, the definitive trial is ongoing in the UK. For those babies randomised to the intervention arm, the parents chose which intervention they preferred from a specific emollient cream / gel, a defined sunflower seed oil with a high linoleic acid / low oleic acid content or a specific emollient ointment, with most choosing the emollient cream (67.2%). Only 23.4% (n=15) of participants in the intervention arm chose sunflower seed oil. Although not reported this may provide an insight into parental preferences. It is not possible to separate the results which are specific to the sunflower seed oil as the findings were presented as a total of participants in the treatment arm. Furthermore, the study was not powered to detect this. The full report of the pilot suggests that a daily full-body emollient therapy from birth can prevent atopic eczema (Simpson et al. 2014).

Horimukai et al (n=118; 2014) also conducted an RCT at the same time as the BEEP study (Simpson et al. 2014) addressing the prevention of atopic eczema, and appeared to be modelled on Simpson’s study. It is unclear what the randomisation process involved and whether a power calculation was performed; the authors state that the study may suffer from being under-powered. Although the authors report that the sample size was 118 babies, the actual number who consented was higher (n=128). The number of babies
who continued to endpoint at 32 weeks was reduced to 99 babies (completion rate 77.3%). For other aspects of critical appraisal this was a high quality, robust study; for example, the study was assessor-blinded which minimised the chance of observer bias (Schultz and Grimes 2002) and used validated data collection tools. This study came to the same conclusion as Simpson’s study (2014) using a different emollient (Shiseido 2e Douhet Milk Baby Lotion); that the use of a daily emollient therapy from birth significantly reduces the incidence of atopic eczema in those with a genetic predisposition to the condition. The ethics review board requested that all participants were also prescribed petroleum jelly, which may have affected results; however, as this was an RCT any effect of this additional treatment should have been evenly spread across the intervention and control groups.

The Horimukai study, like Simpson’s, only recruited babies with a family history of atopic eczema. Using topical oils and emollients on babies at high risk of the condition under investigation is likely to have a different effect to that resulting from healthy babies. Most of the research which considers the population of term babies is investigating prevention of atopic eczema, which understandably leads to recruitment of those with a family history of the condition. There are no studies addressing the possibility that the use of topical oils on the skin of healthy babies from birth causes atopic eczema, and yet this practice is a potentially contributory environmental factor.

Another RCT conducted in India (Solanki et al. 2005), compared safflower oil (ratio of linoleic acid to oleic acid was not reported), coconut oil and no oil amongst preterm (<34 weeks gestation, n=42; 34-37 weeks gestation, n=30) and term babies (>37 weeks gestation, n=46). The subset of term babies (n=46) comprised 40% of the sample. The main outcome for this trial was fatty acid profiling; however clinical observations and atopic eczema were monitored during the treatment period, but not followed up long-term. The randomisation process was computer-generated; however it is unclear whether assessors were blinded to the treatment allocation. The study was not powered due to funding limitations. Like Garcia-Bartel’s (2010) and Simpson’s (2014) studies, there could have been contamination from use of other skincare products. However, unlike Garcia-Bartel's study, this study reports allocation concealment and assessor-blinding, reducing the chances of selection and observer bias (Schultz and Grimes 2002; Altman and Schultz 2001). One term baby in the safflower oil group developed a rash, but this disappeared within 48 hours and no other side-effects were reported amongst the term babies.

One European study conducted by Roberta et al (2014) compared newborn babies (n=52) washed with water only to newborn babies (n=42) washed once daily with a liquid baby cleanser (product name not reported) and moisturised with almond oil (components not reported). The study found a statistically significant difference in trans-epidermal water...
loss between the groups at day ten. Trans-epidermal water loss was higher in the
intervention group. As the intervention group was using a cleanser in addition to the
topical oil, the effect of the oil alone cannot be determined. The cleanser may have had an
adverse effect on skin barrier function, particularly if it contained sodium lauryl sulphate
(SLS) which has been shown to adversely affect the skin barrier (Danby and Cork 2011).
This would consequently provide a skewed result compared to the control group who were
using water alone. The age range for babies in the study was 32.3 weeks to 42.3 weeks
gestation and the total number of preterm babies is not reported. Baseline characteristics
are not illustrated so it is unclear how homogeneous the groups were. There is no report
of a power calculation and adherence to the protocol is not confirmed. All of these
omissions are evident despite the recommendations of the globally adopted CONSORT
statement for reporting of randomised trials (Moher et al. 2010). The authors conclude that
cleansing and moisturising with oil may delay the natural maturation of skin barrier
function, which resonates with the conclusion of one of the preterm studies (Kanti et al.
2014), however in view of the methodological limitations of the Roberta study the results
should be construed prudently.

Of the remaining small studies, one compared olive oil to no treatment (Erenel et al.
2010); however, this study investigated oils particular to umbilical cord care and is
therefore irrelevant to our outcomes of interest. The study is mentioned here to confirm
the lack of research for the most commonly used topical oil in the UK. A non-controlled
open-label phase one study by Lowe et al. (2012) investigated the use of EpiCeram™, a
ceramide-dominant triple lipid, as a preventative measure for, rather than treatment of,
atopic eczema, in babies greater than 36 weeks gestation. Only ten out of 339 eligible
babies participated in the study and findings are descriptive: there was only one
assessment group. A diary was maintained by the participants and the cream was
weighed to assess compliance, but it is not reported if participants also used other
emollients or oils during the treatment period. Trans-epidermal water loss values were
reported to be lower compared to another study (Nikolovski et al. 2008), although the
babies in Nikolovski’s study were older. Results are limited in their application due to the
small size of the study and lack of control group. Another study (Simpson et al. 2010)
without a comparison or control group, investigated the use of Cetaphil® cream (oil-in-
water, petroleum-based) in term babies at high risk of developing atopic eczema (n=20).
Trans-epidermal water loss and other skin capacitance measurements were within
expected ranges, and there were no adverse effects. This is suggested as a safe cream to
help prevent the onset of atopic eczema but this claim is made with a condition that larger,
controlled studies are required. Finally, one non-randomised experimental study
(Takahashi et al. 2009) was only provided in abstract form. It does not report the age of
the babies, described as ‘newborns’ at risk of developing atopic eczema. There were two
groups, moisturiser (Locobase Repair®) as a preventative measure (n=10) and no
treatment (n=10). Trans-epidermal water loss and skin surface pH showed no differences between groups. The researcher has written to the authors to request further details to conduct a more robust quality appraisal, but the authors have not responded.

In summary, none of the studies investigating oils and emollient use for term babies are sufficiently robust to infer evidence-based clinical guidance about which products can be safely used from birth. All of the studies are weakened by small sample sizes which reduce the ability to detect clinically meaningful results. Apart from the BEEP study (Simpson et al. 2014), all of the studies are single-centre studies which limits the generalisability of the findings. Many of the studies omit to disclose important aspects of their methodology such as whether a power calculation was conducted, despite the reporting guidelines of the CONSORT statement (Moher et al. 2010). There is no evidence from large-scale RCTs to inform health professionals about recommending and using the most common topical oils. Furthermore, none of the reviewed studies have investigated whether topical oils and emollients used on healthy, full-term babies from birth are a possible contributory factor in the development of atopic eczema in babies who do not have a genetic predisposition to the condition.

2.10 Comparison with other literature reviews

There are no published systematic reviews which consider the use of topical oils and emollients in healthy newborn, full-term babies. There have been two Cochrane systematic reviews which investigate the prevention of infection in preterm babies (Conner et al. 2009; Seliem et al. 2009) and one which reviews the evidence for prevention of napkin dermatitis in babies (Davies et al. 2009). The researcher has registered a title and published a protocol to conduct a Cochrane systematic review entitled “Topical oils for the prevention and treatment of dry skin in term infants” (Cooke et al. 2014; appendix 2). The review is ongoing and should be completed in 2015. This review will complement the body of work for neonatal skincare held in the Cochrane Database of Systematic Reviews.

2.11 Recommendations for future research

There is an urgent need to conduct more research, preferably a large RCT, to investigate the impact of using topical oils on the skin of healthy newborn, full-term babies. There is no evidence which investigates whether the use of topical oils on the skin of healthy term babies is a contributory factor in the development of atopic eczema in those babies who are not genetically predisposed to develop this condition. The existing body of evidence involves research designs which encompass different populations, aims, interventions and outcome measures. In the first instance a pilot study would therefore be recommended.

Initially a UK pilot RCT could establish proof of concept that a topical oil intervention has a biological effect on baby skin (Thabane et al. 2010), and establish the optimal trial
parameters and processes. It was established in a national survey that the most routinely recommended and used topical oils on babies in the UK were olive oil and sunflower oil (Cooke et al. 2011). These two oils should be tested in the pilot RCT. The literature review showed that there were no studies which investigated the use of topical olive oil for term babies, and this is the most commonly recommended oil in the UK with 80% of midwives recommending this for baby dry skin (Cooke et al. 2011). Although sunflower oil has been investigated in a variety of studies, it would be optimal to compare this oil under the same conditions as the olive oil to gain the most informative results for future research. A pilot study, with the aim of assessing feasibility, can also incorporate a questionnaire and qualitative component which could determine from parents what types of other skincare products they use on their babies to inform future studies. The qualitative component could assess maternal satisfaction pertaining to the intervention, information provision, treatment allocation and having a newborn baby participating in an RCT.

2.12 Conclusion

The evidence investigating the use of topical oils and emollients in skincare is fairly diverse; with different populations and different study designs. Small studies involving volunteer participants can have many underlying confounding variables which can affect the results, and the results from these studies must therefore be interpreted cautiously. Many of the studies are in populations which are different than the term baby population of interest, but results showing adverse effects in adults are likely to have a greater effect in babies, due to the differences between adult and baby skin discussed in chapter one.

Some oils, such as olive oil, were shown to be harmful to skin barrier function and some, such as sunflower oil, were shown to have a beneficial effect. Of the studies which included term babies, only one considered olive oil (Erenel et al. 2010) but this was in the context of umbilical care, not dry skin. Health professionals in the UK recommend the use of olive oil for baby dry skin, and to a much lesser extent sunflower oil, to parents of healthy newborn, full-term babies (Cooke et al. 2011). As reported in this review, there is no robust evidence to support this practice.

This structured literature review has considered the current evidence available for baby skincare, with particular attention to the use of topical oils and emollients. It is evident that current clinical practice for term babies is based on traditional and anecdotal evidence due to the dearth of relevant robust research, or based on evidence which is inappropriate for healthy, full-term babies, such as those studies in mice, adults and preterm babies. It was highlighted in chapter one that term baby skin is different than that for adults or preterm babies. There is consequently an evidence gap in the literature.

The literature review has demonstrated that a robust study, preferably in the form of an RCT, is required to assess the impact of those topical oils most commonly used, against
no treatment, on baby skin barrier function. Further studies can begin to establish
evidence that can determine whether there is a link with the development of atopic
eczema. In view of the dearth of existing relevant evidence, it is necessary to initially
conduct a pilot RCT to ascertain the feasibility and acceptability of conducting an optimal
future study, with particular emphasis on recruitment, protocol compliance, acceptability of
the intervention and of having a newborn baby participating in an RCT.

The next chapter in this thesis therefore provides the methodology for the proposed study,
which aims to begin to provide an evidence base to support clinical practice with regard to
the prevention or treatment of dry skin in term babies.
CHAPTER THREE: Research Methodology

3.1 Introduction to the chapter

Part one of this chapter considers the purpose of this study, the aims and objectives, research questions and hypothesis. Part two addresses the theoretical perspective which underpins the study design. The final part summarises the methods chosen for the OBSeRvE: Oil in Baby SkincaRE study, and the rationale for choice of study design. This lays the foundations for the following chapter, where the methods are presented in detail.

CHAPTER THREE: PART ONE

3.2 Purpose of the research

The literature review highlighted a gap in evidence which the proposed study aims to address. There is a dearth of research regarding the use of topical oils for the prevention or treatment of newborn term baby dry skin. The proposed study considers proof of concept of what 'effect' the use of topical oils has on baby skin barrier function. This type of 'cause and effect' question is ideally addressed by a randomised controlled trial (RCT) (Torgerson and Torgerson 2008). A pilot RCT was deemed to be the best way to assess proof of concept, and feasibility relating to optimal primary outcome measures, trial parameters and trial management processes.

3.3 Study aims and objectives

3.3.1 Aims

The aim of the study was to generate pilot data comprising the following:

i. To assess proof of concept regarding the effect of olive oil and sunflower oil on baby skin barrier function

ii. To examine the feasibility of using infrared spectroscopy investigations in a clinical trial within a healthy newborn term baby population, and to determine optimal trial design, processes and parameters

3.3.2 Objectives

The objectives required to fulfil the aim of the study comprise the following:

i. To measure the rate of change in spectral profile of lipid lamellae and trans-epidermal water loss

ii. To explore the acceptability of trial participation for parents of newborn babies

iii. To assess the extent of the effect of the intervention on skin barrier function

iv. To observe the rate of compliance to the treatment regime

v. To observe the rate of loss to follow-up

vi. To observe the acceptability of infrared spectroscopy to parents and babies
vii. To observe any disruption of services in the hospital, the community or in primary care
viii. To assess intra-subject variability of infrared spectroscopy measurements at each time-point in the conditions under which the trial will be conducted (i.e. for babies with/without vernix; for babies who had received a first bath prior to assessment)
ix. To estimate the magnitude of infrared spectroscopy measurements in the newborn baby and use this, together with clinical judgement, to estimate an effect size for a definitive trial*
x. To estimate inter-individual variability (standard deviation) at each assessment and thus to estimate the pooled sample size for the definitive trial*
xii. To inform potential recruitment rates
xiii. To determine parents' views of the information provided
xiv. To determine the dropout rate for follow-up assessment
xv. To pilot measures of the clinical condition of the skin (erythema, dryness and scaling)
xvi. To examine the feasibility of measures of skin surface pH
xvii. To examine the feasibility of measures of stratum corneum hydration
xviii. To determine the optimal primary outcome measure for a definitive trial*
ixix. To inform consent processes and pilot participant information sheets
xx. To pilot data collection sheets (case report forms)
xxi. To test data retrieval processes

3.4 Research questions

The research questions addressed by this study comprise:

- Is it feasible to conduct an RCT to evaluate the effect of topical application of oils on newborn baby skin barrier function?
- Is participation in this study, the protocol and the intervention acceptable to parents and babies?

*Objective not reported: a definitive RCT was not supported from the pilot data as the optimal next step
3.5 Research hypothesis

The research hypothesis for this study is:

- The regular application of topical sunflower oil, when compared to no oil or topical olive oil, has an effect on the skin barrier function of newborn term babies

The null hypothesis is:

- The regular application of topical sunflower oil, topical olive oil or no oil, makes no difference to the skin barrier function of newborn term babies
CHAPTER THREE: PART TWO

3.6 Methodological choices from a philosophical perspective

This part of the chapter considers the philosophical perspective that has influenced the choice of methodology for this study. Although the main part of the research is quantitative, being a pilot RCT, there is also a qualitative component incorporating interviews to explore participants’ views and experiences. The rationale for why post-positivism has been chosen as the paradigmatic position is examined. The context of the clinical focus of the research is also a part of the rationale, and this is discussed.

When developing a research proposal it is not only necessary to consider the study design. It is also important to understand the justification for that design and what underpins that justification; what assumptions about one’s view of the real world are included in one’s decision-making. Crotty (1998; p3) describes theoretical perspective as “the philosophical stance informing the methodology and thus providing a context for the process and grounding its logic and criteria”. One’s theoretical perspective is informed by one’s understanding of ‘what is’ (ontology) and ‘how one knows what one knows’ (epistemology).

To understand the rationale for choosing post-positivism as the paradigmatic stance of the research, alternative stances were considered, including positivism. How these stances resonate with the quantitative key concept of objectivism and the qualitative key concept of interpretivism were also examined. The acceptance or rejection of the stance is discussed in the context of the methodology. The discussion clearly highlights the appropriateness of post-positivism as the approach best suited to this type of clinically-focused research design. The philosophical perspective and methodological choices deliberated in this chapter also underpin the choice of methods outlined in the next chapter.

3.7 Paradigms

A paradigm can be defined as a collection of beliefs and practices that inform the conduct of an investigation by providing the appropriate lenses and processes through which to accomplish it (Weaver and Olsen 2006). Paradigms evolve through shared beliefs about knowledge construction and the nature of reality (Hinshaw 1996; Jacob 1989). As they are human constructions, they are based on differences and similarities in human values and beliefs. It is therefore impossible to prove or disprove the paradigm (Guba 1990; Moccia 1988). Kuhn (1970) suggests that all empirical research is conducted within paradigms.
The choice of paradigm influences the intent, motivation and expectations for the research (Mackenzie and Knipe 2006; Weaver and Olsen 2006).

The research paradigm is influenced by multiple factors; ontology, epistemology and methodological choice (Guba and Lincoln 1994). These factors culminate in a mechanism to provide a vehicle for obtaining knowledge and the process to produce that knowledge.

3.7.1 Exploring ontology and epistemology

Early philosophers questioned what reality is, looking for convincing answers. Religion and the belief in the existence of a Deity played a major part in their theories. Modern philosophers ask the same question, but look for answers in a more rigorous way (Robinson and Groves 2007). The beginning of modern philosophy is attributed to René Descartes (1596-1650). Descartes was an autonomous philosopher who refused to accept orthodox philosophical answers. His background as a mathematician meant that his search for answers to philosophical questions was objective and logical. Descartes suggested that no knowledge can be guaranteed. He surmised that although he could not be sure that his body was real, he could be certain that his thoughts existed (Robinson and Garratt 2010). The examination of this scepticism or 'Cartesian Doubt' resulted in the well-known philosophy of “Cogito Ergo Sum” or “I think therefore I am”, resonating with the positivist and post-positivist search to find out about reality (Guba 1990). Descartes suggested that clear mathematical thinking about the world is correct, but that the human sensory experience of the world is subjective and therefore flawed (Crotty 1998). Descartes’ philosophy could be used to seek objective certainty; however it led to more unanswered philosophical questions about human consciousness and its influence over finding true knowledge. Empiricism, founded by a later philosopher John Locke (1632-1704), adopted many of the ideas of Descartes in its insistence that human knowledge is always indirect. This meant that the knowledge was derived through the senses; human minds experience only representations or mental images, never obtaining direct knowledge of the ‘substance’ of the world (Robinson and Groves 2007).

The ideas of philosopher David Hume (1711-1776) were important in the development of clarification of causation. His ideas were more technical in nature. He suggested that findings which were based on observation and induction remain conjecture and temporary as induction cannot provide the certainty that logic can (Crotty 1998). Hume defined ‘cause’ as a human belief based on previous experiences. He confirmed that causation is based on induction and does not have any logical certainty; this view is sometimes labelled Subjectivism (Lincoln and Guba 1985). Immanuel Kant (1724-1804) disagreed with Hume’s inference that humans believe in causation only because of past experiences. Kant surmised that the human mind is active and already has the apparatus
to make sense of the experiences. Kant deduced that human science explores the world as it happens, but religion remains in the unknowable world. The two do not therefore need to conflict with each other (Lincoln and Guba 1985).

The philosophy of Georg Wilhelm Friedrich Hegel (1770-1831) contemplates the nature of thought itself. He surmised that any concept (thesis) brings with it an opposite concept (antithesis) and comparison between them will occur until a synthesis is eventually achieved. Hegel deduced that any philosophical idea that is described as objective, as compared to subjective, is ambiguous, as ideas are constantly changing. He suggested that knowledge is an active process which changes through time and is not a constant that is waiting to be found. Hegel believed that eventually human beings would reach a certain knowledge of ‘what is’ (Robinson and Groves 2007).

Philosophy has contributed to the development of scientific theory. Induction is one scientific method with theory development arising through observation. However, as Hume surmised, induction only really offers probability rather than certainty. Scientific theory will probably always begin with inductive reasoning providing a contribution to a theory. This theory then needs to be tested to provide a more objective answer. In research, the cyclical and indirect nature of philosophical questioning encourages in-depth thinking and generates additional research questions which optimise research design (Allsop 2013; Crossan 2003). Exploring personal beliefs can improve understanding of the fundamental ontological, epistemological and methodological research questions (Proctor 1998).

In healthcare research, the philosophical position is unlikely to be a purely objective positivist one. Patient and health professional experiences often inform research to improve the health service experience and provide patient-centred evidence-based care. This often results in a mix of quantitative and qualitative methods to learn the most about the phenomenon being researched (Polit and Beck 2014).

3.7.2 Objectivist epistemology

Objectivism has an epistemological stance of objective truth and meaning, independent of consciousness and experience (Crotty 1998). Research using an objective stance is often experimental as the research question is frequently a ‘cause and effect’ question. This may test the efficacy of a new treatment; for example, patients with a medical condition may be prescribed a new treatment and compared against a group of patients with the same medical condition who do not receive the new treatment. This experimental research approach is often used in healthcare settings in the form of randomised controlled trials or cohort studies (Torgerson and Torgerson 2008). Objectivist
epistemology is concerned with obtaining factual and objective results that are unbiased, robust and as certain as can be. Randomised controlled trials, often labelled the ‘gold standard of research’ (Pocock 1983), have a validated structure and process to minimise bias (Bowling 2009). This ensures a high level of certainty that the results form the best evidence possible, and that another trial conducted with the same method would yield the same result (Rees 2011).

Although the randomised controlled trial fits well within the positivist epistemology, a purely objectivist approach does not allow for aspects that cannot easily be measured such as views, opinions, feelings and experiences (Guba and Lincoln 1994). Post-positivist epistemology allows for the human factor; the subjective, psychosocial and interpretive elements that can influence the research (Clark 1998).

3.8 Paradigmatic stance

This section explores the various paradigmatic positions which were considered before arriving at the choice of post-positivism. Positivism was considered due to its framework of objectivity, experimentalism, generalisibility and certainty of facts and evidence. Pragmatism was explored as it considers human knowledge as an adaptive response to a real life problem. Interpretivism was also considered as it involves the subjective view of reality and incorporates the views and experiences of human beings. Post-positivism was adopted as it fits well with a mix of quantitative and qualitative methods, but with an emphasis on the objective and experimental concepts that underpin a randomised controlled trial.

3.8.1 Positivism

The key concepts of positivism are observation, experiment and comparison. Auguste Compte is seen as the founder of positivism in the nineteenth century, but these concepts can be seen in much earlier work by Francis Bacon in the early seventeenth century (Robinson and Groves 2007). Positivism has changed over time but the underpinning notion of empirical science at its centre remains. Positivism asserts that answers to research questions are quantifiable and that knowledge can be obtained through scientific enquiry (Roberts and Priest 2010). The objectivity of empirical science encompasses the components of validity, accuracy and certainty and refutes subjectivity such as views, opinions, feelings and experiences (Guba and Lincoln 1994).

RCTs are at the top of the hierarchy of research design, after systematic reviews and meta-analyses (Guyatt et al. 1995), due to their rigorous design processes. They are the role model of empirical research and fit well into realist ontology and objectivist
Positivism can manipulate methodology to control for bias and confounders (Guba 1990). The theoretical perspective of positivism accepts that this truth and meaning can be found through rigorous scientific enquiry and experimental research; however positivism is fairly rigid in its claims that only scientific knowledge fulfils the concepts of absolute objectivity, validity, accuracy and certainty.

3.8.2 Rejection of positivism

Some scientists have questioned the certainty aspect of positivism. Many scientific beliefs are based on large bodies of evidence which can justifiably be trusted, however these beliefs can still be challenged (Phillips 1990). Further, there is no flexibility within the positivist perspective for the influence of human beings and other factors which cannot be measured (Guba and Lincoln 1994).

Crotty (1998) argues that although it makes sense that our theoretical perspective informs the study design and methods, in reality the process often starts in reverse with a real life problem which generates a research question. A decision is then made regarding what methods would best address that question. This stance could be described as pragmatism, where a problem-centred common sense approach is taken (Cresswell 2009). In the proposed doctoral study the research question asks what effect the use of topical oils has on term baby skin barrier function; however, this question requires outcomes that are objective, arising from experiment and comparison. The decision was taken that the best way to address this question was by conducting an RCT, based on the requirement for results that are objective, valid and generalisable. The theoretical perspective encompasses, strengthens and supports the scientific rigour of the study, the study design and the decision-making process (figure 3.1). The choice of an RCT design to answer the research question harmonises with a post-positivist perspective, which underpins the researcher’s stance to provide robust results which are as certain as possible.

Alternative perspectives considered included those of interpretivism and critical theory. Interpretivism emphasises that natural (scientific) reality and social reality are different and require different methods of inquiry (Gray 2009). The interpretivist approach evolved from the study of interpretive understanding or hermeneutics (Mertens 2005). The interpretivist aim is to understand the human experience (Cohen and Manion 1994), which suggests that knowledge is a social construct (Mertens 2005). Reflexivity, the influence of the researcher on the research participants, is valued in interpretivism (Horsfall 1995). Critical theory combines a range of possible methods and perspectives to investigate not only cultural phenomena, but also its social, political, historical and cultural context. The
alternative paradigms considered here were rejected in favour of post-positivism which is now discussed.

Figure 3.1: Theoretical perspective: research studies usually evolve from the identification of an issue (in this doctoral study, a clinical issue), to the formation of a research question, to the decision on what would be the optimal study design; the theoretical perspective encompasses the whole research process.

3.8.3 Post-positivism

Positivism adopts the principles of truth, certainty and knowable facts of reality (Clark 1998). One German scientist, Werner Heisenberg (1901-1976), introduced the concept of an ‘uncertainty principle’ to science, from an epistemological stance. In his discovery of quantum theory, he reported that it could not be stated with certainty or accuracy the exact position and momentum of a particle (Heisenberg 1927). This meant that the laws of physics became relative rather than absolute. Another physicist, Niels Bohr (1885-1962), suggested that this uncertainty arose from an ontological perspective: how a particle is, rather than how humans know what it is (Bohr 1948).

A concept put forward by Sir Karl Popper (1902-1994) suggests that many scientific mechanisms are not directly observed at all, but assumptions are made about how they work. This does not resonate with positivism. Popper philosophises that scientific laws are not laws which have been proven, but instead laws which have yet to be disproved (Popper 1959). Later work by Thomas Kuhn (1922-1996) questions the objectivity of scientific discovery. His work emphasises that science is based on a background of theory, which has arisen through a set of beliefs about scientific knowledge, or paradigm (Guba 1990), which is taken for granted. When unexplained events occur which call the paradigm into question, a paradigm shift takes place. Kuhn refutes the concept of science being objective, valid, accurate and therefore unchallengeable. Instead he perceives that human views, values and beliefs all contribute to scientific enquiry. However, Kuhn stands
by the importance of the concept of problem-solving being at the centre of scientific
enquiry (Kuhn 1970). The physicist and philosopher of science Paul Feyerabend (1924-
1994) takes this stance a step further by stating that scientific findings are no more than
beliefs. He emphasises the importance of scientists testing their ideas, and having them
tested by others through ‘counterinduction’. By this he does not mean proving existing
theories to be false but instead finding something else with which to compare them
(Feyerabend 1978).

How we arrive at a judgement is as important as the judgement itself. Popper (1959),
Kuhn (1970) and Feyerabend (1978) have questioned the principles of positivism. Some
researchers suggest that positivism is incompatible with nursing research as it denies the
importance of the subjective, psychosocial and interpretive elements of humans (Clark
1998). This doctoral study adheres to the principles of the RCT; to minimise bias, and
consequently provide findings that are as objective, valid, accurate and certain as
possible. Whilst maintaining this stance, the researcher is aware that humans are a factor
in the research, so findings cannot be absolutely objective or irrefutably certain. This
theoretical perspective is recognised as post-positivism. Post-positivism is grounded in
critical realism ontology and modified objectivity epistemology (Guba 1990). Findings can
be based on multiple sources of data. This resonates well with the proposed doctoral
study having a qualitative component. Post-positivism recognises that the rigour of
qualitative methods can be equal to that of quantitative methods (Cresswell 2009). Post-
positivist researchers acknowledge that answers to complex phenomena are unlikely to
be achieved through the use of only one research method (Thomas 2003), rather they
assert that a mix of methods will more likely procure the depth of answer required
(Silverman 2010).

Even with the acceptance of the human element, this doctoral study aims to be
transparent about the research and decision-making process, allowing readers of the
research to assess its credibility and generalisability. The research is transparent about
any assumptions made and provides justification for the methodology and methods
underpinning the study. The qualitative component of the study was also conducted in a
rigorous manner in order that findings may be viewed as trustworthy. The concept of
quantitative and qualitative paradigms being able to sit side-by-side in a post-positivist
perspective was central to the work of Jacob Bronowski who highlighted the shared aim of
scientists and artists to capture likeness in diversity (Bronowski 1956).

Post-positivism supports the use of different methods of inquiry in research. The
combination of multiple methods focusing on meaning and understanding, as a means of
studying a phenomenon, can establish “warranted assertibility” (Dewey 1941; p169) rather
than the absolute truth required by positivism (Crossan 2003). Dewey (1941) introduced
the term ‘warranted assertibility’ as a replacement for absolute knowledge or truth. The term implies that knowledge is gained as a result of an ongoing cyclical process of strategic inquiry and modification, rather than by internal mental deliberation. An assertion is a judgment identified after analysing the significance of the generated research data. If this assertion is a successful solution to the identified research question, it is warranted. Any warranted assertion requires refinement and justification through ongoing testing with regard to changes in time and experience.

An RCT is important to objectively investigate the efficacy of an intervention and this can be combined with a qualitative study to explore the views and experiences of the participants in the RCT. This culminates in a set of holistic data which can inform a complex healthcare issue and provide health professionals with the evidence base to provide the best all-round care.
CHAPTER THREE: PART THREE

3.9 Research design

Choosing the optimal research design is essential to ensure that the data generated from the study will answer the research question(s). Research design is defined as the overall structure for the study (Bowling 2009). The research design sets out the plan for the study parameters and processes; sample and setting, recruitment, consent, data collection and analysis. It is a blueprint for the conduct of a study which maximises the validity of the study findings (Burns and Grove 2005).

Quantitative methods are employed when a research question needs results that are objective and as certain as possible. This is particularly important in a clinical setting where the research question is therapeutically-focused and results will have an influence on patient care and treatment provision (Machin and Fayers 2010). At the same time, qualitative methods are also important in a clinical setting in view of the desire to provide evidence-based care that is patient-centred (Bowling 2009). Health professionals’, patients’ and users’ views and experiences are increasingly becoming more important to generate data from the user perspective to enable a research question to be addressed in a holistic manner.

For the OBSerV study, a pilot randomised controlled trial was proposed to assess the feasibility of testing the hypothesis that the regular application of topical sunflower oil, compared to no oil or topical olive oil, has an effect on the skin barrier function in newborn term babies. A quantitative approach was selected to investigate the primary research question as this involved the assessment of an intervention in babies with a ‘cause and effect’ focus. Alongside the RCT, it was also important to consider how the protocol and processes of the quantitative component were perceived by participants; a nested qualitative study explored parents’ experiences of having a baby participating in an RCT. These issues were best addressed by a qualitative approach. If research is to truly investigate a phenomenon in-depth then both approaches are necessary and complementary to each other (Cresswell 2009; Thomas 2003).

This part of the chapter focuses on summarising the methods chosen for the OBSerV study, and the rationale for choice of study design.

3.9.1 Medical Research Council (MRC) Complex Intervention Framework

The study was structured around the development and feasibility phases of the Complex Intervention Framework (Medical Research Council 2008; figure 3.2). In healthcare settings, interventions are often complex, comprising several interacting factors. The multi-factorial nature of the healthcare intervention presents practical and methodological
difficulties that need to be resolved. This framework was chosen for the OBSeRvE study as there may be a need to modify multiple avenues of behaviour: organisational, parents' and health professionals'. Behaviour is just one dimension of complexity defined by the Medical Research Council. The development and feasibility phases of the framework enabled the study to address all of the areas required to ensure that findings had the robustness necessary to inform further research that could enable a change in practice, if appropriate.

A pilot study can generate data for proof of concept, optimal primary outcome measure, recruitment strategy, consent processes, practicalities of assessment, protocol compliance and required sample size to provide results which are significant; statistically and clinically. A qualitative study can provide an understanding of the practical issues of participation and acceptability; how participants feel about taking part in an RCT and views of treatment allocation and information provision.

3.9.1.1 Development phase

The development phase incorporated a UK national survey of all maternity and neonatal units to assess what topical oils were recommended to new parents and used within maternity services (Cooke et al. 2011). This phase also incorporated the benefit of learning from the existing body of work undertaken in baby skincare (Lavender et al. 2013;
2012; 2011; 2009; Furber et al. 2012), and included a structured review of the existing evidence which was provided in chapter two.

3.9.1.2 Feasibility and piloting phase

The feasibility phase incorporated a pilot RCT to assess the feasibility of testing the hypothesis that the regular application of topical sunflower oil, when compared with no oil or topical olive oil, has an effect on the skin barrier function of newborn term babies. A study assessing the impact of the use of topical oil in baby skincare was timely, as baby skincare has been the subject of much debate in a number of international conferences (Excellence in Pediatrics 2014, 2013, 2011; International Confederation of Midwives Triennial Congress 2014, 2011). There is a dearth of research in this area. A pilot study was chosen to generate data to inform the design of future research. A qualitative component was also incorporated as part of the feasibility assessment. The qualitative study explored parents' experiences of having a newborn baby participating in an RCT, protocol compliance, treatment allocation and information provision.

3.9.2 Quantitative research

An overview of quantitative research and its various designs is presented here to provide some context to the decision to choose an RCT design to answer this research question.

Traditional quantitative research is focused on larger sample sizes, deduction, objectivity, theory/hypothesis testing, cause and effect questions, measurement and observation, explanation, prediction, confirmation, precision, generalisation, standardised data collection and numerical testing (Cresswell 2009; Johnson and Onwuegbuzie 2004).

A researcher makes a decision on the choice of research design based on assumptions of prior knowledge (Cresswell 2009). The strategies of inquiry used also contribute to the overall research approach (Cresswell 2009). These strategies include causal (experimental, quasi-experimental), correlational, and descriptive (Parahoo 2006; Burns and Grove 2005).

Experimental studies can be identified as a classic scientific experiment where participants are randomly allocated to an intervention or a control group (Gray 2009). The researcher has some control over the independent variable to investigate its effect on the dependent variable or the response being measured (Parahoo 2006). It can be difficult to conduct truly experimental research unless there is homogeneity across the baseline characteristics of the intervention group and control group. Where homogeneity cannot be assured a quasi-experimental design may be utilised, developed for studies of effects under less controlled conditions (Campbell and Stanley 1963). For this type of design,
existing population groups are used rather than selecting a random sample. The researcher aims to find groups of participants who have experience of the independent variable in their natural setting and then compares their behaviour with that of a similar group who have no experience of the phenomenon under investigation (Gray 2009; Burns and Grove 2007). It is difficult to control for confounding variables in this design and therefore the findings are less robust than a truly experimental design such as a randomised controlled trial (Parahoo 2006). Quasi-experimental research cannot prove cause and effect relationships but can establish strong associations between variables. This research design is generalisable as the research takes place in a natural setting (Parahoo 2006).

Correlational research investigates relationships between variables and develops hypotheses which can be tested in experimental research (Parahoo 2006). It is more difficult to draw firm conclusions as the data collected is usually retrospective. Surveys are often the design choice for correlational research. The investigation can be conducted at various levels: description of the relationship (descriptive correlational), prediction of a relationship between two variables (predictive correlational) and testing of a relationship proposed by a theory (model testing design) (Burns and Grove 2007). The sample in a correlational design needs to reflect the full diversity of the population in order to capture the existence of a relationship. This usually results in large sample sizes.

Descriptive research describes situations as they exist in the world (Burns and Grove 2007). This type of research provides accurate accounts of characteristics of individuals, groups or situations, determines new meanings, categories of information and frequencies of events. Like correlational research, descriptive research can develop new hypotheses for testing in experimental studies.

Quantitative research can be prospective or retrospective. Retrospective studies involve collecting data about phenomena that occurred in the past (Burns and Grove 2005). Any retrospective study could potentially be affected by selective reporting, human error, or bad record keeping. Recall bias is consequently an issue for retrospective studies. Prospective studies take place over the forward passage of time. Experimental research that tests an intervention will be a prospective study design, so that the effect of an intervention can be measured contemporaneously, and under a set of controlled conditions set out within the protocol (Bowling 2009). In prospective studies, the cause may have already occurred but the effect has not. Prospective studies are deemed to be more powerful than retrospective studies in examining causality, as the intervention is tested for statistical and clinical significance whilst controlling for extraneous variables (Burns and Grove 2005).
Decisions on healthcare are increasingly made on the best available evidence (Evans 2003). This has resulted in a generally accepted hierarchy of evidence for study design. The most popular hierarchy tends to reflect study designs which consider effectiveness of interventions; systematic reviews and meta-analyses at the peak, followed by RCTs, cohort studies, case-control studies, cross-sectional studies and case reports at the base (Guyatt et al. 1995; figure 3.3). Systematic reviews and meta-analyses sit at the top of the hierarchy of evidence due to their ability to ‘pool’ the results of RCTs to provide a more powerful result overall of how effective an intervention is. The gold standard of empirical research design is the RCT in this model (figure 3.3).

There are many types of study design not included in Guyatt’s hierarchy of evidence. Evans (2003) suggests a more holistic hierarchy to be used when determining best evidence (figure 3.4). Evans’ hierarchy considers appropriateness and feasibility in addition to effectiveness, incorporating qualitative research designs. The OBSeRvE study considers the effectiveness of an intervention. Both hierarchies of evidence therefore support the choice of an RCT to measure the effect of using topical oils on baby skin. The addition of the qualitative component to explore parents’ experiences of having a newborn baby in an RCT, which uses Framework analysis, also ranks highly in Evans’ hierarchy.
3.9.2.1 Experimental study design

Experimental study design is concerned with why things happen, and questions of cause and effect. Experimental designs have a hypothesis; the study collects data to support or refute the hypothesis. Experimental study designs are systematic and rigorous to ensure that the results obtained (effect) can only be attributed to the intervention (cause). This is established by using a control group and by controlling for confounding variables. The researcher can be confident that results are unaffected by confounding variables if the control and intervention group baseline characteristics are homogeneous. This can be confirmed in various ways.

‘Matched pairs’ are useful when the researcher knows which variables to control, but it is difficult to know all of the variables to control, and there may not be sufficient time to find matches for an adequate sample size. A ‘between-subject design’ allocates subjects to intervention or control groups and compares the groups. There may be more than two groups depending on the purpose of the experiment, for example, there may be multiple interventions. ‘Randomisation’ removes any selection or allocation bias. A ‘crossover or within-subject design’ will control for all variables, as the subject is in both the control and the intervention arm so the subject is paired with themselves. One limitation of the crossover design is there may be a carry-over effect of first treatment (Parahoo 2006). One simple experimental study design is the ‘pre-test post-test’ design where a problem is identified, the patient is tested, an intervention is implemented and the patient is retested. The results are attributed to the intervention (Torgerson and Torgerson 2008).}

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Appropriateness</th>
<th>Feasibility</th>
</tr>
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| Excellent     | • Systematic review  
• Multi-centre studies | • Systematic review  
• Multi-centre studies | • Systematic review  
• Multi-centre studies |
| Good          | • RCT  
• Observational studies | • RCT  
• Observational studies  
• Interpretive studies | • RCT  
• Observational studies  
• Interpretive studies |
| Fair          | • Uncontrolled trials with dramatic results  
• Before and after studies  
• Non-randomised controlled trials | • Descriptive studies  
• Focus groups | • Descriptive studies  
• Action research  
• Before and after studies  
• Focus groups |
| Poor          | • Descriptive studies  
• Case studies  
• Expert opinion  
• Studies of poor methodological quality | • Expert opinion  
• Case studies  
• Studies of poor methodological quality | • Expert opinion  
• Case studies  
• Studies of poor methodological quality |

Figure 3.4: The hierarchy of evidence (Evans 2003)
groups can be incorporated, including a no treatment and a placebo group. Multiple intervention groups can receive different variations of the intervention, such as a different frequency, intensity or duration (Burns and Grove 2005). This type of design is deemed to be the weakest as it is subject to various flaws including temporal changes and regression to the mean (Cooke and Campbell 1979). A more complex, multivariate design is a factorial design, where two or more variables are independently considered within the study to investigate multiple causality. The most common design is the 2x2 factorial design where two factors are involved. This design produces four investigation cells: one which addresses the control group (no treatment), one for each of the variables separately, and one where the interaction between the two independent variables is considered. This design is appropriate for controlling for confounding variables, where the confounding variable is examined as an independent variable so that interactions can be assessed (Burns and Grove 2005).

The gold standard of experimental design is the RCT (Guyatt et al. 1995; Pocock 1983) as randomisation is the best method of overcoming selection bias, temporal changes and regression to the mean (Torgerson and Torgerson 2008). Where bias is excluded, and the study is blinded and rigorously conducted, a clear outcome can be produced (Day and Altman 2000).

3.9.2.2 Randomised controlled trial (RCT)

The RCT has been used in medical research since 1945 (Burns and Grove 2005). The first RCT in medicine led by Sir Austin Bradford Hill tested whether streptomycin was effective in treating tuberculosis (Streptomycin in Tuberculosis Trials Committee 1948). Streptomycin was in short supply so Hill devised a system of randomisation as a method to avoid selection bias as doctors attempted to manipulate their patients into the streptomycin arm of the trial. Initially, the randomisation method was just a system of alternating the patients into the control or intervention arm. Randomisation was later developed by Hill to a more complex system of using a random numbers table to avoid selection or allocation bias resulting from the easy prediction of an alternating strategy.

The RCT uses a large sample to assess the effects of a particular treatment or intervention in comparison to a control group that has not received the treatment or intervention. Inclusion and exclusion criteria are strict and baseline characteristics are usually homogeneous due to the randomisation process. A protocol is followed to ensure that all participants have the same intervention or control experience, and confounding variables are controlled. The RCT may be multi-centred to allow results to be highly generalisable.
Interactions in the field of healthcare often involve complex phenomena. The RCT is the best method to investigate healthcare interventions because it is able to separate the ‘noise’ from the findings to establish whether or not an intervention is effective (Torgerson and Torgerson 2008).

3.9.2.3 Sampling

The sample size is important to avoid type I and type II errors. A type I error is the error of rejecting a true null hypothesis that there is no difference between the groups. A type II error is the failure to reject the null hypothesis when there are actually differences between the groups (Bowling 2009). The larger the sample size, then generally the less chance of a sampling error. It is important to perform a power calculation to ensure that the study recruits the correct sample size when conducting a definitive trial. For a pilot trial, a power calculation is not necessary as findings are descriptive, not inferential. A sample size of 30 per group is deemed to be appropriate for a pilot trial (Lancaster et al. 2004).

Sampling is defined as the process by which participants are selected for research to be as representative of the total population being studied as possible (Burns and Grove 2005). The total population is every subject that fits the inclusion criteria for a study. A sample is a subset of that population (Kerlinger 1986). Descriptive studies are likely to use convenience sampling; correlation and quasi-experimental may use convenience or random sampling, but robust experimental studies will use random sampling under controlled conditions.

It is important to make the distinction between random sampling and random allocation. Random sampling is a sampling method which allows estimation of a parameter within a stated population (Torgerson and Torgerson 2008). It means that inferences about the characteristics of the sample can be generalised to the total population, that is, a random sample has high external validity. Random allocation is associated with internal validity. When random allocation is used then selection bias is eliminated (Cooke and Campbell 1979) and the results are valid for the intervention (Torgerson and Torgerson 2008). Random allocation means that allocation of participants at random will result in groups that have, on average, the same baseline characteristics, known and unknown, which could affect the outcomes. Random allocation can therefore cancel out the effect of confounding variables.

3.9.2.4 Randomisation

There are several approaches to randomisation. Randomisation can be achieved through various practical methods such as the toss of a coin, the use of odd and even numbers in a street, or by date of birth. In an empirical study, where it is important to minimise all
forms of bias, more complex methods are preferred in order to conceal allocation from participants and the research team. The more rigorous the method of randomisation, the more robust the results are.

Simple randomisation uses a random number table or a computer-generated random number list. A secure system is necessary to ensure that the researcher responsible for allocation cannot tamper with the system and undermine the process. There is always a risk of some imbalance between the groups, such as when the sample size is small or when there is an important key variable which has a higher prevalence in one area than another for example. These differences can usually be corrected by regression analysis, but can also be reduced by other randomisation techniques such as block randomisation and stratification (Torgerson and Torgerson 2008).

Block randomisation can reduce the probability of chance imbalances. In the OBSeRvE study randomisation was stratified according to family history of atopic eczema. The randomisation was in blocks within eczema history strata (yes, no). The block size varied at random between six and fifteen (i.e. 6, 9, 12 or 15) to guard against predictability and to ensure allocation concealment (Machin and Fayers 2010). If block sizes are stagnant, a researcher can predict allocation. For example in a constant block size of four, the fourth allocation can be predicted. This can lead to bias as the researcher can withhold the allocation for a participant where the researcher would prefer that participant to be in a different group. By determining the allocation of a participant to a specific group, the intervention or control group can be biased in favour of or against the intervention, and the results will be flawed.

Matched randomisation uses a process whereby participants are placed in pairs (two-arm trial) or triplets (three-arm trial) based on one or two important variables. One of each pair/triplet is then placed in each study group (intervention(s) or control). This particular randomisation process means that stratification of the matched variables is in place so that groups will be homogeneous for those variables. This process is not as commonly used as simple or block randomisation as it is difficult to precisely match the participants. Where a match cannot be found the participant pairing is lost and this reduces the sample size and consequently the statistical power for results to be robust.

Pairwise randomisation is a process by which patients are recruited in pairs for convenience; one is randomised to the control group and one to the intervention group. The participants are not matched in any way; the type of recruitment in pairs is purely for practical reasons when resources dictate this. This approach does not allow stratification of individual variables but can allow stratification by centre, which would prevent temporal bias (Torgerson and Torgerson 2008).
3.9.2.5 Blinding

Blinding is a process where ‘expectation’ of an effect of an intervention is removed from the assessor (researcher) and/or the participant (Lewith and Little 2013). This means that neither the assessor nor the participant can influence the findings of the study (Machin and Fayers 2010). An RCT that is double-blinded is the optimal form of experimental study (Allsop 2013). Bias can be introduced in a trial with no blinding (Schulz 1995), and this can result in false estimates of the effect of an intervention (Lewith and Little 2013).

A single-blind trial is where the researcher delivering the intervention is aware of which group the participant is in, but the participant is unaware. Alternatively the trial can be assessor-blinded where the participant is aware of their allocated study group but the researcher is not. A double-blind trial requires a placebo. Despite the optimal research design being double-blind, the requirement for a placebo often makes double-blinding impossible. The placebo needs to be an identical colour, shape, texture, smell and taste. If such a ‘copy’ does not exist then a double-blind trial cannot occur (Machin and Fayers 2010). In the OBSeRvE study, a placebo oil was not available, as there is no topical oil that is known to be safe to apply or that would not have some effect on skin barrier function (Darmstadt et al. 2005). The study was assessor-blinded, and participants in the intervention groups were blinded to which oil they were using; oils were labelled X and Y. Participants in the control group knew that they were in the control group, but participants in the intervention group did not know to which intervention they had been allocated. This was the nearest arrangement to double-blinding that could be designed.

3.9.2.6 Validity

There are several dimensions of validity within a study. The outcome measure should have face validity, content validity, construct validity and criterion validity (Lewith and Little 2013). Face validity is held where a relevant outcome measure provides data which can answer the research question. Content validity addresses the range of issues considered important by the population being studied and by experts in the field. Construct validity shows that the outcome measure behaves in the appropriate way relevant to the factor under investigation based on previous studies. Criterion validity means that the outcome measure is consistent with an acknowledged validated measure (Lewith and Little 2013; Bowling 2009).

If the research findings can credibly infer that the results were as a result of the intervention then the study has internal validity (Bowling 2009). Internal validity reflects to what extent the study findings are close to reality rather than a result of confounding variables. Internal validity is most relevant in a study addressing causality (Burns and Grove 2005). If it is possible to generalise the study findings to the wider population then the study has external validity (Bowling 2009). External validity is more likely if a trial
samples from multiple diverse settings (Burns and Grove 2005). If an intervention works in one setting, then other settings may want to adopt the intervention. External validity is consequently an important issue for researchers to address. The study should be designed so that it can be replicated in other settings. This can be addressed in a pilot study. If the pilot finds that a definitive trial is feasible, the definitive trial can be conducted in multiple settings (Polit et al. 2001).

3.9.2.7 Pilot intervention studies

There is no agreed definition of a pilot trial (Lancaster et al. 2004). A pilot study may be conducted to assess the feasibility of conducting a definitive trial, test and refine a trial process or new technique, identify any ethical issues, collect data which can inform a power calculation, explore the optimal methods to collect the outcome data, and assess recruitment strategies and attrition rates (Lewith and Little 2013; Torgerson and Torgerson 2008).

There is some argument over whether a pilot trial should be randomised or not. If non-randomised, the recruitment rate can be overestimated and the sample size can be incorrectly calculated. Advantages of using randomisation include that a pilot RCT can be incorporated into a meta-analysis of RCTs and contribute to the overall evidence base, or the pilot data can be added to the data resulting from the definitive RCT.

A pilot study can assist in the design of a definitive trial. The sample size of a pilot study is generally too small to detect statistically significant results and even if the results are significant they should be interpreted cautiously as no power calculation has been performed. The benefits of knowledge gained from a pilot study prior to conducting a full trial mean that the cost of a full trial is not expended unless the trial is found to be feasible. Furthermore, the finished design of the full trial will be of the highest standard as all trial processes and parameters will have been fully tested and refined.

3.9.3 Qualitative research

An overview of qualitative research is presented to provide some context to the decision to choose a questionnaire- and interview-based design with Framework analysis (Ritchie and Spencer 1994) to answer the research question.

Qualitative research is based on smaller sample sizes, induction, discovery, exploration, meaning, developing theory, subjectivity, interpretation, words and themes, and reflexivity (Cresswell 2009; Johnson and Onwuegbuzie 2004).

Qualitative research provides a means of exploring the emotions, perceptions, views and experiences of a person experiencing a phenomenon. It is person-centred and can provide a level of understanding of a behaviour or medical condition that is not readily
accessible to someone who has not experienced it (Holloway 2005). This is extremely important in a healthcare setting where patient-centred care is a priority (Ring et al. 2011; Feeley et al. 2008).

A qualitative study fits within a post-positivism paradigm as post-positivism recognises that findings can be based on multiple data sources and that qualitative methods can be as rigorous as quantitative methods (Cresswell 2009). Post-positivism also acknowledges that answers to complex phenomena are unlikely to be answered by quantitative research alone (Thomas 2003). The Framework approach for analysis (Ritchie and Spencer 1994) also fits with post-positivism by having a methodical organised approach to data management and analysis which is transparent throughout; still looking for some truth or objectivity whilst acknowledging individuals.

The choice of methodology depends upon the ontological and epistemological stance and the phenomenon under investigation; examples include grounded theory, ethnography, or phenomenology. The chosen approach determines the method of data collection. Methods used, such as observation, interviews or focus groups, will generate textual data rather than statistical data. Data relies heavily on a deep level of interaction between the participant and the researcher. The researcher is flexible and the data generated is participant-led. The researcher continually reflects on their influence on the data collection process in an important concept of qualitative research known as reflexivity (Avis 2005).

The OBSeRvE study considers a complex intervention which may require a change of behaviour (Medical Research Council 2008). A qualitative study is essential to fully inform the feasibility phase of the framework, to assess whether the intervention, the protocol and the trial processes are acceptable to parents.

Sampling within qualitative studies is usually purposive. A purposive sampling strategy ensures that the views and experiences of those with experience of the phenomenon are represented. For the OBSeRvE study, criterion purposive sampling ensured that particular criteria were fulfilled (Patton 2002); this created a diverse subset of the RCT participants who had varying positive and negative experiences of the research process and were selected from across the three treatment groups. This provided the depth of experience-rich data required.

Qualitative research is often regarded as non-generalisable due to its small sample sizes and subjective nature. The concept of validity in qualitative research is framed around a number of criteria to assess whether the findings are an authentic representation of the phenomenon. The main criteria fulfil the question of trustworthiness of the study: credibility, transferability, dependability and confirmability (Lincoln and Guba 1985). Rigour is an important requirement to demonstrate the reliability and validity of a study.
There is some debate concerning how rigour fits with the qualitative paradigm. One such argument supports rigour as an empirical analytical term that does not fit an interpretive pathway (van Manen 1990). Reviewers are often critical of qualitative papers that cannot prove rigour.

To ensure rigour, there is a suggestion that researchers use a transparent systematic process (Barbour 2001). Dissemination of findings should include details regarding decision/audit trails, member-checking, and methods of bias minimisation. Although these strategies may help readers to assess rigour, they do not ensure rigour (Morse et al. 2002). Strategies to ensure rigour should be incorporated into the entire research process, including the protocol, data collection and data analysis phases. The iterative qualitative process means that the researcher moves from the protocol to the data and back again which will confirm adherence to the research design on a regular basis. Reliability is achieved through proving consistency in making the application of research processes visibly transparent, and reporting limitations and reflexivity (Davies and Dodd 2002). There should also be transparency of how the interpretation has arisen; whether meaning is inherent within the data or has been imposed on the data by the researcher (Savage 2000).

In the same way as quantitative studies, qualitative studies can be replicated in different settings and pooled data can be reinterpreted in systematic reviews of qualitative research or metasynthesis. It is becoming increasingly important to combine quantitative studies with a qualitative component to ensure that a holistic approach is taken to the investigation of a phenomenon, particularly in healthcare settings where the patient is at the centre of care.

3.9.3.1 Questionnaires

Questionnaire data can provide an invaluable context for qualitative research (Silverman 1998). Data generated can include the demographic background of the participants being interviewed. It can also provide the basis for purposive sampling of a specific subset of participants, or data which requires further exploration (Low 2013). Questionnaires can be structured or semi-structured. Structured questionnaires will include standardised questions which are presented in the same way to every participant with pre-coded response choices (Bowling 2009). Semi-structured questionnaires will include some open-text responses which enable participants to raise any issues not addressed by the structured questions. Most questionnaires use a mixture of both closed- and open-text questions (Bowling 2009). The OBSeRvE study questionnaire included mainly structured questions, but also incorporated two open-text questions. The qualitative data generated by these two questions informed the purposive sampling and was included in the qualitative analysis.
The advantage of a structured questionnaire is the ability to ‘count’ answers, providing a large volume of quantitative data. The weakness is that participants are forced to answer with one of the pre-coded response choices, which may not be appropriate. Questionnaires should be piloted in advance to ensure that there are no ambiguous answers, or where possible use a previously validated questionnaire. Participants may interpret a question differently to a researcher (Mallinson 1998). Questionnaires are best for collecting factual data, where all participants are going to read and understand the question in the same way with no ambiguity. There is always a possibility of recall bias (where responses rely on memory) and social desirability bias (where the participant answers what they believe the researcher wishes to hear) (Bowling 2009).

3.9.3.2 Interviews

Interviews are the most common tool used for data collection in qualitative research (Silverman 2011; 2010; Riessman 2008; Taylor 2005) and particularly in healthcare settings (Miczo 2003; Silverman 1998). An interview can be described as structured, semi-structured, in-depth or unstructured. There is an argument that no interview can be completely unstructured as there will probably be at least one open question to start the conversation (Mason 2002). For structured interviews the conversation is likely to be too rigid and inflexible to collect rich in-depth data. Structured interviews are routinely used in surveys and therefore are usually a quantitative data collection tool. The majority of interviews used in qualitative research use a semi-structured approach (Leicester and Lovell 1997). Questions should be open, neutral, sensitive and clear (Patton 2002). A topic guide can ‘prompt’ the researcher to ensure that the subjects which need to be addressed are covered (Burgess 1982).

It is important to establish a rapport between the interviewer and the participant so that the participant feels comfortable in divulging their experience to the researcher (Yeo et al. 2014). The way in which a participant responds to the researcher can be affected by the researcher’s background. In a healthcare setting, this can be an issue where the researcher may be wearing a uniform and is conducting the interview in their place of work. Researchers must be aware of their influence on the research (McCracken 1988). The participant may feel as though the researcher is in a position of power and may feel uncomfortable about discussing their experience in-depth (Richards and Emslie 2000). It is important to allow the participant the choice of where and when the interview takes place (Yeo et al. 2014; Johnson 2002). The OBSeRvE study offered the participants the choice of their home, a local café, the hospital or a telephone interview, at a time of their choosing. The disadvantage of the telephone interview is the loss of non-verbal communication such as body language and reasons for pauses (Taylor 2005), which are important cues for further probing (Yeo et al. 2014).
The aim of the qualitative interview is to explore the phenomenon under investigation by active listening and delving more deeply into the personal experience of someone who has lived the experience of the phenomenon. The researcher aims to capture the experience in the participant’s own words, thoughts, perceptions and feelings (Taylor 2005). Van Manen (1990; p66) suggests that the interview "may be used as a vehicle to develop a conversational relation with a partner (interviewee) about the meaning of an experience". Burgess (1984; p102) defines interviews as "conversations with a purpose". Robson (2011) suggests that interviews should be flexible and adaptable. The two-way process of a qualitative interview allows the researcher and the participant to have a dialogue that can explore the phenomenon in-depth. The participant is able to describe their experience in detail and to give their own perspective and interpretation of events, and the researcher can probe into their accounts (Taylor 2005; Corbin and Morse 2003). Field notes are made by the researcher during the interview and immediately afterwards. These include details of emotions portrayed by the interviewee whilst conversing, their tone of voice and body language, the setting and also the researcher’s feelings and thoughts which can aid the decision trail and reflexivity during the analysis process.

Interview was chosen as the method of data collection in order to obtain sensitive data and allow deeper exploration that could not be obtained from open-text answers on a questionnaire (Walsh and Baker 2004). Focus groups were considered as an alternative, but due to the small sample size it would have been difficult to maintain anonymity. Furthermore, focus groups can carry the research in unexpected directions. This can be an advantage, but negative effects can often dominate and the richness of the data depends on the group dynamics (Carey 2004). As this was a feasibility study it was important to obtain positive and negative views of what worked and what did not work, to inform the optimal study design for future research. This may not have been obtained in a focus group but could be explored more efficiently in an interview.

3.9.4 Methodology used in term baby skincare research

The majority of research studies investigating term baby skincare have been RCTs (Horimukai et al. 2014; Simpson et al. 2014; Lavender et al. 2013; 2011; Garcia-Bartels et al. 2012; 2010; 2009; Visscher et al. 2009; Galzote et al. 2007; Solanki et al. 2005) or non-randomised experimental studies (Lowe et al. 2012; Simpson et al. 2010; Takahashi et al. 2009). There has been one qualitative study (Lavender et al. 2009). One study, with two papers, used a mixed-method approach (Furber et al. 2012; Lavender et al. 2012). It is not surprising that many of the studies have been experimental, as the studies are often assessing the impact (cause) of skincare products on baby skin (effect).
3.10 Choice of methodology and methods for this study

The philosophical perspective of post-positivism is suitable for the choice of study methodology and methods. Both quantitative and qualitative research paradigms are adopted to ensure that objectivity will be encompassed together with the human perspective. This generates a holistic body of data that will inform the evidence base for baby skincare and the parameters and processes for future research design. Quantitative and qualitative researchers have been perceived as ‘paradigm warriors’ (Tashakkori and Teddlie 1998), unable to combine the two paradigms, perceived to be the polar opposite of each other. However, there is an increasing move towards drawing on both approaches to provide a more holistic approach to answering a research question, particularly in healthcare RCTs (Snowdon et al. 2004).

Recommending topical oils for prevention or treatment of baby dry skin is a traditional clinical practice. An RCT is the only type of study design that is sufficiently robust for results to have the power to change a clinical practice that is so ingrained, and sufficiently credible to inform clinical guidelines. The qualitative component will provide further data to ensure that any future research design is acceptable to new parents. The factors that affect recruitment or protocol compliance may not be obvious to the researcher, but a qualitative study can generate informative data to ensure that a future study is acceptable to participants (Snowdon et al. 2004). The use of quantitative and qualitative methods are complementary in this study and provide a wider comprehension of the effect of using topical oils on term baby skin barrier function together with the experience parents face of having a newborn baby participating in a research trial.

An RCT, generally considered to be the gold standard of research design (Guyatt et al. 1995; Pocock 1983), has been chosen to test the hypothesis over other designs due to the requirement for objective results that are generalisable to a wider population (external validity), and a randomisation process that minimises bias and controls for known and unknown variables (internal validity) (Torgerson and Torgerson 2008). Other non-randomised experimental and observational designs were discounted as bias and confounding are more difficult to control (Grimes and Schulz 2002) and due to the requirement that findings needed to be sufficiently credible to change clinical practice if necessary.

3.11 Conclusion

This chapter has discussed the philosophical perspective of post-positivism which underpins the OBSeRvE study and the methodological choice of conducting a pilot RCT with a nested qualitative component. The pilot, three-arm, assessor-blinded, RCT was chosen as the optimal design to assess a cause and effect relationship between the use of two defined topical oils on newborn term baby skin barrier function. The qualitative
component was included to ensure that the experience of parents having a newborn baby participating in an RCT could be taken into account in relation to acceptability, practicality and convenience, protocol compliance and information provision. The study was designed as a pilot study to ensure that the research design for a future study was the correct one, and that optimal parameters and processes were incorporated. The next chapter discusses the methods in more detail.
CHAPTER FOUR: RESEARCH METHODS

4.1 Introduction to the chapter

Building on the previous chapter, which provided a discussion of the underpinning philosophical perspective and methodological choices for the OBSeRvE study, part one of this chapter presents the quantitative study methods. The quantitative component comprises a pilot randomised controlled trial (RCT) to assess the feasibility of assessing the impact of topical oils on term baby skin barrier function, and weekly questionnaires to assess skincare and product use. Part two presents the qualitative study methods: open-text questionnaire responses and semi-structured interviews with parents, to explore the acceptability of having a baby in an RCT and the trial processes involved.

PART ONE: QUANTITATIVE STUDY

4.2 The OBSeRvE: Oil in Baby SkincaRE quantitative study

4.2.1 Hypothesis

The regular application of topical sunflower oil, when compared to no oil or topical olive oil, has an effect on the skin barrier function of newborn term babies.

4.2.2 Design

A pilot, single-centre, assessor-blinded, three-arm, RCT to assess the feasibility of testing the hypothesis was conducted. Babies were randomised to a control group (no treatment) or one of two intervention groups (olive oil or sunflower oil).

4.2.3 Setting

The sample was drawn from St. Mary’s Hospital, a large regional teaching hospital in the North West of England. This setting was chosen due to its ethnic diversity and high number of term births, in addition to its research culture which could be expected to support the RCT. St. Mary’s Hospital is part of Central Manchester University Hospitals NHS Foundation Trust (CMFT). The hospital is purpose-built for maternity care and was newly opened in June 2009. The maternity service provides care to woman and families in North, Central and South Manchester, and surrounding areas. Furthermore, the hospital is a tertiary referral centre and accepts referrals from both local and other hospitals within the North West Region. Provision of maternity care follows a traditional pattern; however Domino options, home birth, and midwife-led care are available. To meet the needs of the local population, the service provides a unique range of services for women and families, including specialist midwife support for teenagers, asylum seekers and women with haemoglobinopathies. The hospital has a well-developed research and audit ethos and participates in local, national and international studies.
In 2013/14, approximately 8,000 births occurred, of which over 7,000 were full-term (≥37 weeks of pregnancy gestation) (Central Manchester NHS Foundation Trust 2014). During this period, the Caesarean birth rate was 22.3% (Health & Social Care Information Centre 2014).

The population of Manchester is diverse. In 2006, it was estimated that non-white ethnic minority groups made up around 23.2% of the population in the Manchester area (Manchester City Council 2008). This increased to 33.4% in 2013/14 (Manchester City Council 2014). There was also an increase in the population of those whose first language was not English; more than double the national average of Manchester households have no English speaker at home (10.3%; Manchester City Council 2013).

Between 2010/2011, 35,000 people moved into Manchester, the majority as a result of international migration (asylum seekers, refugees, and migrant workers from Eastern Europe) (Manchester City Council 2013). The Manchester area also has a high student population (Manchester City Council 2013).

Manchester is the fourth most deprived local authority in England, second most deprived in terms of income and third in terms of employment. Around 46% of Lower Tier Super Output Areas across Manchester were in the most deprived 10% in England (Manchester City Council 2013).

Participants were not excluded if English was not their first language; an interpreting service was available. At the beginning of May 2014, a phone contract was purchased so that it would be possible to use a telephone translation service at the bedside. This allowed a six-week period to establish if including non-English speakers in the study inclusion criteria was feasible. This is covered in more detail in chapter 7 (section 7.5). Previous research did not find any differences for skin of varying ethnicities (Lavender et al. 2013; 2012; 2011), however results from this study (chapter six) were explored to determine if there was a need to address this in a future study.

4.2.4 Sampling

4.2.4.1 Eligibility criteria

The eligibility criteria were determined according to criteria used in previous work (Lavender et al. 2013; 2012; 2011), and with safety as a priority. During the first phase of the study, eligibility screening was conducted by the clinical team. It became apparent that this was an onerous task for the team (discussed in more detail in chapter seven). As this screening process was affecting recruitment, a substantial amendment was submitted to
the local Research Ethics Committee and quickly approved. This allowed the researcher to screen patients to determine whether they met the eligibility criteria.

4.2.4.1.i Inclusion criteria for screening phase:

Women carrying singleton pregnancies who were booked to give birth at St. Mary’s Hospital, Manchester were eligible.

4.2.4.1.ii Exclusion criteria for screening phase:

Women were excluded during the screening phase if known to be carrying a baby with a chromosomal abnormality or other syndromic diagnosis; women known to be having their baby placed in foster care or adopted; women with multiple pregnancies; maternal age of less than 16 years.

4.2.4.1.iii Inclusion criteria for trial:

- newborn term babies (born on/after 37\(^{10}\) weeks gestation) less than 72 hours old
- in good health (determined by investigator)

4.2.4.1.iv Exclusion criteria for trial:

Women
- maternal age of less than 16 years
- unable to communicate consent for their baby to take part in the trial

Babies
- admission to neonatal unit
- phototherapy
- limb defects
- non-traumatic impairment of epidermal integrity defined as abnormal epidermis or dermis, such as collodion baby or congenital ichthyosis
- any medical history that may prevent the participation in the study until study conclusion
- currently participating in another clinical trial
- evidence of active skin disease or disorder at first visit – for the purposes of this study the following normal variations were not considered as skin disorders: erythema neonatorum / erythema toxicum; milia
4.2.4.2 Sample selection

It was planned to consecutively recruit participants. Consecutive sampling intends to recruit all eligible subjects who meet the eligibility criteria over a specified time period, or for a specified sample size, so that it is a more representative sample of the whole population (Polit and Beck 2014). Unselected consecutive sampling was necessary, as opposed to random sampling, as no sampling frame existed. Mothers of newborn term babies were approached by the researcher within 72 hours of birth to discuss the study and, after a reasonable time, provide informed consent. Babies were randomised using a computer-generated varying block randomisation to use an intervention (olive oil or sunflower oil) or no treatment (no oil) for 4 weeks on three body sites (left forearm, abdomen and left thigh).

4.2.4.3 Sample size

The original target sample size was 100 babies, randomising at least 33 per group, allowing for 10% drop-out to collect outcome data on 30 per group. The design of the study was a pilot RCT and a formal sample size power calculation was not therefore required. The sample size of 30 per group was suggested as a suitable number of participants for a pilot RCT (Lancaster et al. 2004) in order to estimate trial parameters, assess recruitment and attrition rates, estimate differences between groups and confidence intervals. On the basis of a conservative recruitment rate of five per week (one per working day), a recruitment period of twenty weeks was calculated. However this assumed that the researcher could recruit on every working day. Unfortunately the hospital was only able to allow the researcher access to the clinical room on alternate working days (Mondays, Wednesdays and Fridays). This reduced the anticipated recruitment rate to three per week; a recruitment period of 33 weeks.

The decision was taken to increase the sample size to 120 to provide the best opportunity to obtain the required number of participants in each study group for analysis, when loss to follow-up was higher than anticipated. Previous research also found a high loss to follow-up due to participants having to return to the hospital for the assessment (Lavender et al. 2011). In the final phase of the study (May 2014 to July 2014), a home visit was offered for follow-up measurements with the exception of Attenuated Total Reflectance Fourier Transform Infra-Red spectroscopy (ATR-FTIR) for which the equipment was not portable. A home visit was not offered throughout the whole study as it was important to collect sufficient ATR-FTIR data in order to determine the optimal primary outcome for a future study. The aim was to continue recruitment until ATR-FTIR data were collected for 90 participants.
Measures were employed to minimise attrition including: remaining persistent in measures to contact women; calls and texts were made at various times of the day on different days; 24-hour telephone support was provided by the researcher for women; home visits were offered to those women who asked to withdraw in the final phase of the study. The recruitment flow chart can be viewed in chapter six (figure 6.2).

4.2.5 Recruitment and consent

All potentially eligible women were provided with summary information about the study during the antenatal period (appendix 12) between 20 and 28 weeks of pregnancy when the hospital gave out a set ‘bundle’ of antenatal leaflets. This provided women with time to consider participation in the trial, which was important from an ethical perspective (ICH 1996). Willing participants were asked to give consent to be approached about the trial following the birth of their baby by returning a tear-off reply slip in the antenatal leaflet to their midwife. A box was made available for the return of the slips in the Community Midwives office of St. Mary’s Hospital Antenatal Clinic. The researcher visited the box at regular intervals during the recruitment period. The researcher examined the in-patient lists for the potential participants who had made contact antenatally as they approached their estimated delivery dates.

Initially, other eligible women were identified postnatally by the clinical team and verbal consent obtained by the clinical team for the researcher to approach them about the study. After approval of a substantial amendment, the researcher was able to identify eligible women. Discussions were held with the women about the study after permission to approach the women was obtained by the clinical team.

All consenting eligible women were approached within 72 hours of birth by the researcher, at the bedside on the postnatal wards, and given a copy of the detailed Participant Information Sheet (appendix 13). They were given the opportunity to ask questions. The researcher then left the woman to consider the information and discuss participation with her partner, family and clinical staff as required. The researcher returned to the postnatal ward after at least one hour had passed. Those who wished to participate were asked to confirm their eligibility according to the eligibility criteria in the case report form (appendix 14), after which the researcher requested written consent for their baby to participate (appendix 15). All women who consented to take part in the study were asked to complete a short baseline questionnaire (appendix 16) requesting demographic details and family history of atopic eczema. The researcher recorded relevant background medical information about the birth for the mother (appendix 17) and baby (appendix 18). The baseline measurements were taken after which the babies were randomised to their study group by an independent research midwife. Following randomisation, women were given the appropriate demonstration of treatment application, advice, and materials by the
independent research midwife. The midwife recorded which bottles of oil had been allocated to which participant by number, and this record was kept by the randomisation midwife for the duration of the study. At the end of the study the record was sealed and only opened by the researcher after data analysis.

4.2.6 Randomisation

Babies were randomised to an intervention or control group, using a telephone-based service offered by The Christie Hospital NHS Foundation Trust Clinical Trials Unit, within 72 hours of birth. This process was conducted by an independent research midwife to maintain assessor-blinding. Randomisation was documented on a case report form (appendix 19) and stored in a file maintained by the independent research midwife. The randomisation sequence was computer-generated. The allocation of babies was therefore concealed. Randomisation was stratified according to family history of atopic eczema. Family history of atopic eczema was defined as ‘at least one of father, mother, or sibling who has had a medical diagnosis of atopic eczema and who has had topical steroid treatment’. The randomisation was in blocks within eczema history strata (yes, no). The block size varied at random between six and fifteen (i.e. 6, 9, 12 or 15) to guard against predictability and to ensure allocation concealment (Machin and Fayers 2010).

The researcher was blinded to which group babies were allocated, and participants in the intervention groups were blinded to which oil they had been allocated, only aware of being allocated oil X or oil Y. All of the research team and all of the participants were unaware of which oil was olive oil and which oil was sunflower oil. The decanting of oil into individually labelled bottles was arranged by an independent researcher at The University of Manchester who decided which oil would be ‘X’ and which would be ‘Y’. The allocation was recorded on a signed document in duplicate; each copy was then sealed in an individual opaque envelope and the two envelopes were held by two independent members of staff at The University of Manchester until the Trial Steering Committee met on 4th November 2014. The envelopes were not opened until the blinded data analysis had been presented to the Trial Steering Committee. In this study it was not possible to blind the participants as it was obvious if they were using a treatment or not and it was not possible to identify a placebo oil. However, all participants were reminded at every opportunity not to tell the researcher if they were using a treatment or not. There was no oil that could have been used as a placebo as all oils have some effect on skin barrier function. Furthermore, it was important to establish what happens to the skin normally (without the use of products) over the treatment period (first 4 weeks after birth).

Every possible step was taken to reduce bias. Groups X, Y and C (no treatment) were randomly assigned to numbers 1, 2 and 3 for the purposes of the blind analysis, by an independent research midwife at Central Manchester NHS Foundation Trust. This
allocation of group number was double-checked by a second independent person (Research Fellow at The University of Manchester) prior to conducting the analysis. All data entry in IBM SPSS Statistics version 20 was then checked for accuracy against email confirmation of allocation sent from The Christie Hospital NHS Foundation Trust Clinical Trials Unit following unblinding after data analysis.

The approach used for the pilot study was the same as that which would be intended for a definitive trial. This therefore provided a valuable assessment of feasibility and could identify any potential issues with the process.

4.2.7 Assessor-blinding

All initial and follow-up clinical assessments were performed by the researcher, with assistance from a Senior Research Technician from the University of Sheffield. Both remained blinded to the allocation to reduce treatment and measurement bias.

Before meeting the researcher at the follow-up clinical assessment, women were asked to place any remaining oil in a box in the reception area of the Maternal and Fetal Health Research Centre Clinical Suite of St. Mary’s Hospital, by the Centre receptionist. The layout of the Research Centre meant that the reception area could not be seen from the clinical assessment room. The Research Centre receptionist would then let the researcher know that the participant had arrived. During the previous telephone call confirming the appointment the participants were reminded not to use oil on the day of the assessment. This was to avoid any residue interfering with results and also being seen by the researcher during the clinical assessment. The researcher used the same wording to all participants on the phone, who were pre-warned at the beginning of the conversation not to comment if these statements were not applicable to them. They were also asked not to discuss what group they were allocated to during the assessment. At the beginning of every weekly telephone call women were asked not to mention which group they were in during the conversation. Where the treatment was mentioned by the participant, this was documented on the weekly questionnaire. Oils were labelled X and Y to avoid participants knowing which oil group they were in. If it was disclosed that they were in a treatment group, they were immediately reminded not to say which one it was. None of the women mentioned the use of Oil X or Oil Y. If it was disclosed they just used the word “oil”.

4.2.8 Procedures

All babies in the study followed conventional care up until the point of enrolment in the study. This care included the possibility of first bath, and use of baby skincare products. Although no particular products are recommended to parents on postnatal wards (apart from olive oil for dry skin), suppliers do provide the hospital with free sample products and these are evident in the bath store areas of the postnatal wards. It is possible that the
sight of these products in the ward area may influence parental choice of whether to use a product during the first bath or not. For this study, the case report form (appendix 18) documented whether the baby had received a first bath prior to enrolment in the study and whether any products were used. These details were considered during the analysis.

4.2.8.1 Intervention

Babies were randomised to one of three groups: olive oil, sunflower oil or no oil (control). Olive oil (high oleic acid and low linoleic acid) and sunflower oil (low oleic acid and high linoleic acid) of specific defined formulation was obtained from William Hodgson and Co., in Congleton, UK. The components of the two oils are illustrated in table 4.1.

In the two intervention groups, parents were asked to apply oil on the designated areas of the baby, as instructed, from the day after the initial assessment (day 2/3 after birth) up until approximately ten hours (the night before follow-up assessment) prior to the time of follow-up assessment (4 weeks). This timing was set to avoid any interference with the results caused by oil residues and to maintain assessor-blinding. The treatment period was chosen as, after 4 weeks, it was more likely that parents would want to use a range of products on their baby’s skin (Lavender et al. 2009). It was also considered inappropriate to conduct a further follow-up assessment at six to eight weeks or longer, as more frequent applications of oil to the baby’s skin may cause an adverse effect beyond what was required to provide proof of concept. ATR-FTIR could determine any change in the skin profile at 4 weeks before it became visible clinically.

<table>
<thead>
<tr>
<th>Component</th>
<th>Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil</td>
<td>11.5%</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>6.0%</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>C16:0</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>C18:1</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>C18:2</td>
</tr>
<tr>
<td>Linolenic acid</td>
<td>C18:3</td>
</tr>
</tbody>
</table>

Table 4.1: Specification of natural oils used in the OBSeRvE study

4.2.8.2 Control group

Those in the control group did not apply any oil to their baby's skin for 4 weeks. Participant-blinding was not achievable in this group as it was impossible to identify a control oil that was safe to apply and would have no effect on skin barrier function (Darmstadt et al. 2005). Parents were also asked not to apply any other baby skincare products on the three study sites of the baby (left forearm, abdomen and left thigh) and to bathe the baby in water only.

4.2.8.3 Intervention groups

Women in the intervention groups were asked to apply four drops of the oil provided twice daily on each of three sites; baby’s left forearm, abdomen (above umbilicus and below
nipple line) and left thigh (figure 4.1). These body sites were chosen to avoid any vernix-rich areas such as skin folds and creases, the possibility of ingestion of the oil by the baby, and any sites which commonly have more skin problems such as the napkin area and the scalp. The amount of oil to be used was chosen after testing what the spread of oil was on the researcher’s skin, and the resulting ‘greasiness’. A volume of four drops of oil provided a spread on the skin surface of approximately 6cm². This was considered an appropriate area of coverage for the baby sites without making the baby too greasy or ‘slippery’. The chosen frequency of application ensured that the intervention was not too onerous for parents, therefore aiming to improve protocol adherence. This frequency was also chosen for ethical reasons to ensure that the baby was not exposed to unnecessary oil applications.

![Figure 4.1: Diagram for parents to illustrate where to administer the oil. Picture from www.shutterstock.co.uk (2013a). ©Licence for use granted.](image)

Oil was provided in opaque plastic dropper bottles, which were weighed before and after treatment. Plastic bottles were chosen instead of glass bottles for safety reasons. The weight of oil after the treatment period was intended to help the researcher to assess compliance. The researcher documented the weights of all of the returned oil at the end of the study after data analysis, on the original allocation sheet maintained by the randomisation midwife. A laminated diagrammatic picture card was provided to ensure that parents applied oil to the correct areas of their baby's skin at each application, or avoided the study areas when using other baby skincare products (figure 4.1). Parents in the intervention groups were also advised to bathe their baby in water only.
4.2.8.3.i Components of the intervention

The instructions given to parents were as follows:

a) The intervention treatment will start on the first full day at home following discharge from the hospital
b) The parent will choose a convenient time in the morning
c) The baby will be undressed to nappy only
d) The parent will drop 4 drops of the treatment on to the baby’s left forearm using the pipette provided
e) The parent will spread the oil drops over the baby’s left forearm using the palm of the hand. The oil does not need to be massaged in until it has disappeared. It can remain on the surface of the skin
f) The parent will repeat d) and e) on the baby’s abdomen in the area above the umbilicus and below the nipple line
g) The parent will repeat d) and e) on the baby’s left thigh
h) The parent will wrap the baby loosely in a blanket for approximately 15 minutes to allow the oil to absorb into the skin
i) The parent will re-dress the baby
j) The parent will choose a convenient time in the evening
k) The parent will repeat the process c) to i)
l) The parent will repeat process b) to k) each day up to and including the night before the follow-up assessment appointment
m) The parent will not use other skincare products on the baby on the three study sites for the duration of the treatment period
n) The parent will not apply any treatment to the baby on the day of the follow-up assessment

4.2.9 Parental choice of use of baby skincare products

Parents were asked not to use alternative skincare products on their baby during the treatment period. This applied to all participants (intervention and control). During a weekly phone call parents were asked whether they had used any alternative products during the treatment period, and these details were recorded. Additionally, parents were asked what specific products (manufacturer and type) had been used each week, if any. This information was collected to inform the need for additional study arms in a future study, to explore if certain products had a noticeable effect on outcome measurements, and to contribute to awareness of what products parents favoured for newborn babies.
4.2.10 Protocol compliance

Parents were advised in full of the reason why the study was being conducted. Parents were provided with verbal and written instructions on how to care for their baby according to their allocated group. During each weekly phone call women were asked whether any other skin products had been used on their baby and this information was recorded. Details of the product used, frequency of use and which parts of the baby the product was used on were requested and recorded. During the weekly telephone calls, women were also asked not to disclose which group they were in, and were asked a generic question “With regard to your treatment group, have you had any difficulty following our instructions this week?” and provide a yes/no answer. This provided an idea of self-reported treatment compliance. If they were experiencing any difficulties which required more in-depth conversation occasionally it was obvious if they were using a treatment or not, but not which treatment. All disclosures were documented on the weekly telephone questionnaire form. Any problems were discussed, and advice or referrals were made as appropriate. During the data collection phase, a 24-hour telephone contact service was maintained by the researcher in order to monitor any problems.

During the data analysis phase, use of other baby skincare products was explored to ensure that this was evenly spread across the groups. Results were examined to look for any spurious data which may have resulted due to the influence of other skincare product use. Treatment and product compliance could also be confirmed by the ATR-FTIR spectroscopy data.

4.2.11 Data collection

All data were collected by the researcher. Only the randomisation data were collected separately by independent research midwives working in the Maternal and Fetal Health Research Centre at St. Mary’s Hospital. Five research midwives were registered with the randomisation service at The Christie Hospital NHS Foundation Trust Clinical Trials Unit. Training for the process and associated record keeping was provided to the midwives by the researcher prior to recruitment of the first participant. Randomisation information was collected on the relevant case report form (appendix 19) for each participant and stored in a folder which was kept in a locked cupboard in the Research Midwife Office. The folder was sealed in an envelope at the end of the study by one of the research midwives. The forms in the randomisation folder were checked against the analysis after unblinding took place at the OBSeRvE Trial Steering Committee on 4th November 2014.
4.2.11.1 Data collection forms

Data were recorded on data collection forms at baseline and follow-up. Baseline data collected included:

- demographic information about the mother and baby, including family history of atopic eczema for mother, father or sibling
- randomisation allocation
- clinical measurements and observations

During the treatment period information was collected regarding skincare product use. Follow-up data recorded included:

- clinical measurements and observations
- skincare product use and views of participation in the trial
- endpoint information

The data collection forms were informed by those used in the Baby Skincare Programme (Furber et al. 2012; Lavender et al. 2012), and revised to make them specific to the OBSeRvE study. There were no issues with the form structure for the duration of the study. Data were collected on the following forms:

- Consent Form for Mothers and Babies (appendix 15)
- Case Report Form 1 Part A: Eligibility (appendix 14)
- Case Report Form 1 Part B: Randomisation (appendix 19)
- Case Report Form 1 Part C: Background of Mother (appendix 17)
- Case Report Form 1 Part D: Background of Baby (appendix 18)
- Case Report Form 2: Baseline Observations (appendix 20)
- Baseline Questionnaire (appendix 16)
- GP Letter (appendix 21)
- Weekly Telephone Questionnaire (appendix 22)
- Case Report Form 3: Follow-up Assessment (appendix 23)
- Follow-up Questionnaire (appendix 24)
- Long term follow-up Contact Form (appendix 25)

4.2.11.2 Clinical data recording

The case report forms which required the recording of clinical measurements were Case Report Form 2 (baseline: appendix 20) and 3 (follow-up: appendix 23). These two forms were completed by the researcher and the research technician for all participants.
4.2.11.3 Questionnaire data recording

Questionnaires were used to capture demographic information and the practices and views of parents of babies participating in the study at follow-up. The follow-up questionnaire (appendix 24) provided quantitative data about baby skincare product use and protocol compliance, in addition to quantitative data about participation in the study. The questionnaire had two open-text questions which provided qualitative data which were further explored in a subset of twenty parents via an in-depth semi-structured interview. Questionnaires are a form of data collection regularly used in health research (Bowling 2009). The follow-up questionnaire was created to generate data to assess protocol compliance and maternal satisfaction. These data informed the feasibility of conducting a definitive study from the parental viewpoint. The questionnaires were self-completed by the parents. The researcher did not examine the follow-up questionnaires for completion to maintain blinding to treatment allocation; missing answers were not therefore requested. All participants were asked to complete the questionnaire at the same time (during the follow-up appointment). The questionnaire was the same for all participants (standardised) to increase reliability. It was six pages long and took approximately ten minutes to complete. Questionnaires were also sent out to those who did not attend for the follow-up appointment with a pre-paid envelope.

The follow-up questionnaire was informed by a questionnaire used in the Baby Skincare Programme (Furber et al. 2012; Lavender et al. 2012). The questionnaire therefore had internal validity as it had been satisfactorily tested in a population for which it had been designed (Bowling 2009). The questions were agreed by the whole research team to be relevant, reasonable, unambiguous and clear, therefore providing face validity. The researcher was present in the clinical room to answer any queries about the questionnaire whilst parents completed it. Participants were requested not to ask any questions which may disclose which treatment group the baby was in during the clinical assessment.

With regard to content validity, the questionnaire was constructed to incorporate parental views and experiences of having a newborn baby participating in a randomised controlled trial in a balanced way in order to obtain the positive and negative aspects (Bowling 2009). The first part of the questionnaire requested details about the baby, including family history of atopic eczema, feeding, skincare product use, bathing, moisturising, medication, consultations and skin concerns. A Likert scale was incorporated in the questionnaire to assess parental views on their baby’s treatment allocation and its effect on the skin. The final part of the questionnaire aimed to assess parents’ feelings on study participation including whether they would still take part if asked again, what they thought about the information provided, their treatment allocation, whether they would recommend the treatment to friends and their views on the equipment used to test the baby’s skin. All
of the questions to this point in the questionnaire were closed questions and analysed quantitatively. There were then two open-text questions to establish the positive and negative aspects of participation in the study. The responses to these questions were analysed qualitatively using Framework analysis.

4.2.11.4 Outcome measurements

One of the aspects of the pilot study design was to address which outcome measure would be an optimal primary outcome measure for a future study, and explore the feasibility of using that outcome measure with a population of newborn babies. As the main clinical indicator for the study was skin barrier function, the two main outcome measures considered included the change in spectral profile of lipid lamellae measured by ATR-FTIR spectroscopy, and trans-epidermal water loss measured by the Biox AquaFlux tool. Both measurements were included as co-primary outcome measures for the pilot RCT.

ATR-FTIR spectroscopy is a novel technique which has not been widely used in this population. ATR-FTIR data provide evidence of clinical change to skin barrier function before changes are visible clinically. This was important from an ethical perspective for a baby population. As there is some evidence from small functional mechanistic studies in mice (Jiang and Zhou 2003; Darmstadt et al. 2002) and adults (Danby et al. 2013; Naik et al. 1995) that some oils may be harmful to skin barrier function, a method that can detect changes to the skin before the skin is irreparably damaged is important.

Trans-epidermal water loss (TEWL) is a measure which is routinely used in dermatological studies. It was included as a co-primary outcome measure as this would allow comparisons across this study and existing studies, and was a validated measure that would stand well as the primary outcome measure if the ATR-FTIR data proved unreliable.

Other outcome measures were included as secondary outcomes, including stratum corneum hydration, skin surface pH, clinical observations (including assessment of erythema) and maternal satisfaction. The feasibility of all of the measurements was assessed at the completion of the pilot RCT. Assessment of optimal outcome measures for a future study was considered on the basis of clinical and practical aspects of the measures and population, rather than the statistical results. Statistically significant results were interpreted with the awareness that this was a pilot trial.
4.2.11.5 Procedures for assessment of trial outcomes

Anatomical markers for the left forearm, abdomen (above umbilicus and below nipple line) and left thigh were used to ensure consistency of assessment. Consistency was achieved by measuring from defined anatomical markers as follows:

At baseline measurement
- skin crease of the wrist to two thirds along the volar forearm,
- above the patella to two thirds along the thigh, and
- two thirds along from the umbilicus to the nipple line

At follow-up measurement
- skin crease of the wrist to one third along the volar forearm,
- above the patella to one third along the thigh, and
- one third along from the umbilicus to the nipple line

The chosen outcomes were informed by previous research and the need for minimal harm. For the primary outcome measures, two measurements were taken at each treatment site. In between these two measurements, three consecutive D-Squame discs (CuDerm Corporation, Dallas, USA) were applied to and removed from the site. The D-Squame discs remove (tape-stripping) the very top skin cells which are already dead and about to be lost naturally from the surface of the skin in a process known as desquamation. The second measurement following tape-stripping allowed reassessment of the deeper cornocyte layers of the stratum corneum. Assessment measurement points were intentionally different at baseline and follow-up to avoid tape-stripping at the same site twice. All of the outcomes chosen were optimal for the assessment of effect on skin barrier function. All tools were non-invasive which was important from an ethical perspective. The layout of the clinical room ensured that all assessments could be taken as quickly and efficiently as possible (figure 4.2).

Figure 4.2: Layout of equipment for clinical assessments. The ATR-FTIR Spectrometer is shown in the photograph on the right. Photographs ©Alison Cooke.
4.2.11.6 Primary outcomes

4.2.11.6.i Lipid lamellae structure

The novel co-primary outcome was skin barrier function as measured by the change in spectral profile of the lipid lamellae which is a determinant of stratum corneum permeability barrier function (Damien and Boncheva 2010). This was assessed by Attenuated Total Reflectance Fourier Transform Infra-Red spectroscopy (ATR-FTIR) between 2 days and 4 weeks after birth (figure 4.3), which was calibrated daily according to the manufacturer guidelines (Thermo Scientific 2012). ATR-FTIR spectra were collected non-invasively using a silver halide fibre-optic probe (FTIR Flexispec PIR 900, Art Photonics, Berlin, Germany; figure 4.3) attached to a Nicolet iS50 FTIR Spectrometer (Thermo Fisher Scientific Inc., Waltham, USA; figure 4.2), equipped with a cooled mercury-cadmium-telluride detector and purged with dry nitrogen. Data analysis of absorbance spectra was performed initially in Omnic 9.0 and TQuant (Thermo Fisher Scientific Inc., Waltham, USA) to convert the graphical spectra into numerical data. The numerical data were then transferred for analysis in IBM SPSS Statistics version 20. A typical spectral profile of the skin is illustrated in figure 4.4, with the lipid and water peaks highlighted.

![Figure 4.3: Measurement tools (clockwise from top left to lower left: Aquaflux (TEWL), Corneometer (hydration), skin pH meter, ATR-FTIR probe, Mexameter (erythema), D-Squame plunger). Photographs ©Alison Cooke, with kind permission of participant.](image)

The difference in the quantity of lipids and lipid esters in the skin was determined based on the change in peak intensities of the spectral regions centred on ~2920 and ~2850 wavenumbers, corresponding to the symmetric and asymmetric stretching of the CH₂ group of all lipids, and 1740 wavenumbers, corresponding to lipid esters of triglycerides in sebum and topically applied oils, respectively (Brancaleon et al. 2000). Quantities were normalised to regions of the spectra showing no absorbance, at 3800 and 1800 wavenumbers respectively, to account for differences in contact pressure between the skin and the probe.
Lipid chain conformation ($\nu_{\text{asym CH}_2 \text{COG}}$) was based on the location (centre of gravity: COG) of the peak between ~2853 and ~2848 wavenumbers, corresponding to the asymmetric stretching of the CH$_2$ bond of lipids (Boncheva et al. 2008; Mendelsohn et al. 2006). A peak centre of gravity at ~2848 wavenumbers corresponds to tightly packed lipid chains, and is associated with optimum skin barrier function, whereas higher wavenumbers indicate increasing lipid fluidity and decreasing skin barrier function (see figure 4.5).
Lateral chain packing was determined from the second derivative reflectance spectra by measuring the full width at half maximum (FWHM) of the spectral region centred at 1468 wavenumbers (Damien and Boncheva 2010). A change in the width of this region corresponds to changes in lateral lipid chain packing. A higher proportion of orthorhombic packing of lipids is indicated by a FWHM of \( \geq 11 \) wavenumbers. A higher proportion of orthorhombic structuring throughout the depth of the stratum corneum is associated with improved skin barrier function (see figure 4.6).

The difference in the quantity of surfactants in the skin, measured to assess adherence regarding use of wash products, was determined based upon the change in peak intensity of the spectral region centred on 1240 wavenumbers, corresponding to the sulphur group of surfactants found in wash products, normalised to the reference region at 1800 wavenumbers (Hoppel et al. 2014).

![Second derivative spectra in region 1478 to 1460 wavenumbers](image)

**Figure 4.6**: Primary outcome measure: lateral lipid chain packing 1468 CH\textsubscript{2} scissoring. The graph on the left illustrates the FWHM for healthy skin. The graph on the right illustrates the FWHM for atopic eczema/dermatitis (AD).

ATR-FTIR spectroscopy is a biophysical measurement that has been used previously to demonstrate the effects of oleic acid on skin barrier (Naik et al. 1995). Topical applications may disrupt stratum corneum lipid lamellae structures and induce permeability defects (Jiang et al. 2000). ATR-FTIR is the most sensitive and specific method to detect changes in the lipid lamellae induced by the application of oils to the skin, before the effect on the skin becomes visible clinically. This measure was included as a co-primary outcome as the data collected were novel data, which have not been extensively assessed previously in babies, but have the potential to be the best indicator of change in skin barrier function.
Without a purpose-built clinical area the use of ATR-FTIR requires two people; one to hold the baby and one to conduct the assessment. In view of the mobility of the baby the number of scans taken per assessment was increased from 32 to 40 (resolution 4 wavenumbers), as some frames were lost if the baby moved and the probe lost contact with the skin. The only disadvantage to this was that the assessment took an extra 10 to 15 seconds per site. This was acceptable when compared to TEWL which required the assessment to be started again if the baby moved, potentially adding another 45 to 60 seconds to the assessment.

4.2.11.6.ii Trans-epidermal water loss

The validated co-primary outcome was skin barrier function measured by the rate of change of basal trans-epidermal water loss (TEWL) between 2 days and 4 weeks after birth. TEWL is defined as the flux of water vapour evaporating from the skin surface. A closed chamber TEWL instrument was used to take the measurement (Biox AquaFlux Model AF200; figure 4.3). The researcher took the measurements at both time-points, in accord with published guidelines for TEWL measurements (Rogiers 2001). TEWL is the most widely assessed baby skin parameter (Stamatas et al. 2011). It is a marker for skin barrier function (Levin and Maibach 2005). High TEWL values are indicative of skin barrier dysfunction (Rim et al. 2005; Chamlin et al. 2002; Berardesca et al. 1990). Although TEWL is a routinely used and validated outcome measure (Fluhr et al. 2006), it proved to be the most difficult tool to use with this population due to its sensitivity to movement.

4.2.11.7 Secondary outcomes

All of the secondary outcome measures were easy to conduct in this population.

4.2.11.7.i Stratum corneum hydration

The rate of change in stratum corneum hydration between 2 days and 4 weeks after birth was measured at the same times and sites as the primary outcome measures using a Corneometer® Model CM825 (Courage & Khazaka electronic GmbH, Germany; figure 4.3). Hydration is an indicator of skin barrier function (Tagami et al. 1982). This measure has been used in previous trials with babies (Lavender et al. 2013; 2012; 2011; Garcia-Bartels et al. 2012; 2010; 2009; Lowe et al. 2012; Galzote et al. 2007). The data collected informed the diagnosis of any skin barrier dysfunction.

4.2.11.7.ii Skin surface pH

The rate of change in skin surface pH between 2 days and 4 weeks after birth was measured using a skin pH meter® Model PH905 (Courage & Khazaka electronic GmbH, Germany; figure 4.3). Use of skincare products can alter skin pH (Danby and Cork
A baby is born with a near neutral skin pH (6.6 – 7.5) (Hoeger and Enzmann 2002; Giusti et al. 2001; Yosipovitch et al. 2000; Visscher et al. 2000). After birth, the pH gradually decreases. An acidic skin pH assists the activity of lipid enzymes in maintaining skin barrier function (Hachem et al. 2005; Mauro et al. 1998), influences protease activity responsible for desquamation (Deraison et al. 2007; Hachem et al. 2005), and regulates bacterial activity particularly in the napkin area (Wolf et al. 2000; Berg et al. 1994). The near neutral pH of newborn skin means that babies are susceptible to irritation and infection and this may hinder repair (Fluhr et al. 2004). This outcome has been used in previous baby skincare research (Lavender et al. 2013; 2012; 2011; Garcia-Bartels et al. 2012; 2010; 2009; Lowe et al. 2012; Takahashi et al. 2009; Visscher et al. 2009; Galzote et al. 2007).

4.2.11.7.iii Clinical observations

Changes in clinical observations (erythema, dryness and scaling, need for medical products/attention) between 2 days and 4 weeks after birth were observed and recorded by the researcher using a modified Neonatal Skin Condition Score (NSCS) tool (table 1.2, p21; Lund et al. 2001). The modified tool can be viewed in appendix 26. Rating was based on the severity of dryness and/or scaling. A score of zero indicated no evidence of abnormal skin increasing to a score of 4 which indicated a degree of severity. Using this tool ensured consistency. The NSCS tool is recognised globally, having been used in previous baby skincare studies (Lavender et al. 2013; Brandon et al. 2010; Garcia-Bartels et al. 2010; 2009). Details of skin condition and need for medical products/attention were also collected via a weekly telephone questionnaire conducted with mothers by the researcher. Erythema was measured at each visit using a Mexameter® Model MX18 (Courage & Khazaka electronic GmbH, Germany; figure 4.3).

4.2.11.7.iv Maternal satisfaction

Women’s views on having a baby participating in a clinical trial were explored, with consideration to acceptability, practicality, protocol compliance, group allocation, convenience, and information provision. Data were assessed quantitatively and qualitatively for the follow-up questionnaire at 4 weeks for all participants, and qualitatively for semi-structured in-depth interviews with 20 participants who were purposively sampled.

4.2.12 Data analysis

4.2.12.1 Quantitative statistical analysis

The randomisation was stratified according to family history of atopic eczema, to ensure that the groups were homogeneous. Intention-to-treat analysis was used, to avoid undermining the randomisation process (Torgerson and Torgerson 2008). Data were
double-entered into IBM SPSS Statistics version 20 (IBM Corporation 2013) by the researcher. This process was finalised on 25th August 2014. There were two data files; one for the observational data (numeric) and one for the questionnaire data (numeric/word). The double-entered data files were cross-checked in Microsoft Excel for errors by a Statistician at The University of Manchester. All corrections were made by the researcher by re-examining the original documentation in the participant’s records. It was planned that a second person (Primary Supervisor) would make any decisions on errors that could not easily be rectified.

The main analyses for a pilot study should be descriptive (Lancaster et al. 2004). The analyses for this study involved the estimation of recruitment rates, attrition rates, non-compliance rates, means and standard deviations of primary and secondary outcomes by group at baseline and 4 weeks, and 95% confidence intervals for differences of means of primary and secondary outcomes between groups at 4 weeks. Primary and secondary outcomes at 4 weeks were also compared by group adjusted for baseline values using analysis of covariance. Inferential results were interpreted cautiously: the study was not powered to detect statistically significant differences, as the main aim was to assess proof of concept, feasibility and inform a future study.

Data analysis commenced once all data had been collected. Data analysis was conducted on the basis of intention-to-treat, where all of the participants were analysed according to their original randomised group (Torgerson and Torgerson 2008), as this is the most robust analytical method for randomised trials (Hollis and Campbell 1999). Pure intention-to-treat analysis is difficult to achieve as it would require all participants to remain in the study from baseline to follow-up with no attrition. However, all high quality randomised trials should adhere to the principles of intention-to-treat analysis (Torgerson and Torgerson 2008). For the OBSeRvE study, missing values at 4 weeks were not carried forward or imputed; descriptive analysis at follow-up was based on complete data, compared by randomisation group.

4.2.13 Summary

The data generated from this study were expected to show that using topical sunflower oil was more beneficial to skin barrier function than using topical olive oil or no oil for the prevention or treatment of baby dry skin.

However, it is important to note that this was a pilot study and therefore any statistically significant findings must be considered as such, as no power calculation informed the sample size. The aim of the study was to provide proof of concept that the use of topical oils had an effect on baby skin barrier function, and what patterns were evident that required further investigation. The full study protocol can be viewed in appendix 27.
CHAPTER FOUR PART TWO: QUALITATIVE STUDY

4.3 Study design

The nested qualitative study was designed to inform the feasibility of conducting a future study by exploring mothers' views and experiences of having a baby participating in a randomised controlled trial. The design included two open-text questionnaire responses (appendix 24) and twenty in-depth semi-structured interviews (appendix 28).

All interviews were conducted by the researcher. Interviews were recorded and transcribed verbatim by 1st Class Secretarial Services (Lawson Hardwick Limited, Scotland). Transcriptions were examined for errors and corrected by the researcher by listening to the interview several times. Field notes were added to the transcripts by the researcher to indicate any non-verbal body language which the researcher had recorded during the interview.

4.3.1 Questionnaire

Questionnaires were chosen as a method of data collection to assess protocol compliance and maternal satisfaction. Two open-text questions were included at the end of the questionnaire to collect some descriptive qualitative data from which participants could be purposively sampled in order to conduct an in-depth semi-structured interview. The two open-text questions were:

- What do you think are the positive aspects of taking part in this study?
- What do you think are the negative aspects of taking part in this study?

The questionnaires were informed by those used in previous baby skincare research (Lavender et al. 2012); thus providing content validity (Polit and Beck 2006).

Questionnaires are a useful tool for quantitative data collection (Robson 2011). They are also often used for the collection of qualitative data, however open-text answers are unlikely to produce the richness often required for full exploration (Silverman 2011). Furthermore, collecting qualitative data in this way prevents the researcher from probing participants to expand their answers. Twenty interviews were therefore conducted to build on the responses given in the questionnaires.

4.3.2 Semi-structured interviews

In-depth semi-structured interviews were considered the most suitable form of data collection. Interviews allowed the researcher to ask questions which were necessary to inform the feasibility of conducting a future study, and allowed the participant to answer those questions in their own words and provide the depth of data required.
Van Manen (1990; p66) suggests that the interview “may be used as a vehicle to develop a conversational relation with a partner (interviewee) about the meaning of an experience”. Interviews were chosen rather than focus groups, as opposing views were sought and participants may have been uncomfortable to discuss these in a group. Negative aspects can often dominate a focus group (Carey and Smith 1994). As the participants were mothers with young babies, it would have been difficult to arrange a time that would be convenient for all. It may also have been difficult to maintain anonymity in a small focus group.

Interviews are an appropriate method of data collection to obtain in-depth rich data that explores views, experiences and opinions (Walsh and Baker 2004). The researcher has the opportunity to ask for clarification and elaboration on topics the participant has raised (Tashakkori and Teddlie 1998). There is a risk that the researcher may influence or 'lead' the participant to provide certain data, be it knowingly or unknowingly (Walsh and Baker 2004). After due consideration, interviews were deemed to be the optimal method to obtain the type of rich informative data required.

Maternal satisfaction was a secondary outcome, and mother's opinions of having a baby in a trial were necessary in order to assess the feasibility of conducting a future study. Questions in the interviews therefore evolved from the topics of acceptability, practicality, convenience, protocol compliance, treatment allocation and information provision. The questions were framed around the basis of having a newborn baby taking part in this type of research, to establish what mothers thought about the study design and processes.

4.4 The OBSeRvE: Oil in Baby SkincaRE qualitative study

4.4.1 Sampling and sample size

Purposive sampling of eighteen to twenty participants was proposed for the in-depth interviews. Criterion purposive sampling was chosen to ensure recruitment of a diverse group who had varying experiences of the research process (Patton 2002). All participants were eligible to take part. To ensure that there were a variety of participants across the treatment groups, a list was made of study number and study group. The researcher remained blinded to which group was which; an independent research midwife labelled the study numbers as group 1, 2 or 3 but sealed the identification of this grouping in two opaque envelopes which were passed to two independent researchers at The University of Manchester for safe-keeping. Originally the sample size was set at ten to twelve interviews, which was considered appropriate to obtain the data required, however it was not absolute. Due to the higher than anticipated loss to follow-up it was agreed with the Trial Steering Committee that the qualitative component of the study had become even more important to endeavour to identify the issues mothers faced. The number of interviews required was therefore increased to eighteen to twenty.
4.4.1.1 Inclusion criteria for qualitative interviews:

Any mother with a baby taking part in the OBSeRvE pilot RCT who consented to take part in the qualitative study, and was purposively selected for interview, was eligible.

4.4.2 Recruitment

Mothers were provided with information about the qualitative study when they were informed about the RCT. Consent was obtained for interview at the same time-point as consent for participating in the RCT. A second request for permission to phone the participant to arrange an interview was made at the end of the follow-up questionnaire (28 days). This was a second form of written consent. The mothers were contacted by telephone after a period of time had elapsed after the follow-up appointment to ask if they still wanted to take part in an interview. A date was agreed and further verbal consent was obtained at the beginning of the interview recording. The time elapsed between follow-up appointment and interview ranged between one and six months. The reason for the longest duration between follow-up and interview was to ensure that data input had been completed. This meant that when the participant disclosed whether they were in a treatment group during interview, the researcher could not associate that disclosure with their trial data. This maintained the assessor-blinding for data analysis. At all of the time-points the participant was reminded that taking part was voluntary. Each participant chose their own pseudonym to maintain confidentiality and anonymity.

4.4.3 Data collection

4.4.3.1 Questionnaire

All participants in the pilot RCT (intervention and control groups) were asked to complete two written questionnaires, and three weekly telephone questionnaires. The first written questionnaire (completed within 72 hours of birth before starting treatment) collected demographic information (appendix 16). The follow-up written questionnaire (completed at 28 days once the treatment period ended) contained questions concerning taking part in the trial; acceptability, practicality and convenience, protocol compliance, group allocation, and information provision (appendix 24). The weekly telephone questionnaires recorded details of skincare product usage, health professional consultations and prescriptions, and any skin concerns (appendix 22).

4.4.3.2 Interviews

The interview schedule comprised 18 questions divided between five topics which were appropriate to assess the feasibility of having a newborn baby in an RCT from the mother’s perspective (appendix 28). The interviews were audio recorded and transcribed verbatim. Field notes were taken during the interview and immediately afterwards. These notes formed part of the data, providing details of emotions, tone of voice, body language,
setting and the researcher’s feelings and thoughts to aid reflexivity (Mauthner et al. 2002). Participants chose a pseudonym for any quotations used in publication or at conference presentations, to maintain confidentiality and anonymity. The interview schedule was informed by the literature review and study design.

4.4.4 Data analysis

Qualitative data were managed using NVivo 10 software (QSR International Pty Ltd., Australia) and were subjected to framework analysis (Ritchie and Spencer 1994). Framework analysis was chosen as a methodical approach to data management which fits with the post-positivist perspective underpinning the study, whilst maintaining the qualitative concepts of dwelling with the data to establish the emerging themes during the analysis phase.

Framework analysis is a matrix-based method of data analysis which uses five distinct phases; ‘familiarisation’, ‘developing a thematic framework’, ‘indexing’, ‘charting’, and ‘mapping and interpretation’ (figure 4.7). It is an on-going inductive and iterative process. The framework is developed early on in the process; at each stage the framework is redefined and conceptualised. Each phase is transparent which enhances rigour.

![Figure 4.7: The process of Framework analysis](image)

**4.4.4.1 Familiarisation**

This phase involved the researcher becoming familiar with the data by listening to the interviews and reading the transcripts and field notes repeatedly (Spencer et al. 2014; Furber 2010). The audio data was transcribed verbatim by 1st Class Secretarial Services (Lawson Hardwick Limited, Scotland). The researcher examined and amended the transcripts accordingly after assessing each transcript word for word whilst at the same time listening to the original recorded interview. Field notes were added to the transcript for coding, together with each participant’s questionnaire responses. The
questionnaire responses for those participants who were not interviewed were added individually as transcripts in NVivo 10 (QSR International Pty Ltd., Australia). After reading all of the transcripts several times, the researcher coded the transcripts by identifying topics and issues that were recurrent across the data and relevant to the research aims (Spencer et al. 2014; Ward et al. 2013; Furber 2010). All of the interviews were initially coded in this way. A final reading of all of the transcripts identified any missing codes. Memos were made at this point recording initial thoughts about the thematic framework.

4.4.4.2 Developing a thematic network

The thematic framework was developed using Post-it® notes so that themes could be moved around easily to be able to visualise the hierarchy of themes and sub-themes (Spencer et al. 2014). Once this framework seemed to ‘fit’ the data, the various themes were entered into NVivo 10 (QSR International Pty Ltd., Australia) as ‘nodes’. At this stage all of the nodes were descriptive and grounded in the data to ensure that all of the relevant data would be easily assigned to that node in preparation for data analysis. The researcher fulfilled this stage alone (Ward et al. 2013); the thematic framework was then discussed and agreed with the wider research team.

4.4.4.3 Indexing

This phase involved examining each transcript stored in NVivo 10 (QSR International Pty. Ltd., Australia) line by line to establish what the data were saying, and then determining which part of the framework each part applied to (Spencer et al. 2014; Furber 2010). The phrase was assigned to the node in NVivo 10. On occasion the data would be linked to more than one node. Memos were made to reflect these links in preparation for the analysis stage.

Thematic sets were created so that all of the data relating to a particular theme were stored together. The data extracts in these sets were reviewed to ensure that they were a coherent fit (Spencer et al. 2014). The transcripts were examined to ensure that no data had been left unassigned to a node; where this occurred a further node was added to the thematic framework. All of the thematic sets were reviewed to ascertain whether any further themes were required. This phase of the data management was completed by the researcher (Ward et al. 2013).

Although participants were recruited for interviews purposively to ensure that there was representation from all three treatment groups, a decision was taken not to split the data by treatment group for analysis. The reason for this decision was that the various treatments were discussed openly by participants as ‘using oil’ or ‘not using oil’; the data were more comprehensive when considered as a whole.
4.4.4.4 Charting

All of the original data were inspected to assess meaning and relevance and the main themes and sub-themes were reviewed and finalised. The indexed data were used to populate chart matrices in NVivo 10 (QSR International Pty. Ltd., Australia) to match the data to the thematic network. Each theme was allocated a column in the matrix and each participant a row. Data were summarised within the matrices, whilst maintaining the context of the participant voice with the use of verbatim quotes (Spencer et al. 2014). At this stage of the process there was some repetition of data across the themes, but the easy visualisation of the data within the matrices as a whole enabled this to be considered in preparation for interpretation (Furber 2010).

4.4.4.5 Mapping and interpretation

This was the most time-consuming stage of the process as all of the data needed to be mapped to framework matrices for each main theme, resulting in much larger matrices than those produced in the charting phase. This was undertaken to provide a position from which to analyse data for participants within the theme, but also for each participant across the themes (Spencer et al. 2014).

The emphasis in this phase was on the language of the participants together with their attitudes, behaviours, views and motivations. Some sub-themes were combined and re-labelled where there was repetition of data. The matrix was reviewed across the themes to commence a higher level of interpretation.

The researcher looked for patterns of association in the data. It was important to determine influential factors in decision-making about recruitment, and experiences of participation. Most of the data were explicit; based directly on participant accounts. Some implicit explanation also evolved based on the researcher’s inferences (Spencer et al. 2014). Links were made to the existing literature and to practice. The interpretation of findings was agreed with the wider research team.

4.5 Summary

This chapter has discussed the methods for the OBSeRvE study. The pilot study aimed to assess the feasibility of testing the study hypothesis, and to inform the design of a future study. Quantitative and qualitative methods were combined to generate a holistic dataset to provide the most informative evidence to meet the aims of the study. The methods for the pilot RCT were designed according to previous baby skincare trials and clinical trial guidance to ensure that the pilot would be robust. The qualitative study incorporates Framework analysis to provide transparency. All of the methods are underpinned by the philosophical position of post-positivism. The next chapter discusses the ethical considerations for the study.
CHAPTER FIVE: ETHICAL CONSIDERATIONS

5.1 Introduction to the chapter

All research involving humans must adhere to strict ethical principles. The ethical principles should be considered in the methodology and design of the research; they must address any potentially harmful aspects of the study, consent processes and confidentiality. These principles are considered in this chapter. Some populations are considered to be more vulnerable than others, including babies and pregnant women. Consequently, as the OBSERvE study was recruiting newborn babies, it was important to ensure that these ethical aspects were considered in-depth during the design phase and throughout the conduct of the study.

The recommendation and use of topical oils is common practice. A national survey found that 80% of UK midwives recommend olive oil and 20% recommend sunflower oil for baby dry skin (Cooke et al. 2011). There is some research that suggests that topical oils may not always have a beneficial effect on skin. There have been no large and adequately powered studies to inform clinical practice or relevant studies which include babies. The available evidence includes small functional mechanistic studies with mice (Jiang and Zhou 2003; Darmstadt et al. 2002) and adult volunteers (Danby et al. 2013; Naik et al. 1995). The OBSERvE study was a pilot randomised controlled trial (RCT) which assessed the use of topical oils for baby skincare. Ethical aspects were considered in the study design in order to ensure that babies were protected from any harm.

5.2 Ethical considerations of the research

5.2.1 Methodology

The Nuremberg Code (1949) set the standard for the current ethics framework and provided the principle of voluntary informed consent. Guidance for medical research involving humans was provided by the Declaration of Helsinki (World Medical Association 1964). The issue of children as research participants has also been examined (Greig et al. 2007). The promotion and safeguarding of the health of patients, and acting in the patient’s best interests are important ethical considerations. The primary aspects of ethical guidance include respect for all human beings, protecting their health and rights, and protection of those who are vulnerable. The Declaration of Helsinki asserts that research protocols should address ethical considerations, and must be submitted to a research ethics committee (REC) for approval. Informed consent and voluntary participation should be prioritised. The Declaration provided the basis for the Good Clinical Practice guidelines (ICH GCP (1996) and subsequent directives). Studies should also act in accordance with the Research Governance Framework (Department of Health 2005). This framework outlines the standards for ethics and clinical trials.
Research that includes National Health Service patients as participants must receive a favourable ethical opinion before the study can begin. Full details of how ethical issues have been or will be addressed must be included in all applications to the REC. When the research involves children, ethical issues are likely to be more complex. This is due to children being less likely to be able to express their needs or to defend their interests (Campbell and Groundwater-Smith 2007).

A clinical trial that is considering involving children should firstly contemplate upon whether the research could be carried out with adults. If it is deemed likely that the same results would be possible with adults, then the study should not go ahead with children (Department of Health 2004; Medical Research Council 2004; RCPCH: Ethics Advisory Committee 2000). The use of adult data to inform the treatment of children is often inappropriate due to physiological differences between adults and children (Edwards and McNamee 2005; Medical Research Council 2004). This is particularly relevant in terms of differences between newborn and adult skin (Fluhr et al. 2011; Stamatas et al. 2011; 2010; Nikolovski et al. 2008). Children are not small adults (Medical Research Council 2004). Developing effective treatments for children will often require the need for testing on children (Yeung 2007). Where possible, older children should be recruited rather than younger ones (RCPCH: Ethics Advisory Committee 2000). The REC will evaluate the risks and benefits for the participants in detail before giving approval for a study to go ahead.

The sample comprised newborn term babies within 72 hours of birth. Routine clinical advice currently given to parents is to use topical olive oil or topical sunflower oil for the prevention or treatment of baby dry skin or baby massage. It is not confirmed by evidence whether this practice is good for, or harmful to, babies. This study was required to inform clinical practice and enhance the current evidence base. The OBSeRvE study was a minimal harm study; parents were not asked to apply any oil to baby skin that was not already currently recommended and routinely used by parents on their baby’s skin across the UK. A UK national survey was undertaken prior to the commencement of the trial to establish which topical oils were the most commonly recommended (Cooke et al. 2011). The two most commonly recommended oils: olive oil and sunflower oil, were taken forward for assessment within the pilot trial.

5.2.1.1 Clinical equipoise

Clinical equipoise occurs when there is collective genuine uncertainty over whether a treatment is beneficial (Weijer et al. 2000). This is the ethical status required to allow a clinical trial to commence. In some countries, such as the UK, the uncertainty principle is
more widely endorsed. This reflects the same uncertainty but from an individual clinician rather than a collective group of clinicians (Peto and Baigent 1998). If equipoise or uncertainty did not exist, it would be unethical to conduct a clinical trial; researchers and clinicians would believe that one treatment was more beneficial than another and ethically would want to recommend the best treatment to their patients. In these circumstances, randomisation to an unknown study treatment in a clinical trial would go against their duty of care to their patient.

In the case of the OBSSeRvE study, topical olive oil and sunflower oil are commonly recommended to new parents for the prevention or treatment of baby dry skin. The two oils are quite different to each other, one being high in oleic acid and the other in linoleic acid, and are likely to affect skin differently. There is a dearth of research in this area and it is not known by clinicians which oil is best for baby skin, if any. Recommendation is made on the basis of tradition or anecdotal evidence. In view of the uncertainty of best practice, there exists a status of clinical equipoise and ethically it is acceptable to conduct a trial to assess the impact of these topical oils on skin barrier function. Freedman (1987) states that a trial should be designed so that, once complete, results are provided that are sufficiently significant to resolve any dispute amongst clinicians in the best treatment for patients; that is, clinical equipoise will be disturbed (Weijer et al. 2000).

There is some controversy over the principle of clinical equipoise. The definition of duty of care to a clinician involves making an individualised judgement over what treatment is best for their patient. There is therefore a dilemma over allowing a patient to enter into a randomised trial where the clinician does not know to which treatment arm their patient will be allocated and, in a double blind trial, also would not know what the treatment was (Miller and Brody 2007). However, this tends to be more controversial in a decision over drug treatment; in a cancer trial for example, prescribing a patient a new treatment may mean a difference in quality and/or length of life. In the OBSSeRvE trial, this controversy is minimised as recommendations for using topical oils for the prevention or treatment of baby dry skin are subjective, and arguably do not have the same ‘life or death’ impact.

5.2.2 Harm

This study uses topical oils that are already routinely recommended to new parents by health professionals for the prevention or treatment of baby dry skin and for baby massage. Ethically, it is therefore important to investigate the effect of these oils on baby skin. However, some small functional mechanistic studies have found that topical olive oil may be harmful to skin barrier function (Danby et al. 2013; Jiang and Zhou 2003; Darmstadt et al. 2002; Naik et al. 1995). These studies have been conducted with mice and adult volunteer populations and the effect in babies may be different. Consideration was given to the safety of asking parents to apply these oils to their baby’s
skin in relation to the dose, duration and outcome measures that could detect changes in skin barrier before they could affect the skin in the long-term. The OBSeRvE study was not a trial of an investigational medicinal product (appendix 29). Nevertheless the trial was conducted to the same standards as a clinical trial of an investigational medicinal product. Research Ethics Committee (REC), NHS Research and Development (R&D) and University favourable ethical opinions were obtained (appendices 30-36). The study was conducted in accord with the Declaration of Helsinki, the terms of a favourable ethical opinion, the Standard Operating Procedures of the Sponsor and the NHS Research Governance Framework.

A favourable opinion from the REC, R&D approval and Sponsor authorisation were achieved in September 2012. All of the research team had up to date Good Clinical Practice Training between January 2012 and September 2013 which remained current throughout the recruitment and follow-up period. All of the research team involved with patients had recent Disclosure and Barring Service (DBS) enhanced disclosures. The site file was maintained at Central Manchester NHS Foundation Trust (Clinical Room 5, Maternal and Fetal Health Research Centre). The Master file was held at The University of Manchester (researcher’s office). Standard Operating Procedures existed for all procedures: recruitment, randomisation, clinical assessments, cleansing and storing of equipment, and lone working. The Trial Master File was audited by The University of Manchester research governance team in July 2014.

Two substantial amendments were made to the REC, R&D, and Sponsor:

- Amendment 1: December 2013 – addition of protease assay to D-Squame disc analysis
- Amendment 2: February 2014 – changes to inclusion criteria and recruitment strategy, and increase in number of qualitative interviews

A 24-hour on-call cutaneous service was provided. The chance of an adverse event or reaction occurring following the application of topical oil for 28 days was small. However an on-call dermatologist arrangement that was at least as good as any trial of a pharmaceutical product for treating the skin was put in place. A consultant dermatologist who runs a large paediatric dermatology clinic at Sheffield Children’s Hospital was available on-call 24 hours a day during the trial, to give advice to the research team or other healthcare professionals. If the consultant was unavailable, a senior staff-grade in dermatology at Sheffield Children’s Hospital was also available to provide advice. This on-call service was the same service that is provided for patients and volunteers for clinical studies in Sheffield.
If an inter-current skin condition occurred in a baby during this trial, the most likely scenario was that it would be unrelated to the trial. Following a phone call from the researcher, photographs could be sent to the consultant dermatologist via email or Skype. The consultant could ask questions to determine if it was likely that the skin condition was related to participation in the trial. If it was considered that it was/could be related to participation in the trial, the consultant could make an immediate decision regarding further participation. He would then offer advice on any treatment that may be required. The consultant was able to receive emailed photographs of any skin concerns. Where necessary, the consultant’s decision was brought to the attention of the OBSeRvE Trial Steering Committee who could determine whether treatment allocation should continue in these babies.

The researcher phoned the participants weekly. One of the reasons for this was to establish any adverse events/reactions. This included establishing whether any of the babies had seen a General Practitioner, been prescribed any medication, and whether there had been any rashes particularly in the study areas.

5.2.2.1 Safety issues

5.2.2.1.i Adverse event definitions and reporting

An adverse event (AE) is defined as any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the treatment (ICH 1996). For this trial, jaundice, weight loss and feeding difficulties were expected neonatal adverse events which were recorded, but not reported for further investigation. An adverse reaction (AR) is defined as any untoward and unintended response in a participant which is related to the oil. Adverse reactions were reported and investigated using the 24-hour on-call cutaneous service.

A serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR) is defined as any adverse event, adverse reaction or unexpected adverse reaction, respectively, that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, consists of a congenital anomaly or birth defect, or is otherwise considered medically significant (ICH 1996). This categorisation would be determined by consensus between the members of the research team and the Trial Steering Committee.

The following episodes were expected baby serious adverse events which were recorded, but not reported for further investigation:
• Admission to hospital for phototherapy treatment (jaundice)
• Admission to hospital for weight loss
• Admission to hospital for feeding difficulties
• Admission to hospital for viral illness
• Admission to hospital for illness resulting from bacterial infection
• Admission to hospital for elective surgery

All adverse events, adverse reactions, serious adverse events, serious adverse reactions or suspected unexpected serious adverse reactions were recorded as specified in the study protocol (see appendices 27, 37-38).

A system for recording, monitoring and making trial decisions regarding adverse events was detailed in full in the study protocol (appendix 27). The 24-hour on-call dermatology arrangement ensured that any potential adverse reactions could be assessed immediately. A Trial Steering Committee was formed, and the Terms of Reference (appendix 39) provided the means to make decisions electronically if necessary. These systems protected the participants and the researchers and were proven to be effective in previous studies (Lavender et al. 2013; 2012; 2011).

5.2.2.1.ii Monitoring processes

The researcher liaised closely with the supervision team throughout the study. Team meetings were held monthly. The researcher routinely met with the randomisation research midwives to ensure that there were no concerns. All clinical assessments were conducted by the researcher with a research technician present to assist if necessary.

Two Trial Steering Committee meetings were held prior to and during the study in March 2013 and January 2014. All recommendations made were addressed:

• March 2013 – clarifications required to the protocol, including addition of transepidermal water loss as a co-primary outcome measure, rather than secondary outcome; summary section added to beginning of Participant Information Sheet
• January 2014 – amendment to recruitment procedure to allow the researcher to screen potential participants for eligibility rather than the clinical team; amendment to inclusion criteria to extend eligibility to babies less than 72 hours old rather than 48 hours old; offer of home visits in the final phase of the study to assess the impact pertaining to feasibility for a future study; increase number of qualitative interviews in view of higher than anticipated loss to follow-up
5.2.2.1.iii Withdrawal from treatment and stopping rules

Withdrawal from treatment occurred for specific reasons, or if a parent wished to withdraw. The procedures to follow for this scenario were covered in the study protocol (appendix 27). Withdrawals were documented for monitoring purposes (appendix 40). A small number of participants were lost to follow-up during the first phase of the trial due to ambiguity of the protocol wording for withdrawals. The second substantial amendment to the protocol clarified the wording to ensure that no further participants were lost unnecessarily.

It was not anticipated that there would be any reason for stopping the trial as the oils being used were a commonly recommended treatment, and the treatment period was short. This could be reviewed for adverse reactions, as necessary. Any adverse reactions were considered initially by the research team. If there were any concerns with the type of adverse reactions arising, an emergency Trial Steering Committee meeting could be called. This committee consisted of independent clinical specialists (neonatal, midwifery, dermatology, clinical trials) and users (appendix 41). If a safety issue arose, the Committee could decide whether to continue, monitor or stop the trial. In the event of an adverse reaction, the first step was for the researcher to contact the on-call dermatologist. The members of the Trial Steering Committee were kept informed throughout.

5.2.2.1.iv Methods to reduce bias

The study was assessor-blinded, and the two intervention groups were participant-blinded to which oil they were using (bottles were labelled X and Y). Parents were advised not to use oil on their baby on the day of follow-up assessment in order to maintain assessor-blinding. Participants were randomised, aiming to provide homogeneity across the study groups, and allocation was concealed. Analysis was confirmed by the research team, with input from a Statistician. The choice of a randomised controlled trial as the study design was due to the desire to reduce bias and make study findings and processes as robust as possible.

5.2.2.1.v Trial Management

The trial was sponsored by The University of Manchester with dermatology and skin barrier technical support from The University of Sheffield. A Trial Steering Committee was formed, with an independent Chair, and representation from a Clinical Trials Unit, consumers and parents.

User involvement was actively encouraged. Users from the Neonatal Parent Group and the Maternal and Fetal Health Research Centre Parent Group, both based at Central Manchester NHS Foundation Trust, provided advice on Participant Information Leaflets, diagrammatic instructional leaflets and the recruitment and consent processes. Advice
and support for the proposed study was also received from the National Eczema Society. Representatives from parent groups and the National Eczema Society were voting members of the Trial Steering Committee.

5.2.3 Consent

Informed consent is a key principle of good ethical practice (Department of Health 2005). ICH GCP (1.28) asserts that informed consent is

“A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate.”

A baby is not able to consent to participate in a study for themselves; a personal or legal representative must consent for them, usually a parent. It could be argued that if a baby becomes upset by a procedure, then this should be respected as a valid refusal of consent (Twycross and Gibson 2007). For the OBSeRvE study this aspect was considered in detail by the researcher. All of the probes used for assessment were pre-tested on the researcher to ensure that she could guarantee with honesty to parents that the assessment would not hurt the baby. After a full detailed explanation of the probes being used, if the parents were still concerned, an offer could be made to demonstrate their use on the parents for reassurance. This offer was never required as the explanation was always sufficient. If the baby was upset during the procedure, the assessment was stopped until the baby was settled. A cuddle or feed was suggested. The procedure took as long as was necessary to ensure the comfort of the baby and parent(s). Consent was not a single procedure. It was revisited with participants throughout the study period (Medical Research Council 2004). If a parent requested to withdraw at any point in the study, this request was respected (RCPCH: Ethics Advisory Committee 2000).

New parents may be vulnerable from the experience of having just given birth but also from being in a strange and medical environment. Consent to take part in a study may be given due to a feeling of obligation to those caring for them (Boomgaarden et al. 2003). Parents may feel that if they do not consent to take part, their care will be adversely affected (Edwards and McNamee 2005). Conversely they may perceive receiving better care if they become part of a study (Burgess et al. 2003). Parents may believe that by taking part in research their baby will receive the best treatment; that the intervention will be better than standard treatment (Macklin 1999). The researcher was aware of this and allocated sufficient time to explain the research in full, with time for questions and time for consideration on whether to participate (Yeung 2007). The amount of information given was important. Parents who feel they have received too much or too little information assess the risks and benefits of the study more negatively than those who feel they have received the right level of information (Tait et al. 2004).
Ample time should be given (appropriate to the nature of the study) to consider participation in research (Medical Research Council 1998; ICH 1996). Within the OBSeRvE study, recruitment and consent occurred within 72 hours of birth. During this period of time when parents were first introduced to the study, they were potentially anxious about the well-being of their new baby. Parents are likely to assess risks and benefits more negatively if they have insufficient time or privacy to consider their decision (Hoehn et al. 2005). To attempt to mitigate this issue, an antenatal summary Participant Information Leaflet was provided to pregnant women between 20 and 28 weeks gestation. This was only likely to inform a proportion of the potential target population but was put in place to assess its value for a future study. A poster was displayed in antenatal clinics (hospital and community), the scan department and the wards. This would also only inform those who had seen it and read it. Furthermore, it would not provide in-depth information on which to make an informed decision. There would remain a large proportion of mothers who were told about the trial for the first time on presentation to the postnatal ward following birth. The researcher approached eligible new mothers on the ward after obtaining permission from the clinical team. This eliminated the possibility of approaching any mothers who were the subject of social care proceedings, or had experienced perinatal loss. Mothers were given verbal and written information about the study and given as much time as they needed to consider participation, with the condition that this was at least one hour.

The issue of parental responsibility was considered. The Children Act (1989) states that a mother automatically has responsibility for her child; a father only has parental responsibility under certain circumstances. Others with parental responsibility include legally appointed guardians, or those with residence or care orders, including local authorities. Parental responsibility carries increased complexity when it involves mothers under the age of sixteen, adoption, foster care, lesbian/gay parents, step-parents, grandparents, or carers. The researcher had to be certain that consent was obtained from the person with parental responsibility (Medical Research Council 2004). It could be difficult to assess family circumstances. It was also possible that one parent may consent but the absent parent may not wish their child to take part. If the researcher believed that consent was uncertain, then the baby was not recruited to the study. Issues of parental responsibility were minimised by excluding those mothers who were less than 16 years of age, and those babies who were likely to be placed in foster care or adopted.

5.2.4 Confidentiality

All data were collected, maintained and stored to comply with the principles of Good Clinical Practice (ICH 1996). The participants were advised that data would be held
securely, and that all personal information would be kept strictly confidential. All participants were given a unique study number. Identifying personal details were kept separately from data in a locked cabinet within a locked room at the University. Only the researcher had access to the locked cabinet. Pseudonyms, chosen by the participants themselves, were used for the purposes of verbatim quotations. Audio recordings were destroyed after transcription and analysis in the presence of the research team. Any references to identifying information within transcripts such as location or partners name were removed. Audio recordings were uploaded to a secure server for transcription by a reputable transcription service company used previously by the University.

All electronic data were stored on the University secure server accessed via a password-protected University computer and identified by unique study number only. The ATR-FTIR spectroscopy data were stored on the University secure server accessed via a password protected University laptop with Trucrypt software. In cases where there was no internet connection, any outcome data stored on the university laptop at point of clinical assessment were transferred to the University secure server as soon as possible. Data stored in this way were identified by unique study number only.

The researcher followed ethical and legal practice as required by the confidentiality policies of Central Manchester NHS Foundation Trust and The University of Manchester and in accordance with the Data Protection Act, 1998. All data collected for the OBSeRvE study was used only for the purposes for which it was collected.

The University of Manchester policy on storage of personal data is five years after the last publication of the study or for ten years, whichever is the greater. Consent forms will be retained as essential documents, but items such as contact details will be deleted as soon as they are no longer needed. However this study may provide data relevant to public health (atopic eczema) and a small part of the research is based on clinical samples therefore the data will be stored for fifteen years.

5.2.5 Setting

Participants were recruited from St. Mary’s Hospital, Central Manchester NHS Foundation Trust. St. Mary’s is a large tertiary hospital with a high birth rate and a diverse ethnic community. St. Mary’s also has a large Fetal Medicine Unit and is the main referral centre for complex pregnancies across Greater Manchester and further afield. As such, the inclusion and exclusion criteria were carefully framed so that only healthy newborn term babies were included in the OBSeRvE study.

The clinical room that was allocated for use by the researcher for clinical assessments was on the 5th floor of St. Mary’s Hospital in the Maternal and Fetal Health Research
Centre. The postnatal wards from which recruitment took place were on the 2\textsuperscript{nd} and 3\textsuperscript{rd} floors of the hospital. This created an issue for newly delivered mothers and babies transferring from one area to the other. The researcher always first confirmed with the clinical midwife caring for the mother and baby if both were well and able to attend the assessment before escorting them away from the ward. A wheelchair, a baby resuscitation trolley, and adult and baby resuscitation equipment was kept on the 5\textsuperscript{th} floor in case of emergency. Furthermore, the researcher, research technician and research midwives attended adult and paediatric resuscitation training prior to the commencement of the study. Only one participant required use of the wheelchair to return to the ward, and no mothers or babies required any form of resuscitation.

There was a burden on parents to bring their baby to St. Mary’s hospital for the follow-up assessment. This was unavoidable as the ATR-FTIR equipment was not portable. Travel expenses were paid to participants, together with a voucher to remunerate and thank participants for their time. If it was not possible for parents to return to the hospital, a home visit was offered in the final phase of the study to assess the feasibility of providing this service in a future study. Participants were made aware that they were free to withdraw from the study at any time without giving a reason, and without repercussion to care.

Those participants who were asked to take part in the qualitative interviews chose the time and place for the interview, including the opportunity to interview by telephone if desired. The majority chose to have the interview at home (n=14), with a minority choosing a telephone interview (n=6). An identical format for the interview was maintained through the use of an interview schedule. Allowing parents to determine the place of the interview addressed the issue of any power imbalance; the researcher was a guest in the participant’s home so the power rested with the participant. This eliminated any negative effects on the conversation which can occur if the interview takes place in the hospital.

5.3 Conclusion

Ethical principles were considered from the study design stage through to completion of the study. Non-adherence to ethical standards affects the results and credibility of a study. Ethical considerations were re-visited throughout the study to ensure that participants were protected from harm. Recruitment and consent processes were particularly reviewed to assess the optimal methods for a future study. The ethical considerations of a clinical trial involving babies are immense. The guidelines and research governance framework exist to ensure that medical research protects the well-being of participants. Research involving babies is vital to ensuring development and progression in neonatal care. In view of the vulnerability of this population, ethical aspects were meticulously considered and adhered to.
CHAPTER SIX: RESULTS

6.1 Introduction to the chapter

This chapter is presented in three parts. Part one provides a full report of the results of the pilot randomised controlled trial, as stated in the trial protocol. This includes baseline characteristics of the study sample, the primary outcome data results for lipid lamellae structure and trans-epidermal water loss, and the secondary outcome data results for stratum corneum hydration, skin surface pH and erythema / clinical observation of the skin. Part two presents the results of the questionnaire data including alternative product use, treatment compliance and health professional consultations or medication prescriptions. Part three completes the chapter with the results of the data from the nested qualitative component. A summary of the study findings concludes the chapter.

CHAPTER SIX PART ONE: Randomised controlled trial clinical data results

6.2 Overview

The OBSeRvE study is a pilot study. The main analyses are descriptive, involving the estimation of recruitment rates, attrition rates, non-compliance rates, means and standard deviations of primary and secondary outcomes by group at baseline and 4 weeks, and 95% confidence intervals for differences of means of primary and secondary outcomes between groups at 4 weeks. Primary and secondary outcomes at 4 weeks are also compared by group, adjusted for baseline values using analysis of covariance (ANCOVA), suggested to have greater power in an RCT comparing treatments where there are data at baseline and post-treatment follow-up (Petrie and Sabin 2009). Inferential results have been reported with care: the study was not powered to detect significant differences, as the main aim was to assess proof of concept, feasibility and inform a full-scale trial. It would not be appropriate to interpret any significant results as conclusive evidence of effect, as no power calculation was performed (Lancaster et al. 2004). When the sample size is small there is an increased potential for Type I and Type II errors as the sample is more likely to be unrepresentative of the population. Type I errors occur where the null hypothesis is rejected in error. Type II errors occur when clinically important effects are missed as the statistical power is reduced due to the small sample; statistical significance is consequently not evident.

Data were double-entered into IBM SPSS Statistics version 20 by the researcher in preparation for data analysis, with the two data files cross-checked for errors in Microsoft Excel by the statistician. There were two data files: one for clinical data and one for questionnaire data. The accuracy of the data entry is shown in table 6.1. All corrections were made by the researcher after checking the original documentation in the participant’s paper records. It was intended that a second person (Primary Supervisor) would make
any decisions on errors that could not easily be rectified. All errors were straight forward to rectify and a second person was not necessary.

All data analysis was completed by the researcher using IBM SPSS Statistics version 22 whilst remaining blind to randomisation. As the data had to be recorded inclusive of study arm for analysis, continued blinding was achieved via an independent research midwife allocating the groups by random to numbers 1, 2 and 3. The identification of these groups were recorded by the midwife as 1=Oil Y, 2=Oil X and 3=No oil. The recorded information was sealed in two separate envelopes, signed by the research midwife and stored by the two members of staff at the University who were independent of the study and were also holding the sealed envelopes which contained the information of which oil was X and which was Y. Any analysis which could have unblinded the researcher was run in IBM SPSS Statistics version 22 but the results output file was immediately passed to the statistician for review without being viewed by the researcher. This included sebum content in the skin from the spectroscopy data and the compliance data. The results were presented to the OBSeRvE Trial Steering Committee on 4th November 2014. The identification of the treatment arms was revealed following presentation of the blinded data analysis; Oil X was sunflower oil (group 2) and oil Y was olive oil (group 1).

<table>
<thead>
<tr>
<th>Date</th>
<th>Number of errors</th>
<th>Error rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25th August 2014</td>
<td>141 errors (out of 18170)</td>
<td>0.74%</td>
</tr>
<tr>
<td>4th September 2014</td>
<td>1 error</td>
<td>0.00%</td>
</tr>
<tr>
<td>5th September 2014</td>
<td>0 errors</td>
<td>0.00%</td>
</tr>
<tr>
<td>Questionnaire Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25th August 2014</td>
<td>471 errors (out of 21045)</td>
<td>2.24%</td>
</tr>
<tr>
<td>8th September 2014</td>
<td>5 errors</td>
<td>0.00%</td>
</tr>
<tr>
<td>8th September 2014</td>
<td>0 errors</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

Table 6.1: Data entry error statistics

6.3 Flow of participants through the study

In total, 1037 women were approached by the researcher and 115 consented to participate; 318 declined to take part (30.7%) and 603 were not recruited for other reasons (58.2%). Overall, the recruitment rate was 11.1%. On average four babies were recruited each week over three available working days. Data were collected between 11th September 2013 and 23rd July 2014. It was intended that 100 babies were recruited to allow for 30 per study arm and 10% loss to follow-up (Lancaster et al. 2004). Loss to follow-up was higher than anticipated and the target sample was increased to 120 to endeavour to collect data for 30 babies per group. Figure 6.1 provides a graphical illustration of how the actual recruitment compared to what was anticipated. The
CONSORT (Moher et al. 2010) recruitment flow chart is illustrated in figure 6.2, which includes detail of reasons for declining and loss to follow-up.

![Figure 6.1: Target recruitment: original, revised and actual](image)

6.3.1 Recruitment

Of the 4085 mother and baby dyads that were assessed for eligibility, 2886 were deemed to be ineligible (exclusion rate 70.6%). Of the remaining 1199, 162 could not be approached as the baby could not leave the postnatal ward due to being cold or poor feeding (n=52), the clinical midwife was unavailable to obtain permission to approach the woman (n=91), or it was not possible to arrange an interpreter (n=19). The remaining 1037 women were approached to ascertain if they were willing for their baby to take part in the study. A total of 318 women declined to participate. If they offered a reason for this, the information was recorded: some had pre-conceived skincare strategies (n=55), some felt it would be too much to commit to (n=97), or their family would not support them (n=8). There were 158 women who did not give a reason. A further 604 mother and baby pairs were not recruited; the majority for logistical reasons (n=521) such as the mother being asleep or feeding when the researcher came to the ward, the mother having visitors or being provided with clinical care, or because the investigator was undertaking assessments on recruited babies and was not able to visit the ward to recruit at the same time. Other reasons for non-participation included being discharged before the researcher had arrived back after the time provided for consideration (n=78) or not having a randomisation midwife available (n=5). The remaining 115 mothers agreed for their babies to take part in the study.
ENROLMENT

Assessed for eligibility (n=4085)

Excluded (n=3970)
- Not meeting inclusion criteria (n=2886)
- Declined to participate (n=318; see below)
- Other reasons (n=766; see below)

Mothers of eligible babies remaining (n=1,199)

ALLOCATION

Babies recruited (n=115)

Declined (n=318)
- Product preference (n=34)
- Water preference (n=21)
- Too much to commit to (n=97)
- Family would not support (n=8)
- No reason given (n=158)

Other reasons (n=766)
Approached (n=604):
- Discharged (n=78)
- No randomisation midwife (n=5)
- Logistical reasons* (n=521)
Not approached (n=162):
- Could not arrange interpreter (n=19)
- Clinical midwife unavailable (n=91)
- Baby could not leave ward (n=52)

Baseline assessment (n=38)
- Olive Oil (n=38)
- Sunflower Oil (n=38)
- No Oil (n=39)

Loss to follow-up (n=11)
- Follow-up assessment at 4 weeks (n=27)
Excluded from analysis (n=0)

Baseline assessment (n=38)
- Follow-up assessment at 4 weeks (n=30)
Excluded from analysis (n=0)

Baseline assessment (n=39)
- Follow-up assessment at 4 weeks (n=35)
Excluded from analysis (n=0)

FOLLOW-UP

ENROLMENT

ALLOCATION

ANALYSIS

*Mum asleep/feeding/had visitors/clinical care provision/investigator unable to return as conducting assessments

Figure 6.2: CONSORT (Moher et al. 2010) recruitment flow chart
6.3.2 Loss to follow-up

Of the 115 babies whose parents consented to take part, baseline data were collected for all of these. Twenty-three participants were lost to follow-up. These participants either could not be contacted (n=11) or had asked to be withdrawn and did not wish to attend for follow-up assessment (n=12). Total loss to follow-up was 20%.

Withdrawals from the study included:
- one participant whose paediatrician advised withdrawal due to the baby developing infantile eczema,
- one baby who was ill,
- two babies who were readmitted for jaundice and phototherapy treatment,
- eight babies whose parents advised they did not want to continue in the study, and
- eleven babies who did not attend the follow-up appointment and who could not be contacted.

Figure 6.2 illustrates the number lost from each study arm. Consent was obtained to use the baseline data. Reasons given for withdrawing included the parents finding being in the study “too much” (n=6), not using the treatment and not wanting to start (n=1), and starting phototherapy or other treatments affecting the study treatment sites (n=4). One parent did not give a reason for withdrawing. Figure 6.3 illustrates the monthly recruitment split between those participants retained and those lost to follow-up. The illustration clearly highlights the seasonal impact of those who were recruited in November but did not return for follow-up assessment in December. If these participants had returned the attrition rate would have been 13%, much closer to the anticipated loss to follow-up of 10%.

6.4 Baseline Characteristics

Baseline characteristics were recorded during the screening and assessment process, prior to randomisation. During the analysis phase these characteristics were explored descriptively across the three study arms to ensure that the groups were homogenous at baseline (tables 6.2 and 6.3). Table 6.2 summarises the characteristics of the mothers in the study, by study arm. The randomisation process provided a balance of characteristics across the three groups. The mean maternal age for the whole sample was 29.3 years (SD 5.5; range 18 - 41). There were a similar number of primiparous to multiparous women across the groups. One difference in ethnicity was evident; the number of mothers defined as ‘White Other’ in the sunflower oil group (n=9) was higher than the other groups (olive oil n=1; no oil n=3), however when the numbers were added together for White British and White Other, these were balanced across the three groups.
Table 6.2: Maternal baseline characteristics by randomised treatment assignment

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Olive Oil (n=38)</th>
<th>Sunflower Oil (n=38)</th>
<th>No Oil (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Mothers Age, years (SD)</td>
<td>28.4 (4.7)</td>
<td>30.5 (5.9)</td>
<td>28.8 (5.7)</td>
</tr>
<tr>
<td>Parity, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>22 (58)</td>
<td>21 (55)</td>
<td>19 (49)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>16 (42)</td>
<td>17 (45)</td>
<td>20 (51)</td>
</tr>
<tr>
<td>Number of children, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>22 (58)</td>
<td>21 (55)</td>
<td>19 (49)</td>
</tr>
<tr>
<td>Two</td>
<td>12 (32)</td>
<td>10 (26)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Three</td>
<td>3 (8)</td>
<td>2 (5)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Four</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Five</td>
<td>0 (0)</td>
<td>3 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mother Ethnicity, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White British</td>
<td>25 (66)</td>
<td>21 (55)</td>
<td>26 (68)</td>
</tr>
<tr>
<td>White Other</td>
<td>1 (3)</td>
<td>9 (24)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Pakistani</td>
<td>5 (13)</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>White Irish</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mixed Race</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Black African</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Chinese</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Asian Other</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Place of Birth, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Hospital</td>
<td>36 (95)</td>
<td>38 (100)</td>
<td>37 (95)</td>
</tr>
<tr>
<td>Other Hospital</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Home</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Mode of Birth, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>33 (87)</td>
<td>29 (76)</td>
<td>33 (85)</td>
</tr>
<tr>
<td>Elective Caesarean Section</td>
<td>0 (0)</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Emergency Caesarean Section</td>
<td>5 (13)</td>
<td>6 (16)</td>
<td>5 (13)</td>
</tr>
</tbody>
</table>

Figure 6.3: Monthly recruitment split by retention and loss to follow-up
Table 6.3 provides a summary of the baseline characteristics for babies in the study, by study arm. Again the randomisation process provided balanced groups at baseline. The mean gestational age for the total sample was 40.0 weeks (SD 1.2; range 37.4 - 42.3), and the mean birthweight for the total sample was 3405g (SD 452; range 2400 – 4370).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Olive Oil (n=38)</th>
<th>Sunflower Oil (n=38)</th>
<th>No Oil (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby Ethnicity, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• White British</td>
<td>20 (53)</td>
<td>19 (50)</td>
<td>23 (59)</td>
</tr>
<tr>
<td>• White Other</td>
<td>1 (3)</td>
<td>6 (16)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>• Indian</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>• Pakistani</td>
<td>4 (11)</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>• White Irish</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Mixed</td>
<td>8 (21)</td>
<td>7 (18)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>• Black Caribbean</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Black African</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>• Chinese</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Asian Other</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>• Other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Family history of Atopic Eczema, N (%)</td>
<td>11 (29)</td>
<td>13 (34)</td>
<td>13 (33)</td>
</tr>
<tr>
<td>Mean Gestation, weeks (SD)</td>
<td>39.2 (1.3)</td>
<td>39.6 (1.3)</td>
<td>39.9 (1.1)</td>
</tr>
<tr>
<td>Mean Birth Weight, grams (SD)</td>
<td>3322 (410)</td>
<td>3536 (475)</td>
<td>3359 (450)</td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>19 (50)</td>
<td>22 (58)</td>
<td>25 (64)</td>
</tr>
<tr>
<td>• Female</td>
<td>19 (50)</td>
<td>16 (42)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Vernix, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Absent</td>
<td>37 (97)</td>
<td>37 (97)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>• Minimal</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>First bath prior to randomisation, N (%)</td>
<td>1 (3)</td>
<td>7 (18)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>• Yes</td>
<td>1 (3)</td>
<td>7 (18)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>• Products used during bath</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Feeding Method at birth, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Breast</td>
<td>26 (68.4)</td>
<td>26 (68.4)</td>
<td>27 (69.2)</td>
</tr>
<tr>
<td>• Bottle</td>
<td>11 (28.9)</td>
<td>6 (15.8)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>• Combined</td>
<td>1 (2.6)</td>
<td>6 (15.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Feeding method at 4 weeks, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Breast</td>
<td>9 (32.1)</td>
<td>11 (37.9)</td>
<td>12 (34.3)</td>
</tr>
<tr>
<td>• Bottle</td>
<td>14 (50.0)</td>
<td>9 (31.0)</td>
<td>15 (42.9)</td>
</tr>
<tr>
<td>• Combined</td>
<td>5 (17.9)</td>
<td>9 (31.0)</td>
<td>8 (22.9)</td>
</tr>
</tbody>
</table>

Table 6.3: Neonatal baseline characteristics by randomised treatment assignment

Altogether, 32% of babies had a family history of atopic eczema; stratification was implemented in the randomisation process to help ensure that these babies were evenly distributed across the three groups and this was achieved. Although more babies in the sunflower oil group were bathed prior to baseline assessment, only two of these used a product and this was balanced with the other groups. There were no differences in ambient conditions (room humidity and room temperature) across the groups for each visit (table 6.4).

Overall, comparison of the baseline characteristics for both mothers and babies were shown to be balanced across the three study arms following randomisation.
6.5 Assessments during the treatment period

Babies were not seen by the researcher during the treatment period; however, mothers were given direct access via mobile phone to the researcher 24 hours a day, seven days a week, so that any concerns over skin condition could be immediately raised. No calls were received by the researcher to report any adverse events or reactions.

In addition to this on-call facility, the researcher rang the mother once a week to conduct a telephone questionnaire while remaining blinded to the group to which they had been randomised. Parents were reminded not to disclose which group they were in at the beginning of the phone call. One of the questions asked related to skin concerns. One adverse reaction was documented in the study which was identified during this question. The questionnaire data are presented in part two of this chapter.

6.6 Comparison of main outcomes

Details of the main outcomes being explored are provided in chapter four. These include the change in spectral profile of the lipid lamellae (ATR-FTIR), trans-epidermal water loss (TEWL), stratum corneum hydration, skin surface pH and clinical observations. Table 6.5 illustrates the number of measurements of each variable collected. Numbers differ across the variables where an equipment breakdown or home visit occurred. Other outcomes of interest were recruitment and attrition rates which are detailed in sections 6.3.1 and 6.3.2 of this chapter, and treatment / product compliance which is presented in section 6.6.5 with the more detailed questionnaire data being covered in part two of this chapter. The results from the stratification of family history of atopic eczema are provided in section 6.6.3, together with presentation of the results by ethnicity in section 6.6.4. Maternal satisfaction, also a secondary outcome, is covered separately in the qualitative results presented in part three of this chapter.

<table>
<thead>
<tr>
<th></th>
<th>Olive oil group Mean (SD)</th>
<th>Sunflower oil group Mean (SD)</th>
<th>No oil group Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Room Condition</td>
<td>(n=38)</td>
<td>(n=38)</td>
<td>(n=39)</td>
</tr>
<tr>
<td>• Temperature</td>
<td>22.71 (0.49)</td>
<td>22.73 (0.51)</td>
<td>22.89 (0.38)</td>
</tr>
<tr>
<td>• Humidity</td>
<td>44.68 (4.76)</td>
<td>44.68 (4.32)</td>
<td>45.63 (5.12)</td>
</tr>
<tr>
<td>4 week Room Condition</td>
<td>(n=27)</td>
<td>(n=30)</td>
<td>(n=35)</td>
</tr>
<tr>
<td>• Temperature</td>
<td>23.26 (0.62)</td>
<td>22.90 (0.76)</td>
<td>23.15 (0.56)</td>
</tr>
<tr>
<td>• Humidity</td>
<td>43.90 (5.23)</td>
<td>44.68 (7.47)</td>
<td>43.63 (5.56)</td>
</tr>
</tbody>
</table>

*Table 6.4: Room temperature and humidity*
Table 6.5: Number of measurements taken for each variable at baseline and follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olive oil (n=38)</th>
<th>Sunflower oil (n=38)</th>
<th>No oil (n=39)</th>
<th>Olive oil (n=27)</th>
<th>Sunflower oil (n=30)</th>
<th>No oil (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR-FTIR¹</td>
<td>38</td>
<td>38</td>
<td>38*</td>
<td>26*</td>
<td>28**</td>
<td>35</td>
</tr>
<tr>
<td>TEWL²</td>
<td>38</td>
<td>38</td>
<td>39</td>
<td>27</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Corneometer® (Hydration)</td>
<td>38</td>
<td>38</td>
<td>39</td>
<td>27</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Skin pH meter</td>
<td>38</td>
<td>37*</td>
<td>37*</td>
<td>26*</td>
<td>29*</td>
<td>35</td>
</tr>
<tr>
<td>Mexameter® (Erythema)</td>
<td>38</td>
<td>38</td>
<td>39</td>
<td>26*</td>
<td>29*</td>
<td>35</td>
</tr>
<tr>
<td>Clinical observations</td>
<td>38</td>
<td>38</td>
<td>39</td>
<td>27</td>
<td>30</td>
<td>35</td>
</tr>
</tbody>
</table>

*equipment failure / **home visit
¹Attenuated Total Reflectance Fourier Transform Infra-Red Spectroscopy
²Trans-epidermal water loss

6.6.1 Primary Outcomes

6.6.1.1 Change in spectral profile of the lipid lamellae

Table 6.6 summarises and compares the total lipids within the stratum corneum at baseline and follow-up, by randomised treatment arm, pre and post tape-stripping for all three body sites (left forearm, abdomen and left thigh). Table 6.7 summarises and compares the differences in lipid lamellae structure (lipid chain conformation and lateral packing) at follow-up from baseline by randomised treatment arm, pre and post tape-stripping for all three body sites.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olive oil (n=38) Mean (SD)</th>
<th>Sunflower oil (n=38) Mean (SD)</th>
<th>No oil (n=39) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline pre tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>2.45 (1.73)</td>
<td>2.55 (2.24)</td>
<td>2.15 (0.99)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>4.13 (2.06)</td>
<td>4.43 (1.80)</td>
<td>4.38 (2.22)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>2.94 (1.56)</td>
<td>2.70 (1.20)</td>
<td>2.78 (1.15)</td>
</tr>
<tr>
<td>Baseline post tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>2.27 (1.35)</td>
<td>2.24 (1.85)</td>
<td>1.91 (0.89)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>4.01 (2.15)</td>
<td>4.11 (1.72)</td>
<td>3.86 (1.50)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>2.61 (1.24)</td>
<td>2.43 (1.14)</td>
<td>2.65 (1.16)</td>
</tr>
<tr>
<td>Follow-up pre tape-stripping</td>
<td>(n=26)</td>
<td>(n=28)</td>
<td>(n=35)</td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>4.05 (2.04)</td>
<td>4.26 (1.74)</td>
<td>2.82 (1.15)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>6.10 (2.36)</td>
<td>5.90 (2.00)</td>
<td>3.70 (1.86)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>4.62 (2.07)</td>
<td>4.58 (2.02)</td>
<td>2.62 (1.09)</td>
</tr>
<tr>
<td>Follow-up post tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>2.91 (0.93)</td>
<td>3.09 (0.78)</td>
<td>2.64 (0.97)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>4.90 (1.87)</td>
<td>4.27 (1.74)</td>
<td>3.41 (1.33)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>3.44 (1.20)</td>
<td>3.46 (1.44)</td>
<td>2.43 (0.72)</td>
</tr>
</tbody>
</table>

Table 6.6: Comparison of total lipids at baseline and follow-up from FTIR spectroscopy data
The ATR-FTIR spectroscopy data indicated that both oil groups contained a considerably higher proportion of lipids within the stratum corneum at follow-up, compared to the no oil group (table 6.6). All three treatment arms displayed improvement in lipid chain conformation and lateral packing over the 4 week treatment period (table 6.7 and 6.8). This is indicated by a shift in $v_{\text{asymCH}_2}$ COG to a lower wavenumber and an increase in the FWHM respectively. However the extent of this improvement was significantly reduced in the groups using olive oil and sunflower oil compared to the no oil group (table 6.7), suggesting that both oils impede the development of the lamellar lipid structures of the skin barrier from birth. There was a consistent difference between the three groups for both measures for all three sites pre tape-stripping, but the group effect was significant at only four of the six combinations post tape-stripping (table 6.8). The percentage of variance in the outcome explained by group (partial $\eta^2$) ranged from 5% to 34% pre tape-stripping compared with 3% to 22% post tape-stripping. The effect of family history of atopic eczema was not significant in any of the analyses and explained at most 3% of the variance. For the group using olive oil compared to no oil, there was a difference in lipid chain conformation and lateral packing both pre and post tape-stripping, suggesting a more persistent fluid-like (less ordered) state. For the group using sunflower oil compared to no oil, these differences occurred pre tape-stripping but were not so marked post-tape-stripping suggesting that the effects may be more restricted to the superficial layers of the stratum corneum. There were no significant differences between the two oil groups in lipid chain conformation or lateral chain packing.

The adjusted pairwise comparisons (tables 6.9 and 6.10) of differences from baseline to 4 weeks generally supported the results from the unadjusted difference scores illustrated in table 6.7, and the adjusted difference scores illustrated in table 6.8. One exception was post tape-stripping on the left forearm for lipid chain conformation, where the differences between the olive oil and the no oil groups was just significant using differences between ANCOVA adjusted means, and just failed to be significant using the unadjusted confidence intervals for the differences between means.

Some babies had substantially higher bulk water peaks in the spectral profile data and from a visual examination of the dataset these babies often had a greater birthweight. Correlation analysis was conducted to investigate any relationship between all of the variables with birthweight and/or gestational age. The correlation data are illustrated in table 6.11 for the primary outcome variables and table 6.18 for the secondary outcome variables.

There were a few significant values in the correlation data but only one for lipid chain conformation where correlation with birthweight was significant for the abdomen post tape-stripping ($r=-0.39$, $p=0.048$) in the olive oil study arm. There were a number of other variables which were arguably closer to significance than others: abdomen pre tape-
stripping for gestational age in the sunflower oil study arm \((r=-0.35, p=0.069)\); left thigh post tape-stripping in the sunflower oil study arm for birthweight \((r=0.36, p=0.072)\); and abdomen post tape-stripping in the no oil study arm for birthweight \((r=0.31, p=0.073)\). The largest correlation coefficient was \(r=-0.39\) and with correlations around 0.30 considered to be moderate, there was no clear pattern of correlations in the data. With regard to lateral lipid chain packing there were a number of significant values post tape-stripping: in the sunflower oil study arm, the measurement at the left thigh was significant for both birthweight \((r=-0.56, p=0.003)\) and gestational age \((r=-0.43, p=0.028)\); in the no oil study arm, the measurement at the abdomen \((r=-0.35, p=0.041)\) and left thigh \((r=-0.43, p=0.011)\) were both significant for birthweight. There was one other value which was arguably close to significance: left thigh pre tape-stripping in the sunflower oil study arm for birthweight \((r=-0.35, p=0.077)\). Again, there was no clear pattern of correlations.
<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>4 weeks Mean (SD)</th>
<th>Difference in means Mean (CI) (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olive oil</td>
<td>Sunflower oil</td>
<td>No oil</td>
</tr>
<tr>
<td></td>
<td>n=38</td>
<td>n=38</td>
<td>n=39</td>
</tr>
</tbody>
</table>

Lipid chain conformation (v<sub>COG</sub>CH<sub>2</sub> COG)

**Pre tape-stripping**

<table>
<thead>
<tr>
<th></th>
<th>Arm</th>
<th>Abdomen</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2851.72 (1.04)</td>
<td>2851.74 (0.51)</td>
<td>2851.45 (0.60)</td>
</tr>
<tr>
<td></td>
<td>2851.79 (0.70)</td>
<td>2851.82 (0.42)</td>
<td>2851.56 (0.67)</td>
</tr>
<tr>
<td></td>
<td>2851.79 (0.75)</td>
<td>2852.00 (0.74)</td>
<td>2851.74 (0.73)</td>
</tr>
<tr>
<td></td>
<td>2851.73 (0.51)</td>
<td>2851.89 (0.46)</td>
<td>2851.86 (0.64)</td>
</tr>
<tr>
<td></td>
<td>2851.96 (0.78)</td>
<td>2851.91 (0.68)</td>
<td>2851.91 (0.62)</td>
</tr>
<tr>
<td></td>
<td>2851.29 (0.66)</td>
<td>2851.16 (0.61)</td>
<td>2850.91 (0.73)</td>
</tr>
<tr>
<td></td>
<td>-0.02 [-0.48 to 0.44] (0.924)</td>
<td>0.14 [-0.19 to 0.47] (0.401)</td>
<td>0.21 [-0.30 to 0.71] (0.419)</td>
</tr>
<tr>
<td></td>
<td>0.53 [0.13 to 0.94] (0.011)*</td>
<td>1.02 [0.66 to 1.38] (&lt;0.001)*</td>
<td>1.29 [0.77 to 1.81] (&lt;0.001)*</td>
</tr>
<tr>
<td></td>
<td>0.56 [0.14 to 0.97] (0.010)*</td>
<td>0.88 [0.52 to 1.25] (&lt;0.001)*</td>
<td>1.08 [0.55 to 1.61] (&lt;0.001)*</td>
</tr>
</tbody>
</table>

**Post tape-stripping**

<table>
<thead>
<tr>
<th></th>
<th>Arm</th>
<th>Abdomen</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2851.61 (0.81)</td>
<td>2851.58 (0.58)</td>
<td>2851.33 (0.58)</td>
</tr>
<tr>
<td></td>
<td>2851.86 (1.20)</td>
<td>2851.67 (0.70)</td>
<td>2851.48 (0.86)</td>
</tr>
<tr>
<td></td>
<td>2851.50 (1.18)</td>
<td>2851.68 (0.64)</td>
<td>2851.30 (0.73)</td>
</tr>
<tr>
<td></td>
<td>2851.16 (0.70)</td>
<td>2851.49 (0.64)</td>
<td>2851.34 (0.74)</td>
</tr>
<tr>
<td></td>
<td>2851.08 (0.63)</td>
<td>2851.38 (0.59)</td>
<td>2851.38 (0.60)</td>
</tr>
<tr>
<td></td>
<td>2850.80 (0.60)</td>
<td>2850.85 (0.54)</td>
<td>2850.94 (0.74)</td>
</tr>
<tr>
<td></td>
<td>0.38 [-0.23 to 1.00] (0.214)</td>
<td>0.30 [-0.14 to 0.75] (0.179)</td>
<td>0.26 [-0.30 to 0.81] (0.357)</td>
</tr>
<tr>
<td></td>
<td>0.57 [-0.08 to 1.21] (0.083)</td>
<td>0.85 [0.46 to 1.23] (&lt;0.001)*</td>
<td>0.54 [0.03 to 1.05] (0.040)*</td>
</tr>
<tr>
<td></td>
<td>0.18 [-0.48 to 0.85] (0.582)</td>
<td>0.54 [0.15 to 0.93] (0.007)*</td>
<td>0.28 [-0.24 to 0.80] (0.279)</td>
</tr>
</tbody>
</table>

Lateral lipid chain packing (FWHM)

**Pre tape-stripping**

<table>
<thead>
<tr>
<th></th>
<th>Arm</th>
<th>Abdomen</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.76 (1.07)</td>
<td>5.86 (0.57)</td>
<td>5.89 (0.86)</td>
</tr>
<tr>
<td></td>
<td>5.71 (0.74)</td>
<td>5.79 (0.53)</td>
<td>6.21 (0.70)</td>
</tr>
<tr>
<td></td>
<td>5.64 (0.91)</td>
<td>5.68 (0.60)</td>
<td>5.69 (1.04)</td>
</tr>
<tr>
<td></td>
<td>6.15 (0.87)</td>
<td>6.31 (0.85)</td>
<td>6.03 (1.09)</td>
</tr>
<tr>
<td></td>
<td>5.84 (1.10)</td>
<td>5.90 (1.20)</td>
<td>5.80 (1.19)</td>
</tr>
<tr>
<td></td>
<td>6.57 (1.29)</td>
<td>6.95 (0.97)</td>
<td>6.63 (1.13)</td>
</tr>
<tr>
<td></td>
<td>0.09 [-0.56 to 0.73] (0.791)</td>
<td>0.35 [-0.19 to 0.89] (0.198)</td>
<td>0.37 [-0.35 to 1.10] (0.307)</td>
</tr>
<tr>
<td></td>
<td>-0.74 [-1.51 to 0.03] (0.058)</td>
<td>-0.92 [-1.40 to -0.44] (&lt;0.001)*</td>
<td>-0.92 [-1.73 to -0.10] (0.028)*</td>
</tr>
<tr>
<td></td>
<td>-0.83 [-1.55 to -0.11] (0.024)*</td>
<td>-1.27 [-1.82 to -0.73] (&lt;0.001)*</td>
<td>-1.29 [-2.12 to -0.46] (0.003)*</td>
</tr>
</tbody>
</table>

**Post tape-stripping**

<table>
<thead>
<tr>
<th></th>
<th>Arm</th>
<th>Abdomen</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.83 (1.09)</td>
<td>6.03 (0.68)</td>
<td>6.33 (0.95)</td>
</tr>
<tr>
<td></td>
<td>5.97 (1.07)</td>
<td>5.86 (0.77)</td>
<td>6.19 (0.86)</td>
</tr>
<tr>
<td></td>
<td>5.95 (0.97)</td>
<td>6.07 (0.75)</td>
<td>6.38 (0.87)</td>
</tr>
<tr>
<td></td>
<td>6.85 (1.21)</td>
<td>6.61 (1.12)</td>
<td>6.98 (1.29)</td>
</tr>
<tr>
<td></td>
<td>7.12 (1.02)</td>
<td>6.87 (1.21)</td>
<td>6.83 (1.54)</td>
</tr>
<tr>
<td></td>
<td>7.63 (0.90)</td>
<td>7.51 (0.97)</td>
<td>7.39 (1.08)</td>
</tr>
<tr>
<td></td>
<td>-0.47 [-1.26 to 0.32] (0.238)</td>
<td>-0.45 [-1.16 to 0.25] (0.205)</td>
<td>-0.08 [-0.96 to 0.80] (0.856)</td>
</tr>
<tr>
<td></td>
<td>-0.98 [-1.73 to -0.23] (0.011)*</td>
<td>-0.95 [-1.50 to -0.40] (0.001)*</td>
<td>-0.35 [-1.11 to 0.41] (0.360)</td>
</tr>
<tr>
<td></td>
<td>-0.52 [-1.21 to 0.18] (0.141)</td>
<td>-0.49 [-1.12 to 0.14] (0.121)</td>
<td>-0.27 [-0.93 to 0.40] (0.427)</td>
</tr>
</tbody>
</table>

*Table 6.7: Results at baseline and 4 weeks and pairwise comparisons of mean differences from baseline to 4 weeks between treatment groups for primary outcomes: lipid lamellae *p<0.05
<table>
<thead>
<tr>
<th></th>
<th>Pre tape-stripping</th>
<th>Post tape-stripping</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>df</td>
</tr>
<tr>
<td>Lipid chain conformation (ν \text{asym} CH₂ COG) (left forearm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>8.82</td>
<td>2, 82</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.94</td>
<td>1, 82</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>2.57</td>
<td>1, 82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid chain conformation (ν \text{asym} CH₂ COG) (abdomen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>20.95</td>
<td>2, 83</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.36</td>
<td>1, 83</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>0.29</td>
<td>1, 83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid chain conformation (ν \text{asym} CH₂ COG) (left thigh)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>21.15</td>
<td>2, 81</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.12</td>
<td>1, 81</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>0.05</td>
<td>1, 81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral lipid chain packing (FWHM) (left forearm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>3.86</td>
<td>2, 83</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.89</td>
<td>1, 83</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>0.09</td>
<td>1, 83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral lipid chain packing (FWHM) (abdomen)</td>
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<td></td>
</tr>
<tr>
<td>Group</td>
<td>11.79</td>
<td>2, 83</td>
</tr>
<tr>
<td>Baseline</td>
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<td>1, 83</td>
</tr>
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<td>1, 83</td>
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<td></td>
</tr>
<tr>
<td>Lateral lipid chain packing (FWHM) (left thigh)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>3.86</td>
<td>2, 81</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.11</td>
<td>1, 81</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>1.05</td>
<td>1, 81</td>
</tr>
</tbody>
</table>

*Table 6.8: ANCOVA results for primary outcome measures at 4 weeks: lipid lamellae*
Table 6.9: Pairwise comparisons at 4 weeks adjusted for baseline and family history of atopic eczema for primary outcome: lipid chain conformation

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Adjusted difference in means</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>-0.16</td>
<td>-0.48</td>
<td>0.17</td>
</tr>
<tr>
<td>Olive oil – No oil</td>
<td>0.45</td>
<td>0.14</td>
<td>0.77</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>0.61</td>
<td>0.31</td>
<td>0.92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Adjusted difference in means</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.02</td>
<td>-0.29</td>
<td>0.33</td>
</tr>
<tr>
<td>Olive oil – No oil</td>
<td>0.83</td>
<td>0.53</td>
<td>1.13</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>0.81</td>
<td>0.52</td>
<td>1.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Adjusted difference in means</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>-0.06</td>
<td>-0.43</td>
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<td>Olive oil – No oil</td>
<td>0.96</td>
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<td>Sunflower oil – No oil</td>
<td>1.01</td>
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<td>1.36</td>
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<table>
<thead>
<tr>
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<th>95% CI</th>
<th>p-value</th>
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<td>0.03</td>
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<td>Sunflower oil – No oil</td>
<td>0.30</td>
<td>-0.03</td>
<td>0.63</td>
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<th>95% CI</th>
<th>p-value</th>
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<td>Olive oil – No oil</td>
<td>0.67</td>
<td>0.37</td>
<td>0.98</td>
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<tr>
<td>Sunflower oil – No oil</td>
<td>0.54</td>
<td>0.24</td>
<td>0.83</td>
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<th>95% CI</th>
<th>p-value</th>
</tr>
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<td>Olive oil – Sunflower oil</td>
<td>-0.04</td>
<td>-0.44</td>
<td>0.35</td>
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<tr>
<td>Olive oil – No oil</td>
<td>0.39</td>
<td>0.02</td>
<td>0.76</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>0.44</td>
<td>0.07</td>
<td>0.81</td>
</tr>
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Table 6.10: Pairwise comparisons at 4 weeks adjusted for baseline and family history of atopic eczema for primary outcome: lipid lateral chain packing

<table>
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<tr>
<th>Comparison</th>
<th>Adjusted difference in means</th>
<th>95% CI</th>
<th>p-value</th>
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<tr>
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<td>Lower</td>
<td>Upper</td>
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<tr>
<td>Lateral lipid chain packing (FWHM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre tape-stripping (left forearm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.29</td>
<td>-0.32</td>
<td>0.91</td>
</tr>
<tr>
<td>Olive oil – No oil</td>
<td>-0.48</td>
<td>-1.08</td>
<td>0.10</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>-0.79</td>
<td>-1.36</td>
<td>-0.21</td>
</tr>
<tr>
<td>Lateral lipid chain packing (FWHM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre tape-stripping (abdomen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.38</td>
<td>-0.15</td>
<td>0.91</td>
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<td>Olive oil – No oil</td>
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</tr>
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<td>Sunflower oil – No oil</td>
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<td>-0.69</td>
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<td>Lateral lipid chain packing (FWHM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre tape-stripping (left thigh)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.25</td>
<td>-0.38</td>
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<td>-0.82</td>
<td>-1.43</td>
<td>-0.21</td>
</tr>
<tr>
<td>Lateral lipid chain packing (FWHM)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Post tape-stripping (left forearm)</td>
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<td></td>
<td></td>
</tr>
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<td>Olive oil – Sunflower oil</td>
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<td>-0.86</td>
<td>0.28</td>
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<td>Olive oil – No oil</td>
<td>-0.79</td>
<td>-1.33</td>
<td>-0.25</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>-0.50</td>
<td>-1.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Lateral lipid chain packing (FWHM)</td>
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<tr>
<td>Post tape-stripping (abdomen)</td>
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<tr>
<td>Olive oil – Sunflower oil</td>
<td>-0.33</td>
<td>-0.92</td>
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<td>Olive oil – No oil</td>
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<td>-0.36</td>
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<td>Sunflower oil – No oil</td>
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<td>-0.04</td>
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<tr>
<td>Lateral lipid chain packing (FWHM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post tape-stripping (left thigh)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.13</td>
<td>-0.58</td>
<td>0.85</td>
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</tr>
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<td>Sunflower oil – No oil</td>
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<td>-1.18</td>
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</tr>
<tr>
<td></td>
<td>Olive Oil</td>
<td>Sunflower Oil</td>
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</tr>
<tr>
<td>------------------------</td>
<td>------------------------------------</td>
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<td></td>
<td>Birthweight Pearson (p-value)</td>
<td>Gestational Age Pearson (p-value)</td>
<td>Birthweight Pearson (p-value)</td>
</tr>
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<td></td>
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<td>Gestational Age Pearson (p-value)</td>
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<tr>
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<tr>
<td>TEWL</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>0.39 (0.047)</td>
<td>0.30 (0.133)</td>
<td>0.08 (0.687)</td>
</tr>
<tr>
<td></td>
<td>-0.43 (0.019)</td>
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<td>Abdomen</td>
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</tr>
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<td>0.03 (0.885)</td>
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<tr>
<td>Left thigh</td>
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<tr>
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<td>-0.07 (0.735)</td>
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<td>-0.13 (0.451)</td>
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<td>Post tape-stripping</td>
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<tr>
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<td>0.17 (0.422)</td>
<td>0.38 (0.070)</td>
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</tr>
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</tr>
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<td>0.12 (0.573)</td>
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</tr>
<tr>
<td>Left thigh</td>
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<td>0.42 (0.036)</td>
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</tr>
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<td>0.10 (0.631)</td>
<td>0.09 (0.606)</td>
<td>-0.06 (0.747)</td>
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<td>Lipid chain conformation (ν_{\text{sym}}CH_{2} COG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>0.03 (0.883)</td>
<td>-0.06 (0.759)</td>
<td>0.28 (0.146)</td>
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<td>0.04 (0.831)</td>
<td>&lt;0.01 (0.983)</td>
<td>-0.09 (0.636)</td>
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<tr>
<td>Abdomen</td>
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</tr>
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<td>-0.35 (0.069)</td>
<td>0.14 (0.448)</td>
<td>-0.04 (0.843)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>-0.11 (0.595)</td>
<td>-0.03 (0.897)</td>
<td>0.26 (0.197)</td>
</tr>
<tr>
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<td>0.08 (0.695)</td>
<td>-0.02 (0.907)</td>
<td>0.06 (0.751)</td>
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<tr>
<td>Post tape-stripping</td>
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</tr>
<tr>
<td>Left forearm</td>
<td>0.15 (0.472)</td>
<td>-0.05 (0.821)</td>
<td>0.15 (0.439)</td>
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<td>-0.04 (0.836)</td>
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<td>-0.27 (0.120)</td>
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<td>Abdomen</td>
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<td>-0.29 (0.144)</td>
<td>0.31 (0.073)</td>
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<tr>
<td>Left thigh</td>
<td>0.13 (0.528)</td>
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<td>0.36 (0.072)</td>
</tr>
<tr>
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<td>0.27 (0.191)</td>
<td>-0.09 (0.663)</td>
<td>0.23 (0.190)</td>
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<td>Lateral lipid chain packing (FWHM)</td>
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</tr>
<tr>
<td>Pre tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>0.03 (0.904)</td>
<td>0.16 (0.444)</td>
<td>-0.16 (0.414)</td>
</tr>
<tr>
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<td>-0.08 (0.678)</td>
<td>-0.02 (0.896)</td>
<td>0.10 (0.570)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.08 (0.717)</td>
<td>0.06 (0.765)</td>
<td>-0.18 (0.356)</td>
</tr>
<tr>
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<td>0.24 (0.210)</td>
<td>-0.15 (0.406)</td>
<td>-0.24 (0.171)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>-0.01 (0.973)</td>
<td>0.19 (0.342)</td>
<td>-0.35 (0.077)</td>
</tr>
<tr>
<td></td>
<td>-0.17 (0.396)</td>
<td>0.12 (0.520)</td>
<td>-0.09 (0.629)</td>
</tr>
<tr>
<td>Post tape-stripping</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>-0.16 (0.434)</td>
<td>0.24 (0.236)</td>
<td>-0.13 (0.501)</td>
</tr>
<tr>
<td></td>
<td>0.03 (0.897)</td>
<td>0.13 (0.449)</td>
<td>0.04 (0.807)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.18 (0.391)</td>
<td>0.20 (0.323)</td>
<td>0.08 (0.687)</td>
</tr>
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<td></td>
<td>0.17 (0.410)</td>
<td>-0.35 (0.041)</td>
<td>0.01 (0.970)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>-0.14 (0.485)</td>
<td>0.12 (0.565)</td>
<td>-0.56 (0.003)</td>
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<td>-0.43 (0.028)</td>
<td>-0.43 (0.011)</td>
<td>-0.12 (0.493)</td>
</tr>
</tbody>
</table>

Table 6.11: Primary outcome variables correlations with birthweight and gestational age by study arm.
6.6.1.2 Trans-epidermal water loss (TEWL)

Table 6.12 shows the mean values and standard deviations at baseline and follow-up for TEWL, together with the confidence intervals and \( p \)-values for change in TEWL at follow-up from baseline. There were no significant differences in means for TEWL between the trial arms for all body sites at follow-up. The final section of table 6.12 (right-hand columns) provides the results for the mean difference in TEWL between groups at follow-up from baseline with no statistically significant results in differences between all three groups.

Table 6.13 illustrates the ANCOVA results for TEWL, which confirm that there were no significant differences in TEWL at follow-up adjusted for baseline measurements and family history of atopic eczema across groups. The ANCOVA results support the difference scores illustrated in table 6.12. The pairwise comparison analysis of differences from baseline to 4 weeks also agreed with these results (table 6.14).

In the correlation analysis illustrated in table 6.11, TEWL had the most significant values with particular frequency in the olive oil study arm. There were significant correlations pre tape-stripping for left forearm for birthweight \((r=0.39, p=0.047)\) and abdomen for gestational age \((r=0.43, p=0.025)\), and post tape-stripping for the left thigh for both birthweight \((r=0.45, p=0.023)\) and gestational age \((r=0.42, p=0.036)\). Left forearm post tape-stripping for gestational age was also arguably close to significance \((r=0.38, p=0.070)\). In the sunflower oil study arm, only the left forearm pre tape-stripping for gestational age was significant \((r=0.43, p=0.019)\), and in the no oil study arm only abdomen pre tape-stripping for gestational age was significant \((r=-0.38, p=0.023)\). Again, there was no clear evidence of a pattern apart from there being more significant values in the olive oil study arm, but this would need to be confirmed in further research.

6.6.2 Secondary Outcomes

6.6.2.1 Stratum corneum hydration

Table 6.15 provides the mean values and standard deviations at baseline and follow-up for stratum corneum hydration, together with confidence intervals and \( p \)-values for the differences between the groups at follow-up from baseline. The change in stratum corneum hydration at follow-up from baseline demonstrated that both the olive oil and sunflower oil groups were significantly better hydrated than the no oil group at all three body sites.

This was confirmed by the ANCOVA results adjusted for baseline measurements and family history of atopic eczema (table 6.16), where the group effect accounted for between 5% and 18% of the variance. Family history of atopic eczema showed no significant
impact. The pairwise comparisons of differences from baseline to 4 weeks (table 6.17) supported the results from the difference scores illustrated in table 6.15 for all treatment sites.

There was only one significant value in the correlation data (table 6.18) for stratum corneum hydration; abdomen in the olive oil study arm for birthweight ($r=-0.55$, $p=0.003$).

6.6.2.2 Skin surface pH

Table 6.15 also provides the mean values and standard deviations at baseline and follow-up, together with confidence intervals and $p$-values for the change at follow-up from baseline. There were no significant differences at follow-up for skin surface pH between the trial arms for all body sites, apart from the olive oil group compared to the no oil group for the left thigh ($p=0.007$). The result for the sunflower oil group compared to the no oil group for the left thigh was arguably closer to significance ($p=0.066$).

The ANCOVA results adjusted for baseline measurements and family history of atopic eczema (table 6.16) and the pairwise comparisons of differences from baseline to 4 weeks (table 6.17) found no significant differences between groups. This was inconsistent with regard to the unadjusted significant result shown above for the left thigh in the olive oil group compared to the no oil group, but this may be due to the adjustments made by ANCOVA in a small sample.

There was only one significant value in the correlation data (table 6.18) for skin surface pH; abdomen in the olive oil study arm for birthweight ($r=-0.42$, $p=0.031$).
<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>4 weeks Mean (SD)</th>
<th>Difference in means Mean [CI] (p-value)</th>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Olive oil</td>
<td>Sunflower oil</td>
<td>No oil</td>
<td>Olive oil</td>
<td>Sunflower oil</td>
<td>No oil</td>
</tr>
<tr>
<td>TEWL</td>
<td>n=38</td>
<td>n=38</td>
<td>n=39</td>
<td>n=27</td>
<td>n=30</td>
<td>n=35</td>
</tr>
<tr>
<td>Pre tape-stripping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>12.03 (2.44)</td>
<td>11.95 (2.29)</td>
<td>12.43 (2.24)</td>
<td>13.98 (2.98)</td>
<td>13.60 (2.75)</td>
<td>13.38 (3.02)</td>
</tr>
<tr>
<td></td>
<td>0.18 [-1.62 to 1.98] (0.841)</td>
<td>1.17 [-0.64 to 2.98] (0.200)</td>
<td>0.99 [-0.59 to 2.57] (0.214)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>11.25 (2.11)</td>
<td>10.78 (1.96)</td>
<td>11.61 (2.63)</td>
<td>12.00 (3.14)</td>
<td>11.00 (1.69)</td>
<td>11.45 (2.21)</td>
</tr>
<tr>
<td></td>
<td>0.06 [-1.27 to 1.40] (0.925)</td>
<td>0.68 [-0.82 to 2.18] (0.366)</td>
<td>0.62 [-0.67 to 1.91] (0.339)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td>13.16 (3.00)</td>
<td>13.15 (2.22)</td>
<td>13.62 (2.33)</td>
<td>13.40 (2.25)</td>
<td>12.60 (2.79)</td>
<td>13.38 (2.11)</td>
</tr>
<tr>
<td></td>
<td>0.54 [-0.89 to 1.97] (0.454)</td>
<td>0.52 [-0.89 to 1.93] (0.465)</td>
<td>-0.02 [-1.25 to 1.21] (0.973)</td>
<td></td>
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</tr>
<tr>
<td>Post tape-stripping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>13.39 (2.85)</td>
<td>13.24 (3.08)</td>
<td>14.63 (6.10)</td>
<td>16.87 (3.70)</td>
<td>16.63 (4.36)</td>
<td>17.95 (11.11)</td>
</tr>
<tr>
<td></td>
<td>-0.96 [-3.23 to 1.31] (0.401)</td>
<td>0.25 [-5.22 to 5.73] (0.927)</td>
<td>1.21 [-3.94 to 6.37] (0.640)</td>
<td></td>
<td></td>
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<tr>
<td>Abdomen</td>
<td>12.48 (2.83)</td>
<td>12.30 (2.24)</td>
<td>12.59 (2.87)</td>
<td>13.75 (3.14)</td>
<td>13.95 (2.58)</td>
<td>13.56 (2.17)</td>
</tr>
<tr>
<td></td>
<td>-1.32 [-3.15 to 0.50] (0.152)</td>
<td>-0.46 [-2.43 to 1.51] (0.639)</td>
<td>0.86 [-1.02 to 2.74] (0.365)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Thigh</td>
<td>14.30 (3.01)</td>
<td>13.96 (1.94)</td>
<td>14.63 (2.84)</td>
<td>14.70 (3.33)</td>
<td>13.87 (2.58)</td>
<td>15.52 (4.91)</td>
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<tr>
<td></td>
<td>-0.20 [-1.79 to 1.38] (0.798)</td>
<td>-0.71 [-3.28 to 1.86] (0.582)</td>
<td>-0.51 [-2.86 to 1.85] (0.667)</td>
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</table>

*Table 6.12: Results at baseline and 4 weeks and pairwise comparisons of mean differences from baseline to 4 weeks between treatment groups for primary outcome: TEWL*
<table>
<thead>
<tr>
<th>Table 6.13: ANCOVA results for primary outcome measures at 4 weeks: TEWL</th>
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<tbody>
<tr>
<td><strong>TEWL pre tape-stripping (left forearm)</strong></td>
</tr>
<tr>
<td>Group</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
</tr>
<tr>
<td><strong>TEWL pre tape-stripping (abdomen)</strong></td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
</tr>
<tr>
<td><strong>TEWL pre tape-stripping (left thigh)</strong></td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
</tr>
<tr>
<td><strong>TEWL post tape-stripping (left forearm)</strong></td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Baseline</td>
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<tr>
<td>Family history of atopic eczema</td>
</tr>
<tr>
<td><strong>TEWL post tape-stripping (abdomen)</strong></td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Baseline</td>
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<tr>
<td>Family history of atopic eczema</td>
</tr>
<tr>
<td><strong>TEWL post tape-stripping (left thigh)</strong></td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
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<tr>
<td><strong>TEWL Pre tape-stripping</strong></td>
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<tr>
<td>(left forearm)</td>
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<td>Olive oil – Sunflower oil</td>
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<tr>
<td>Olive oil – No oil</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
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<tr>
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<td>Olive oil – No oil</td>
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<td>Sunflower oil – No oil</td>
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<tr>
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<td>Olive oil – No oil</td>
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<td>Sunflower oil – No oil</td>
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<tr>
<td></td>
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<tr>
<td><strong>TEWL Post tape-stripping</strong></td>
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<tr>
<td>(left forearm)</td>
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<tr>
<td>Olive oil – Sunflower oil</td>
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<td>Sunflower oil – No oil</td>
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<tr>
<td>(abdomen)</td>
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<tr>
<td>Olive oil – Sunflower oil</td>
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<td>Olive oil – No oil</td>
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<td>Sunflower oil – No oil</td>
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<tr>
<td>(left thigh)</td>
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<td>Olive oil – Sunflower oil</td>
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<td>Olive oil – No oil</td>
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<td>Sunflower oil – No oil</td>
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*Table 6.14: Pairwise comparisons at 4 weeks adjusted for baseline and family history of atopic eczema for primary outcome: TEWL*
Table 6.15: Results at baseline and 4 weeks and pairwise comparisons of mean differences from baseline to 4 weeks between treatment groups for secondary outcomes: stratum corneum hydration and skin surface pH

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean [CI] (p-value)</th>
<th>4 weeks Mean [CI] (p-value)</th>
<th>Difference in means Mean [CI] (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil</td>
<td>17.65 (4.42)</td>
<td>50.12 (10.06)</td>
<td>-1.27 [-6.63 to 4.09] (0.636)</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>19.13 (5.00)</td>
<td>51.80 (9.77)</td>
<td>5.81 [0.91 to 10.71] (0.021)*</td>
</tr>
<tr>
<td>No oil</td>
<td>16.22 (3.82)</td>
<td>41.79 (9.65)</td>
<td>7.08 [1.88 to 12.28] (0.008)*</td>
</tr>
<tr>
<td>Olive oil</td>
<td>25.61 (5.89)</td>
<td>58.34 (9.81)</td>
<td>-0.07 [-6.54 to 6.41] (0.984)</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>26.90 (7.50)</td>
<td>58.97 (10.29)</td>
<td>7.19 [1.71 to 12.68] (0.011)*</td>
</tr>
<tr>
<td>No oil</td>
<td>24.26 (6.99)</td>
<td>49.25 (9.32)</td>
<td>7.26 [0.85 to 13.67] (0.027)*</td>
</tr>
<tr>
<td>Stratum corneum hydration</td>
<td>Abdomen 25.61 (5.89)</td>
<td>58.34 (9.81)</td>
<td>-0.07 [-6.54 to 6.41] (0.984)</td>
</tr>
<tr>
<td></td>
<td>26.90 (7.50)</td>
<td>58.97 (10.29)</td>
<td>7.19 [1.71 to 12.68] (0.011)*</td>
</tr>
<tr>
<td></td>
<td>24.26 (6.99)</td>
<td>49.25 (9.32)</td>
<td>7.26 [0.85 to 13.67] (0.027)*</td>
</tr>
<tr>
<td>Thigh</td>
<td>19.92 (4.98)</td>
<td>41.23 (9.30)</td>
<td>-1.28 [-6.42 to 3.86] (0.620)</td>
</tr>
<tr>
<td>Skin surface pH</td>
<td>5.90 (0.49)</td>
<td>6.10 (0.57)</td>
<td>0.01 [-0.30 to 0.31] (0.733)</td>
</tr>
<tr>
<td></td>
<td>5.80 (0.42)</td>
<td>4.98 (0.31)</td>
<td>0.18 [-0.11 to 0.46] (0.220)</td>
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<tr>
<td></td>
<td>6.10 (0.57)</td>
<td>4.93 (0.31)</td>
<td>0.22 [-0.06 to 0.50] (0.115)</td>
</tr>
<tr>
<td></td>
<td>6.18 (0.56)</td>
<td>5.02 (0.39)</td>
<td>0.01 [-0.30 to 0.31] (0.973)</td>
</tr>
<tr>
<td></td>
<td>6.03 (0.46)</td>
<td>4.94 (0.31)</td>
<td>0.22 [-0.07 to 0.51] (0.133)</td>
</tr>
<tr>
<td></td>
<td>6.39 (0.50)</td>
<td>5.02 (0.35)</td>
<td>0.22 [-0.07 to 0.50] (0.131)</td>
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<td>5.91 (0.50)</td>
<td>5.13 (0.38)</td>
<td>0.18 [-0.19 to 0.54] (0.338)</td>
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<tr>
<td></td>
<td>5.97 (0.58)</td>
<td>5.13 (0.38)</td>
<td>0.47 [0.13 to 0.81] (0.007)*</td>
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<tr>
<td></td>
<td>6.29 (0.56)</td>
<td>5.29 (0.61)</td>
<td>0.29 [-0.02 to 0.61] (0.566)</td>
</tr>
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<td>5.29 (0.61)</td>
<td>5.20 (0.43)</td>
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<td>5.13 (0.38)</td>
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Table 6.15: Results at baseline and 4 weeks and pairwise comparisons of mean differences from baseline to 4 weeks between treatment groups for secondary outcomes: stratum corneum hydration and skin surface pH

*p<0.05
<table>
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<th>df</th>
<th>P</th>
<th>Partial eta²</th>
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<tbody>
<tr>
<td><strong>Hydration (left forearm)</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Group</td>
<td>7.03</td>
<td>2, 87</td>
<td>0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.38</td>
<td>1, 87</td>
<td>0.127</td>
<td>0.03</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>0.07</td>
<td>1, 87</td>
<td>0.789</td>
<td>0.001</td>
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<tr>
<td><strong>Hydration (abdomen)</strong></td>
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</tr>
<tr>
<td>Group</td>
<td>9.72</td>
<td>2, 87</td>
<td>&lt;0.001</td>
<td>0.18</td>
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<tr>
<td>Baseline</td>
<td>&lt;0.0005</td>
<td>1, 87</td>
<td>0.984</td>
<td>&lt;0.0005</td>
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<tr>
<td>Family history of atopic eczema</td>
<td>1.50</td>
<td>1, 87</td>
<td>0.224</td>
<td>0.02</td>
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<td><strong>Hydration (left thigh)</strong></td>
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</tr>
<tr>
<td>Group</td>
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<td>2, 86</td>
<td>&lt;0.001</td>
<td>0.17</td>
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<td>1, 86</td>
<td>0.174</td>
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<td>1, 86</td>
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<td><strong>Skin pH (left forearm)</strong></td>
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<tr>
<td>Group</td>
<td>0.09</td>
<td>2, 84</td>
<td>0.917</td>
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<td>1, 84</td>
<td>0.038</td>
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<tr>
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<td>1, 84</td>
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<td>&lt;0.0005</td>
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<tr>
<td><strong>Skin pH (abdomen)</strong></td>
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<td></td>
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<tr>
<td>Group</td>
<td>0.20</td>
<td>2, 81</td>
<td>0.823</td>
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</tr>
<tr>
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<td>1, 81</td>
<td>0.056</td>
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<td>1, 81</td>
<td>0.546</td>
<td>0.004</td>
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<tr>
<td><strong>Skin pH (left thigh)</strong></td>
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<td>Group</td>
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<td>2, 81</td>
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<td>0.03</td>
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<td>1, 81</td>
<td>0.043</td>
<td>0.05</td>
</tr>
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<td>Family history of atopic eczema</td>
<td>&lt;0.0005</td>
<td>1, 81</td>
<td>0.991</td>
<td>&lt;0.0005</td>
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Table 6.16: ANCOVA results for secondary outcomes: stratum corneum hydration and skin surface pH
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<th>95% CI</th>
<th>P</th>
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<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Hydration (left forearm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>-1.57</td>
<td>-6.74</td>
<td>3.61</td>
</tr>
<tr>
<td>Olive oil – No oil</td>
<td>7.35</td>
<td>2.21</td>
<td>12.49</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>8.92</td>
<td>3.88</td>
<td>13.97</td>
</tr>
<tr>
<td>Hydration (abdomen)</td>
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</tr>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>-0.82</td>
<td>-6.00</td>
<td>4.37</td>
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<tr>
<td>Olive oil – No oil</td>
<td>8.96</td>
<td>3.93</td>
<td>14.00</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>9.78</td>
<td>4.81</td>
<td>14.69</td>
</tr>
<tr>
<td>Hydration (left thigh)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>-0.23</td>
<td>-4.95</td>
<td>4.48</td>
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<td>Olive oil – No oil</td>
<td>8.17</td>
<td>3.51</td>
<td>12.82</td>
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<td>Sunflower oil – No oil</td>
<td>8.40</td>
<td>3.94</td>
<td>12.86</td>
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<tr>
<td>Skin pH (left forearm)</td>
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<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.03</td>
<td>-0.13</td>
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<td>Olive oil – No oil</td>
<td>0.01</td>
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<tr>
<td>Sunflower oil – No oil</td>
<td>-0.02</td>
<td>-0.19</td>
<td>0.14</td>
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<tr>
<td>Skin pH (abdomen)</td>
<td></td>
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<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.06</td>
<td>-0.13</td>
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<td>-0.16</td>
<td>0.13</td>
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<tr>
<td>Sunflower oil – No oil</td>
<td>-0.03</td>
<td>-0.22</td>
<td>0.15</td>
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<tr>
<td>Skin pH (left thigh)</td>
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<tr>
<td>Olive oil – Sunflower oil</td>
<td>0.11</td>
<td>-0.15</td>
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<td>Olive oil – No oil</td>
<td>0.21</td>
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<td>0.47</td>
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<td>Sunflower oil – No oil</td>
<td>0.10</td>
<td>-0.15</td>
<td>0.35</td>
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Table 6.17: Pairwise comparisons at 4 weeks adjusted for baseline and family history of atopic eczema for secondary outcomes: stratum corneum hydration and skin surface pH
<table>
<thead>
<tr>
<th></th>
<th>Olive Oil</th>
<th>Sunflower Oil</th>
<th>No oil</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Birthweight Pearson (p-value)</td>
<td>Gestational Age Pearson (p-value)</td>
<td>Birthweight Pearson (p-value)</td>
</tr>
<tr>
<td><strong>Hydration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>-0.26 (0.195)</td>
<td>0.01 (0.969)</td>
<td>-0.22 (0.245)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>-0.55 (0.003)</td>
<td>-0.07 (0.713)</td>
<td>-0.10 (0.607)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>-0.15 (0.457)</td>
<td>0.20 (0.310)</td>
<td>-0.13 (0.502)</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
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</tr>
<tr>
<td>Left forearm</td>
<td>-0.30 (0.139)</td>
<td>0.02 (0.921)</td>
<td>0.05 (0.797)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>-0.42 (0.031)</td>
<td>-0.06 (0.761)</td>
<td>0.12 (0.545)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>-0.27 (0.176)</td>
<td>-0.12 (0.574)</td>
<td>0.27 (0.166)</td>
</tr>
<tr>
<td><strong>Erythema</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>0.22 (0.292)</td>
<td>0.37 (0.059)</td>
<td>0.04 (0.835)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>-0.03 (0.876)</td>
<td>0.19 (0.361)</td>
<td>0.27 (0.155)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>-0.16 (0.448)</td>
<td>0.05 (0.816)</td>
<td>0.14 (0.468)</td>
</tr>
</tbody>
</table>

Table 6.18: Secondary outcome variables correlations with birthweight and gestational age by study arm
Table 6.19 summarises and compares the frequency distribution of skin assessment scores at baseline and follow-up by randomised group. At baseline, none of the babies had severe dryness and/or scaling, and very few had mild-moderate to severe dryness and/or scaling (n=14; 12%). The majority had no (n=30; 26%) or slight (n=71; 62%) dryness and/or scaling. The skin assessments scored as no dryness and/or scaling (olive oil group n=12; sunflower oil group n=13, no oil group n=5), and slight dryness and/or scaling (olive oil group n=20; sunflower oil group n=20; no oil group n=31) were very similar for babies in the two oil groups at baseline, but the frequencies were quite different for the no oil group. The researcher conducting the skin assessment scores was blind to which group each baby was randomised to, and the babies were not randomised until after baseline assessment so these frequencies should have occurred completely by chance. If the frequencies for no or slight dryness and/or scaling are summed together, the randomised groups are homogeneous at baseline for skin assessment.

At 4 weeks, skin condition had improved overall. Only one baby in the no oil study arm had mild-moderate to severe dryness and/or scaling. More babies had no evidence of dryness and/or scaling (n=47; 51%) which was almost double the number with no dryness at baseline. The remaining babies had slight dryness and/or scaling (n=44; 48%).

Table 6.20 summarises the mean values and standard deviations at baseline and follow-up for erythema of the skin, together with confidence intervals and \( p \)-values for the differences between the groups at follow-up. Erythema was assessed separately from the clinical observations using a Mexameter® probe. There were no significant differences across treatment groups for erythema at 4 weeks. However, it is noticeable that erythema was consistently higher at follow-up for babies in the olive oil group when compared to babies in the sunflower oil and no oil study arms, for all treatment sites.

The lack of significance of a difference between groups was also shown in the ANCOVA results adjusted for baseline measurements and family history of atopic eczema (table 6.21), with the group effect explaining at most 2% of the variance in erythema. Interestingly, family history of atopic eczema was significant for erythema but only at the thigh \( (p=0.042) \), but even then, it only explained 5% of the variance in erythema. The pairwise comparisons of differences from baseline to 4 weeks (table 6.22) supported the results from the difference scores illustrated in table 6.20.

There was only one significant value in the correlation data (table 6.18) for erythema; abdomen in the sunflower oil study arm for gestational age \( (r=0.49, p=0.007) \). One other value was arguably close to significance; left forearm for gestational age \( (r=0.37, p=0.059) \).
There were no trends evident in the correlation data for any of the secondary outcome variables, apart from all of the significant values being associated with the abdomen treatment site.

6.6.3 Family history of atopic eczema

No significant effect was evident for family history of atopic eczema in ANCOVA for any of the primary or secondary outcomes apart from erythema on the thigh ($p = 0.042$; see table 6.21). The mean erythema scores at follow-up were consistently numerically higher for those babies without a family history of atopic eczema for both the olive oil group and the sunflower oil group at all three body sites (table 6.23). This was also the case on the abdomen and thigh for babies in the no oil group. These results agreed with the clinical observation of rash at follow-up, where a slight or mild rash was observed in 11/61 babies with no family history of atopic eczema compared with 2/31 babies with a family history. There was a similar pattern evident in each of the study arms. While this pilot study found no significant effect for family history of atopic eczema, this would have to be monitored in any further studies.
Table 6.19: Clinical skin assessment (tool adapted from Lund et al 2001; assessed and recorded by researcher)

<table>
<thead>
<tr>
<th></th>
<th>Olive oil group</th>
<th>Sunflower oil group</th>
<th>No oil group</th>
<th>Olive oil group</th>
<th>Sunflower oil group</th>
<th>No oil group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Count (%)</strong></td>
<td>n=38</td>
<td>n=38</td>
<td>n=39</td>
<td>n=27</td>
<td>n=30</td>
<td>n=35</td>
</tr>
<tr>
<td><strong>Dryness and/or scaling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No evidence of dryness or scaling</td>
<td>12 (31.6)</td>
<td>13 (34.2)</td>
<td>5 (12.8)</td>
<td>11 (40.7)</td>
<td>19 (63.3)</td>
<td>17 (48.6)</td>
</tr>
<tr>
<td>Slight dryness and/or scaling</td>
<td>20 (52.6)</td>
<td>20 (52.6)</td>
<td>31 (79.5)</td>
<td>16 (59.3)</td>
<td>11 (36.7)</td>
<td>17 (48.6)</td>
</tr>
<tr>
<td>Mild--moderate dryness to severe dryness and/or scaling</td>
<td>5 (13.2)</td>
<td>4 (10.5)</td>
<td>1 (2.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Moderate-severe dryness and/or scaling</td>
<td>1 (2.6)</td>
<td>1 (2.6)</td>
<td>2 (5.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severe dryness and/or scaling</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No evidence of rash</td>
<td>34 (89.5)</td>
<td>30 (78.9)</td>
<td>35 (89.7)</td>
<td>23 (85.2)</td>
<td>26 (86.7)</td>
<td>30 (85.7)</td>
</tr>
<tr>
<td>Slight rash--slight erythema and/or scaling</td>
<td>4 (10.5)</td>
<td>8 (21.1)</td>
<td>3 (7.7)</td>
<td>4 (14.8)</td>
<td>3 (10.0)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Mild rash--moderate to severe erythema and/or scaling, slight papules and oedema</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>1 (3.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Moderate rash--moderate to severe erythema and/or scaling, moderate ulceration, moderate to severe papules and oedema</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severe rash--severe erythema and/or scaling, severe ulceration, papules, and oedema</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Table 6.20: Results at baseline and 4 weeks and pairwise comparisons of mean differences from baseline to 4 weeks between treatment groups for secondary outcome: erythema

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>4 weeks Mean (SD)</th>
<th>Difference in means Mean [CI] (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olive oil</td>
<td>Sunflower oil</td>
<td>No oil</td>
</tr>
<tr>
<td></td>
<td>n=38</td>
<td>n=38</td>
<td>n=39</td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>463.28 (85.44)</td>
<td>467.14 (83.30)</td>
<td>437.05 (85.93)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>402.75 (75.23)</td>
<td>380.79 (58.69)</td>
<td>385.15 (74.03)</td>
</tr>
<tr>
<td>Thigh</td>
<td>472.76 (90.39)</td>
<td>460.73 (72.79)</td>
<td>457.30 (77.35)</td>
</tr>
</tbody>
</table>

Table 6.20: Results at baseline and 4 weeks and pairwise comparisons of mean differences from baseline to 4 weeks between treatment groups for secondary outcome: erythema
<table>
<thead>
<tr>
<th>Erythema (left forearm)</th>
<th>F</th>
<th>df</th>
<th>P</th>
<th>Partial eta²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1.01</td>
<td>2, 85</td>
<td>0.369</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline</td>
<td>10.82</td>
<td>1, 85</td>
<td>0.001</td>
<td>0.11</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>2.64</td>
<td>1, 85</td>
<td>0.108</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erythema (abdomen)</th>
<th>F</th>
<th>df</th>
<th>P</th>
<th>Partial eta²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>0.19</td>
<td>2, 85</td>
<td>0.828</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline</td>
<td>18.24</td>
<td>1, 85</td>
<td>&lt;0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>0.90</td>
<td>1, 85</td>
<td>0.900</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erythema (left thigh)</th>
<th>F</th>
<th>df</th>
<th>P</th>
<th>Partial eta²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>0.51</td>
<td>2, 84</td>
<td>0.602</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.13</td>
<td>1, 84</td>
<td>0.005</td>
<td>0.09</td>
</tr>
<tr>
<td>Family history of atopic eczema</td>
<td>4.28</td>
<td>1, 84</td>
<td>0.042</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Table 6.21: ANCOVA results for secondary outcome: erythema*
Table 6.22: Pairwise comparisons at 4 weeks adjusted for baseline and family history of atopic eczema for secondary outcome: erythema

<table>
<thead>
<tr>
<th>Erythema (left forearm)</th>
<th>Adjusted difference in means</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>27.38</td>
<td>-11.05</td>
<td>65.81</td>
</tr>
<tr>
<td>Olive oil – No oil</td>
<td>16.25</td>
<td>-20.97</td>
<td>53.46</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>-11.13</td>
<td>-46.91</td>
<td>24.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erythema (abdomen)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>-4.78</td>
<td>-41.44</td>
<td>31.89</td>
</tr>
<tr>
<td>Olive oil – No oil</td>
<td>-10.46</td>
<td>-44.76</td>
<td>23.85</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>-5.68</td>
<td>-38.42</td>
<td>27.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erythema (left thigh)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive oil – Sunflower oil</td>
<td>14.75</td>
<td>-22.44</td>
<td>51.94</td>
</tr>
<tr>
<td>Olive oil – No oil</td>
<td>17.07</td>
<td>-18.21</td>
<td>52.35</td>
</tr>
<tr>
<td>Sunflower oil – No oil</td>
<td>2.32</td>
<td>-47.30</td>
<td>49.11</td>
</tr>
</tbody>
</table>

*Table 6.22: Pairwise comparisons at 4 weeks adjusted for baseline and family history of atopic eczema for secondary outcome: erythema*
<table>
<thead>
<tr>
<th>Erythema</th>
<th>Olive Oil Mean (SD)</th>
<th>Sunflower Oil Mean (SD)</th>
<th>No Oil Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history of AE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>503.85 (60.02)</td>
<td>468.36 (79.69)</td>
<td>461.54 (95.88)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>430.15 (73.68)</td>
<td>366.38 (57.43)</td>
<td>392.87 (80.19)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>530.15 (93.06)</td>
<td>464.46 (73.65)</td>
<td>466.77 (81.95)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>429.46 (75.65)</td>
<td>374.06 (51.11)</td>
<td>418.22 (67.80)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>390.71 (70.46)</td>
<td>363.00 (71.03)</td>
<td>380.36 (72.26)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>395.71 (91.95)</td>
<td>363.88 (63.52)</td>
<td>384.44 (61.09)</td>
</tr>
<tr>
<td><strong>No family history of AE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>446.75 (89.57)</td>
<td>466.51 (86.73)</td>
<td>424.81 (79.65)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>391.59 (74.28)</td>
<td>388.28 (59.08)</td>
<td>381.28 (72.10)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>449.38 (79.59)</td>
<td>458.79 (73.79)</td>
<td>452.56 (76.17)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>443.85 (81.40)</td>
<td>426.17 (79.84)</td>
<td>409.30 (78.40)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>394.19 (57.42)</td>
<td>380.59 (64.29)</td>
<td>391.61 (87.53)</td>
</tr>
<tr>
<td>Left thigh</td>
<td>422.28 (87.47)</td>
<td>407.57 (61.59)</td>
<td>392.49 (63.69)</td>
</tr>
</tbody>
</table>

Table 6.23: Erythema by family history of atopic eczema
6.6.4 Ethnicity

Babies were categorised for ethnic group by their parents. The group options included White British, White Other, Indian, Pakistani, White Irish, Mixed, Black Caribbean, Black African, Bangladeshi, Chinese, Asian Other, Black Other and Other. No babies were recorded by their parents as Black Caribbean, Black Other or Other. For the purposes of analysis for ethnicity between the study arms, ethnicities were grouped into four categories: ‘White’ included White British, White Other and White Irish; ‘Asian’ included Indian, Pakistani, Bangladeshi, Chinese and Asian Other; Mixed and Black African remained the same.

Descriptive statistics were explored for all variables by ethnicity by study arm. Baseline results were compared within the study arm, and then the follow-up results were reviewed for patterns in the data both between groups and compared to baseline. These results are shown in tables 6.24 to 6.27 for babies in the olive oil group, 6.28 to 6.31 for babies in the sunflower oil group and 6.32 to 6.35 for babies in the no oil group. It should be noted that numbers in all but the White group were very small, making detailed comparisons difficult and descriptive findings were considered prudently.

6.6.4.1 Olive Oil group

There were no clear associations in the data at baseline or follow-up for the primary outcome variables of lipid chain conformation and lateral lipid chain packing (table 6.24) or TEWL (table 6.25) for babies in the olive oil group, apart from TEWL at follow-up for babies in the Black African group (n=2) where scores were consistently lower for all treatment sites than for other ethnic groups. There was no consistent pattern between ethnic groups in the change in the three primary outcome variables from baseline to follow-up.

For the secondary outcome variables, hydration at follow-up was consistently highest for all treatment sites for babies in the Black African group (table 6.26). The individual change in hydration from baseline to follow-up was positive at all sites in all babies (data not shown). Skin surface pH was highest for babies in the White group at baseline, but there were no systematic patterns in the scores at follow-up (table 6.26). Scores tended to be lower for most babies at follow-up, the mean reduction being significant where group sizes were large (data not shown). There were no consistent differences in the data for erythema at baseline between groups, but erythema was consistently higher at follow-up for all treatment sites for babies in the Black African group (table 6.27). Again, scores tended to be lower for most babies at follow-up, the mean reduction being significant for the larger White group (n=13) at each site.
Although some differences were evident for babies in the Black African group, it should be noted that there were only two babies in this group and therefore the results should be regarded with this in mind. Further data would be needed to confirm these observations.

6.6.4.2  Sunflower Oil group

There were no clear patterns in the data at baseline or follow-up for the primary outcome variables of lipid chain conformation and lateral lipid chain packing for babies in the sunflower oil study arm (table 6.28). Unfortunately at follow-up there was only one baby in each of the Asian and Black African groups. There was no overall consistent pattern in the change in these two variables from baseline to follow-up in the White and Mixed groups, although in the larger White group (n=18, 19 or 20) and overall, the mean change in lateral lipid chain packing was numerically positive (the 95% confidence interval for the change did not contain zero) at the three sites post tape-stripping.

With regard to TEWL (table 6.29), scores were consistently lowest pre and post tape-stripping at all treatment sites for babies in the Mixed group at baseline and this was also seen at follow-up when compared to babies in the White group. Mean changes in TEWL from baseline to follow-up were positive in the White group on the left forearm pre and post tape-stripping and also on the abdomen post tape-stripping, and for the Mixed group on the arm and abdomen post tape-stripping.

For the secondary outcome variables, hydration was consistently lowest for all treatment sites for babies in the Asian and Black African groups (table 6.30), although it should be noted that there were only three Asian and two Black African babies at baseline. As in the olive oil arm, the individual change in hydration from baseline to follow-up was positive at all sites in all babies. Skin surface pH was highest for babies in the Black African group at baseline for this study arm, but there are no results to compare at follow-up due to the small sample size (table 6.30). The two groups with the lowest skin surface pH at baseline (White and Mixed) are also similar at follow-up (table 6.30). Scores tended to be lower for most babies at follow-up, the mean reduction being significant for the White and Mixed groups. There were no obvious patterns in the data for erythema at baseline or follow-up between groups (table 6.31), but as with other measures, this would need to be monitored with a larger sample in a future study. For both the White and Mixed groups, the mean change in erythema from baseline to follow-up on the thigh was negative.

6.6.4.3  No Oil group

As in the other two study arms, there were no clear patterns in the data at baseline or follow-up for the primary outcome variables of lipid chain conformation and lateral lipid chain packing (table 6.32) for babies in the no oil study arm. However, there was a clear pattern in the changes in these two measurements from baseline to follow-up. The change
in lipid chain conformation at all sites was numerically negative in most babies and the mean change was significant in the larger White group (n=20, 21 or 22) and overall at five of the six combinations of site and tape-stripping for the White group and overall, the exception being post tape-stripping at the thigh.

With regard to the TEWL measurements (table 6.33), babies in the Black African classification generally had the lowest TEWL results at baseline with the exception of pre tape-stripping on the abdomen. This was also seen at follow-up where babies in the Black African group had the lowest TEWL measurements for all treatment sites post tape-stripping and for the left thigh pre tape-stripping. There was no consistent pattern between ethnic groups in the change in TEWL from baseline to follow-up.

For the secondary outcome variables, babies in the Black African group had the lowest hydration and skin surface pH at baseline but there were no consistent patterns at follow-up for any of the groups (table 6.34). Changes in hydration from baseline to follow-up were positive for most but not all babies, and for all but the Black African group (n=2), the mean change in hydration was positive. Skin surface pH tended to be lower for most but not all babies at follow-up, the mean reduction being significant for the White and Asian (n=6) groups. There were no systematic differences in the data for erythema at baseline between groups, but erythema was consistently highest at follow-up for all treatment sites for babies in the Mixed group and consistently lowest for all treatment sites for babies in the White group (table 6.35). For the White group, the mean change in erythema from baseline to follow-up on the thigh was negative.
<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>White n=21</th>
<th>Asian n=7</th>
<th>Mixed n=8</th>
<th>Black African n=2</th>
<th>White n=12</th>
<th>Asian n=4</th>
<th>Mixed n=8</th>
<th>Black African n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Lipid chain conformation (v_{\text{sym}}\text{CH}_2\ COG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre tape-stripping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>2851.74 (1.18)</td>
<td>2851.84 (0.63)</td>
<td>2851.74 (0.97)</td>
<td>2851.05 (1.43)</td>
<td>2851.89 (0.47)</td>
<td>2851.97 (0.47)</td>
<td>2851.89 (0.47)</td>
<td>2851.00 (0.56)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2851.79 (0.55)</td>
<td>2851.68 (0.59)</td>
<td>2851.75 (0.39)</td>
<td>2851.34 (0.23)</td>
<td>2851.93 (0.52)</td>
<td>2851.91 (0.36)</td>
<td>2851.75 (0.50)</td>
<td>2852.13 (0.01)</td>
</tr>
<tr>
<td>Thigh</td>
<td>2851.43 (0.54)</td>
<td>2851.22 (0.76)</td>
<td>2851.59 (0.47)</td>
<td>2851.83 (1.34)</td>
<td>2851.87 (0.71)</td>
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<td>2851.56 (0.57)</td>
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<tr>
<td>Post tape-stripping</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Arm</td>
<td>2851.76 (0.86)</td>
<td>2851.38 (0.78)</td>
<td>2851.48 (0.77)</td>
<td>2851.40 (0.68)</td>
<td>2851.28 (0.81)</td>
<td>2851.20 (0.72)</td>
<td>2851.15 (0.57)</td>
<td>2850.46 (0.38)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2851.54 (0.56)</td>
<td>2851.93 (0.76)</td>
<td>2851.46 (0.48)</td>
<td>2851.24 (0.10)</td>
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Table 6.24: Olive Oil group lipid lamellae structure by ethnicity
Table 6.25: Olive Oil group TEWL by ethnicity

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<td>Mean (SD)</td>
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<td>11.12 (2.37)</td>
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<td>Post tape-stripping</td>
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<tr>
<td>Arm</td>
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<td>13.35 (2.71)</td>
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<td>12.48 (4.33)</td>
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Table 6.26: Olive Oil group secondary outcome variables by ethnicity

*mean is constant

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<th>Black African n=2</th>
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<td>59.48 (5.73)</td>
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<td>19.78 (4.64)</td>
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<td>5.11 (0.75)</td>
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<td>5.02 (0.16)</td>
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<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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*Table 6.27: Olive Oil group erythema by ethnicity*
Table 6.28: Sunflower Oil group lipid lamellae structure by ethnicity

*n=1 therefore result constant

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<td>Arm</td>
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<td>Abdomen</td>
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<td>Abdomen</td>
<td>5.87 (0.51)</td>
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<tr>
<td></td>
<td>Thigh</td>
<td>6.17 (0.70)</td>
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<td>Post tape-stripping</td>
<td>Arm</td>
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Table 6.29: Sunflower Oil group TEWL by ethnicity

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<td><strong>Pre tape-stripping</strong></td>
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<tr>
<td>Arm</td>
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<td>12.55 (1.57)</td>
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<td>Abdomen</td>
<td>11.00 (1.93)</td>
<td>11.48 (1.95)</td>
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<td>Thigh</td>
<td>13.20 (2.28)</td>
<td>14.76 (2.98)</td>
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<td><strong>Post tape-stripping</strong></td>
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<td>15.24 (2.91)</td>
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*n=1 therefore result constant
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<td>19.12 (3.61)</td>
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<td>67.73 (-*)</td>
<td>59.06 (11.27)</td>
<td>69.60 (-*)</td>
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*Table 6.30: Sunflower Oil group secondary outcome variables by ethnicity
*n=1 therefore result constant*
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*Table 6.31: Sunflower Oil group erythema by ethnicity*

*n=1 therefore result constant*
Table 6.32: No Oil group lipid lamellae structure by ethnicity

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<tr>
<td>Abdomen</td>
<td>12.77 (3.16)</td>
<td>12.93 (1.98)</td>
</tr>
<tr>
<td>Thigh</td>
<td>14.12 (2.66)</td>
<td>17.04 (3.58)</td>
</tr>
</tbody>
</table>

Table 6.33: No Oil group TEWL by ethnicity
<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>White n=25</th>
<th>Asian n=6</th>
<th>Mixed n=5</th>
<th>Black African n=2</th>
<th>White n=22</th>
<th>Asian n=6</th>
<th>Mixed n=4</th>
<th>Black African n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Hydration (arm)</td>
<td>17.11 (4.13)</td>
<td>15.57 (2.53)</td>
<td>13.41 (2.52)</td>
<td>13.02 (0.59)</td>
<td>40.18 (8.09)</td>
<td>47.41 (12.24)</td>
<td>44.35 (15.60)</td>
<td>37.42 (0.07)</td>
</tr>
<tr>
<td>Hydration (abdomen)</td>
<td>26.43 (7.07)</td>
<td>19.96 (3.44)</td>
<td>19.77 (4.00)</td>
<td>16.62 (1.39)</td>
<td>47.47 (8.54)</td>
<td>53.79 (9.00)</td>
<td>53.29 (14.92)</td>
<td>47.73 (9.29)</td>
</tr>
<tr>
<td>Hydration (thigh)</td>
<td>18.66 (5.28)</td>
<td>17.43 (4.55)</td>
<td>16.09 (2.68)</td>
<td>14.30 (0.61)</td>
<td>31.32 (7.83)</td>
<td>37.94 (7.59)</td>
<td>28.85 (8.24)</td>
<td>33.58 (4.50)</td>
</tr>
<tr>
<td>pH (arm)</td>
<td>6.08 (0.59)</td>
<td>5.99 (0.51)</td>
<td>5.83 (0.40)</td>
<td>7.02 (0.26)</td>
<td>5.05 (0.36)</td>
<td>4.80 (0.29)</td>
<td>4.98 (0.34)</td>
<td>4.88 (0.02)</td>
</tr>
<tr>
<td>pH (abdomen)</td>
<td>6.34 (0.50)</td>
<td>6.41 (0.31)</td>
<td>6.24 (0.89)</td>
<td>6.83 (0.09)</td>
<td>5.04 (0.40)</td>
<td>4.92 (0.26)</td>
<td>5.11 (0.32)</td>
<td>4.97 (0.42)</td>
</tr>
<tr>
<td>pH (thigh)</td>
<td>6.24 (0.52)</td>
<td>6.13 (0.39)</td>
<td>6.16 (0.85)</td>
<td>7.17 (0.42)</td>
<td>5.22 (0.39)</td>
<td>4.91 (0.34)</td>
<td>5.05 (0.34)</td>
<td>5.17 (0.38)</td>
</tr>
</tbody>
</table>

*Table 6.34: No Oil group secondary outcome variables by ethnicity*
<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Baseline</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White n=25</td>
<td>Asian n=6</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Erythema (arm)</td>
<td>437.56 (90.63)</td>
<td>445.56 (83.80)</td>
</tr>
<tr>
<td>Erythema (abdomen)</td>
<td>367.84 (72.52)</td>
<td>399.44 (68.78)</td>
</tr>
<tr>
<td>Erythema (thigh)</td>
<td>463.25 (83.62)</td>
<td>430.17 (88.61)</td>
</tr>
</tbody>
</table>

*Table 6.35: No Oil group erythema by ethnicity*
6.6.5 Compliance

Adherence to the protocol for both treatment application and alternative product use was analysed to assess feasibility for a future study. Protocol deviations were documented in the Protocol Deviation log (appendix 42). The group that portrayed the best compliance was the control group for both treatment and product use.

6.6.5.1 Adherence to the treatment regime

Adherence to the protocol was assessed by considering the ATR-FTIR sebum data and mother’s self-reporting in the weekly telephone questionnaires and final follow-up questionnaire. It was not possible to use the weight of the unused oil as a measure of compliance as many parents did not return the oil or confirmed that they had spilled and wasted oil. The proportion of lipid esters in the stratum corneum was elevated in the sunflower oil and olive oil groups compared to the no oil group on all treatment sites at follow-up (table 6.36). This increase provided evidence of the use of topical oils, as both sunflower oil and olive oil contain high levels of lipid esters. The ranges of adherence over the 4 week period for study treatment self-reported by mothers were 79% to 93% for the olive oil group, 83% to 94% for the sunflower oil group and 100% for the no oil group (appendix 49). The compliance data resulting from the weekly questionnaires will be discussed in more detail in part two of this chapter.

<table>
<thead>
<tr>
<th>Sebum</th>
<th>Olive oil (n=38)</th>
<th>Sunflower oil (n=38)</th>
<th>No oil (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Baseline pre tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.16 (0.17)</td>
<td>0.21 (0.43)</td>
<td>0.13 (0.09)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>0.36 (0.28)</td>
<td>0.37 (0.25)</td>
<td>0.40 (0.28)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.19 (0.18)</td>
<td>0.16 (0.15)</td>
<td>0.16 (0.08)</td>
</tr>
<tr>
<td>Baseline post tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.13 (0.12)</td>
<td>0.17 (0.28)</td>
<td>0.11 (0.08)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>0.31 (0.28)</td>
<td>0.31 (0.20)</td>
<td>0.30 (0.18)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.15 (0.14)</td>
<td>0.14 (0.13)</td>
<td>0.15 (0.11)</td>
</tr>
<tr>
<td>Follow-up pre tape-stripping</td>
<td>(n=26)</td>
<td>(n=28)</td>
<td>(n=35)</td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.30 (0.29)</td>
<td>0.36 (0.27)</td>
<td>0.13 (0.11)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>0.58 (0.38)</td>
<td>0.62 (0.40)</td>
<td>0.19 (0.17)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.43 (0.37)</td>
<td>0.41 (0.30)</td>
<td>0.10 (0.12)</td>
</tr>
<tr>
<td>Follow-up post tape-stripping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.13 (0.12)</td>
<td>0.15 (0.12)</td>
<td>0.06 (0.07)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>0.38 (0.27)</td>
<td>0.35 (0.27)</td>
<td>0.13 (0.10)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.22 (0.19)</td>
<td>0.23 (0.18)</td>
<td>0.06 (0.08)</td>
</tr>
</tbody>
</table>

Table 6.36: Sebum measurements from the ATR-FTIR spectroscopy
The ranges of adherence over the 4 week period for other skincare product avoidance self-reported by mothers were 57% to 89% for the olive oil group, 70% to 87% for the sunflower oil group and 74% to 100% for the no oil group (appendix 49). Overall, there were no significant differences in adherence across the groups. However, there was a noticeable increase in product use in week 4 for all groups. The actual number of mothers using alternative skincare products on their babies may be higher in reality as adherence was self-reported in the weekly and follow-up questionnaires. However, the analysis of the ATR-FTIR spectra provided evidence to support the data collected from the mothers by displaying no significant differences in the change in proportion of sulphur groups in the skin at follow-up between the study groups. These data suggest that there is no significant difference between the groups in the use of cleansers containing sulphate surfactants, which represent the largest class of cleansers in skincare. Table 6.37 illustrates the means and standard deviations for sulphur groups at baseline and follow-up. The product compliance data resulting from the weekly questionnaires will be discussed in further detail in part two of this chapter.

<table>
<thead>
<tr>
<th>Sulphur Groups</th>
<th>Olive oil (n=38)</th>
<th>Sunflower oil (n=38)</th>
<th>No oil (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Baseline pre tape-stripping</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.47 (0.31)</td>
<td>0.51 (0.38)</td>
<td>0.43 (0.18)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>0.74 (0.34)</td>
<td>0.77 (0.36)</td>
<td>0.76 (0.37)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.53 (0.27)</td>
<td>0.52 (0.29)</td>
<td>0.53 (0.21)</td>
</tr>
<tr>
<td><strong>Baseline post tape-stripping</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.48 (0.28)</td>
<td>0.52 (0.29)</td>
<td>0.45 (0.21)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>0.77 (0.40)</td>
<td>0.75 (0.37)</td>
<td>0.69 (0.27)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.56 (0.27)</td>
<td>0.50 (0.20)</td>
<td>0.56 (0.24)</td>
</tr>
<tr>
<td><strong>Follow-up pre tape-stripping</strong></td>
<td>(n=26)</td>
<td>(n=28)</td>
<td>(n=35)</td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.97 (0.29)</td>
<td>0.89 (0.30)</td>
<td>0.72 (0.24)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>1.10 (0.39)</td>
<td>1.11 (0.39)</td>
<td>0.82 (0.25)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.94 (0.30)</td>
<td>0.95 (0.35)</td>
<td>0.65 (0.22)</td>
</tr>
<tr>
<td><strong>Follow-up post tape-stripping</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Left Forearm</td>
<td>0.79 (0.20)</td>
<td>0.84 (0.16)</td>
<td>0.77 (0.20)</td>
</tr>
<tr>
<td>• Abdomen</td>
<td>0.91 (0.35)</td>
<td>0.97 (0.37)</td>
<td>0.84 (0.23)</td>
</tr>
<tr>
<td>• Left Thigh</td>
<td>0.83 (0.21)</td>
<td>0.86 (0.27)</td>
<td>0.69 (0.19)</td>
</tr>
</tbody>
</table>

Table 6.37: Use of sulphate-based skincare products
CHAPTER SIX PART TWO: Questionnaire data results

6.7 Overview

The weekly telephone questionnaire (appendix 22) asked participants five questions regarding use of products, experience of rash, medical consultation, medication prescription and concerns about the baby's skin. The follow-up questionnaire (appendix 24) was more comprehensive. Part A asked participants the details covered in the weekly questionnaire in addition to details about bathing, moisturising, washing powder brand, and views about the treatment. Part B of the questionnaire incorporated questions about taking part in the research, information provision, treatment allocation, recommending the skincare regime to others, and views about the equipment used for the study assessments. These data were analysed quantitatively using frequencies. The final part of the questionnaire encompassed two open-text questions regarding the positive and negative aspects of taking part in the study. These data were analysed qualitatively using Framework analysis and are presented in part three of this chapter. All of the participants who returned for the follow-up assessment completed the questionnaire (n=92). The questionnaire was also sent out to participants who were lost to follow-up but only one was returned. The response rate for the questionnaire was 80.9% (n=93). The weekly questionnaire also recorded if the participant disclosed their treatment allocation. Only 12 participants (week one n=5; week two n=5; week three n=2) disclosed that they were in an intervention group during the treatment period, but not which treatment. The researcher was not able to associate these disclosures with clinical data, which was kept separately.

6.8 Results

The results from the questionnaire data are presented, including the use of skincare products, reports of rash, the need for medical consultations and medication prescriptions, concerns about baby's skin, views about the treatment and views about the study.

6.8.1 Use of skincare products

Women were asked to acknowledge the frequency of use of any skincare products on their babies including talcum powder, soap, topical oil, bathing wash/cleanser, wipes, cream and lotion, where on the baby the product was used and which brand. These products will be addressed in turn. Table 6.38 illustrates product use over the 4 week treatment period by week of study.

6.8.1.1 Talcum powder

Talcum powder was used by mothers on 19% of babies over the treatment period. Less than 7% of women reported using talcum powder on a daily basis. Others reported usage
after a bath, a nappy change or occasional use only. One parent reported using talcum powder all over the baby’s body in week one, and two parents overall reported using talcum powder all over the baby’s body at some point during the treatment period. All other parents reported avoiding the study areas when using talcum powder. The most commonly used brand was J & J Baby Powder, but one parent used Simple Baby Powder and one used a supermarket own brand.

<table>
<thead>
<tr>
<th>Product</th>
<th>7 days N (%)</th>
<th>14 days N (%)</th>
<th>21 days N (%)</th>
<th>Overall N (%)</th>
<th>Most popular brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talcum powder</td>
<td>12 (10)</td>
<td>12 (10)</td>
<td>15 (13)</td>
<td>22 (19)</td>
<td>J &amp; J</td>
</tr>
<tr>
<td>Soap</td>
<td>3 (3)</td>
<td>5 (4)</td>
<td>4 (3)</td>
<td>4 (3)</td>
<td>J &amp; J</td>
</tr>
<tr>
<td>Topical oil</td>
<td>14 (12)</td>
<td>22 (19)</td>
<td>19 (17)</td>
<td>29 (25)</td>
<td>Olive¹</td>
</tr>
<tr>
<td>Bath wash</td>
<td>45 (39)</td>
<td>42 (37)</td>
<td>48 (42)</td>
<td>49 (43)</td>
<td>J &amp; J Bath²</td>
</tr>
<tr>
<td>Wipes</td>
<td>69 (60)</td>
<td>65 (57)</td>
<td>75 (65)</td>
<td>-⁴</td>
<td>Pampers⁴</td>
</tr>
<tr>
<td>Cream</td>
<td>28 (24)</td>
<td>38 (33)</td>
<td>48 (42)</td>
<td>53 (46)</td>
<td>Sudocrem</td>
</tr>
<tr>
<td>Lotion</td>
<td>10 (9)</td>
<td>13 (11)</td>
<td>10 (9)</td>
<td>12 (10)</td>
<td>J &amp; J</td>
</tr>
</tbody>
</table>

Table 6.38: Use of baby skincare products over the study treatment period.

¹ Olive oil was most commonly used over the rest of the baby’s body, closely followed by J&J Baby Oil
² J&J Baby Bath was the most popular in week 1, but in weeks two to four, J&J Top to Toe was the most commonly used
³ Information regarding wipes use was not collected at follow-up
⁴ Pampers wipes were the most commonly used in week one, but in weeks two and three J&J Extra Sensitive were the most used

6.8.1.2 Soap

Soap was used by mothers on five babies over the treatment period. Less than 3% of women who reported using soap did this on a daily basis. Others reported usage of less than three times per week or on an occasional basis only. One parent reported using soap all over the baby’s body in week one; all other parents avoided the study areas when using a baby soap. The most commonly used brand was J & J Baby Soap but one parent reported using a natural soap.

6.8.1.3 Topical oil

Topical oil was used by mothers on a quarter of babies during the treatment period. Fewer than nine mothers reported using topical oil on a daily basis. Others reported usage of less than three times per week or occasional use only. Two parents reported using topical oil all over the baby’s body in week one, three parents in week two, one parent in week three. Three parents overall confirmed using topical oil all over the baby’s body at some
point during the treatment period. The most commonly used brand was olive oil but this was only slightly more common than J & J Baby Oil. Other topical oils in use included almond oil, lavender oil, vegetable oil, Weleda baby oil and grapeseed oil.

6.8.1.4  Bath wash

Bath wash was used by mothers on 43% of babies over the treatment period. Less than 10% of women reported using bath wash on a daily basis. Others reported usage of less than three times per week or occasional use only. Eight parents reported using bath wash all over the baby’s body in week one, eight parents in week two, and six parents in week three. Twenty four parents overall reported using bath wash all over the baby’s body at some point during the treatment period. The most commonly used brand was J & J Baby Bath in week one, then J & J Top to Toe wash in other weeks. Other wash products used included J & J Baby Shampoo and other non-defined J & J products, Simple, Weleda, Original Sprout, Cussons Head to Toe and supermarket’s own brand.

6.8.1.5  Baby Wipes

Baby wipes were used by up to 65% of mothers on their babies over the treatment period. Half of mothers reported using baby wipes on a daily basis for every nappy change. Other mothers reported using wipes on an occasional basis or for overnight use only. Mothers reported using baby wipes for the napkin area or for the baby’s face. The most commonly used brand was Pampers in week one, then J & J Extra Sensitive in other weeks. Other wipes products reported included J & J Fragrance Free and other non-disclosed J & J products, Huggies, Jackson Reece, Waterwipes, Simple, reusable and supermarket’s own brand.

6.8.1.6  Cream

Creams were used by 46% of mothers on their babies over the treatment period. Approximately 10% of mothers reported using cream on a daily basis for every nappy change. Others reported usage of creams less than three times per week or for occasional use only. Mothers reported using cream for the napkin area and no creams were reportedly used on the three study sites. The most commonly used brand was Sudocrem. Other cream products reported included Bepanthan, Vaseline, Diprovate, Diprobase, Coconut-based, J & J Baby Cream, Drapolene, Metanium, Hydromol, E45 and supermarket’s own brand.

6.8.1.7  Lotion

Baby lotion was used by mothers on 10% of babies over the treatment period. Fewer than seven mothers reported using baby lotion on a daily basis. Others reported usage of less
than three times per week or occasional use only. Use of baby lotion was always reported to avoid the study treatment sites. The most commonly used brand was J & J Baby Lotion. Other baby lotions reported included Sudocrem moisturiser, Oilatum, Cussons, Lansinoh and Aqueous.

6.8.2 Signs of rash

Mothers were asked weekly if the baby had experienced any rash on the study treatment sites. In week one, one rash was reported in the no oil group on the baby’s back. No rashes were reported in week two. In week three, five rashes were reported (n=1 olive oil group; n=2 sunflower oil group; n=2 no oil group). The rash in the olive oil group was generalised over the whole body. Of the two rashes in the sunflower oil group only one was on the study sites; this was classified as an adverse reaction and reviewed by the on-call dermatologist. The remaining rashes in the no oil group were on the chest, neck and face. At the follow-up assessment rashes were recorded by the researcher during the clinical observations in thirteen babies; four babies in the olive oil group, four babies in the sunflower oil group and five babies in the no oil group. Only one of these affected the study sites, which was the adverse reaction mentioned previously.

6.8.3 Medical consultations

Mothers were asked each week if they had needed to consult a medical or health professional and for what reason. In week one, 14% (n=13) of mothers had consulted a general practitioner (GP) or midwife for a variety of reasons including breast-feeding support, colic, infections, diarrhoea and vomiting. In week two, 16% (n=14) consulted a health professional for a range of similar reasons. In week three, the number of mothers consulting a health professional had increased to 20% (n=19) and in week four, this number had increased again to 40% (n=36). Across the four weeks, nine consultations pertained to rash, but only one of these was related to the study sites and was classified as an adverse reaction. This was the same baby as mentioned in section 6.8.2.

6.8.4 Medication prescriptions

Mothers were asked weekly whether any medication was prescribed for their baby, together with what type it was. In week one, nine babies (three in each study arm) had been prescribed medication including Abidec, Chloramphenicol, Diprovate, Gaviscon, Infacol, Nystatin, Trimethoprim and powder for the umbilical cord stump. In the second week, five babies had a medication prescription (n=2 olive oil; n=2 sunflower oil; n=1 no oil). Prescriptions included Clotrimazole, eye drops, Fucidin and Flucloxacillin, Glycerine suppositories and Mandanol nasal drops. In week three, seven babies had a prescription
(n=1 olive oil; n=5 sunflower oil; n=1 no oil). Medications included Doublebase cream, Flucloxacillin, Fucidin, Nystatin, Daktarin, and Saline nasal drops. The number was particularly high in the sunflower oil group but only one of the prescriptions was for a skin cream and this occurred in the olive oil group. In week four, 27 medication prescriptions were reported. This was a substantial increase and was evenly spread across the three treatment arms (n=9 olive oil; n=10 sunflower oil; n=8 no oil). This may possibly be skewed by mothers reporting all prescriptions during the four week treatment period on the follow-up questionnaire, rather than just for the final week of the study. Reported medications in week four included those mentioned previously in addition to Amoxycillin, Colief, Movacol, Oiltatum (prescribed but not used), and Ranitidine.

6.8.5 Concerns about baby’s skin

Mothers were asked a general question each week about whether they had any concerns about their baby’s skin and what those concerns were. In the first week, 24% of mothers reported some concern (n=4 olive oil; n=10 sunflower oil; n=8 no oil). The majority of these concerns were related to dry skin (n=4 olive oil; n=10 sunflower oil; n=7 no oil) and the remaining one was related to jaundice (no oil group). In week two, concerns had reduced to 9% (n=3 olive oil; n=2 sunflower oil; n=3 no oil). Of these concerns, six were dry skin-related (n=2 olive oil; n=1 sunflower oil; n=3 no oil) and two were rashes (n=1 olive oil; n=1 sunflower oil) which were not related to study treatment. The same number of concerns were reported in the third week (n=1 olive oil; n=1 sunflower oil; n=4 no oil). Apart from one in the no oil group for cradle cap, the remaining concerns were rashes which were not in the treatment areas (n=1 olive oil; n=1 sunflower oil; n=3 no oil). In the final week of the study, twelve concerns were raised (n=5 olive oil; n=4 sunflower oil; n=3 no oil). Of these, seven were related to dry skin (n=3 olive oil; n=2 sunflower oil; n=2 no oil). The remainder were related to rash but were not related to study site (n=2 olive oil; n=2 sunflower oil; n=1 no oil). The mother of the baby who experienced an adverse reaction to the study treatment did not report it as a concern, only when addressing the question related to rash.

6.8.6 Safety

6.8.6.1 Adverse events

During weekly phone calls with parents, it was reported that several babies (n=33) had medication prescribed for ailments such as oral thrush (n=9) and eye infections (n=4), and other babies had prescriptions for miscellaneous concerns, such as general rashes, infections, colic and gastric reflux (n=20). Five babies were reported as having a serious adverse event in the first four weeks. These included hospital readmission due to:
infection (n=1), benign neonatal mioclonic jerks (n=1), and neonatal jaundice (n=3). All serious adverse events were recorded as specified in the Protocol.

6.8.6.2 Adverse reactions

None of the reported adverse events were related to participating in the study. No serious adverse reactions or suspected unexpected serious adverse reactions were reported during the study. One adverse reaction was diagnosed during the study; treatment was stopped.

6.8.7 Other practices

6.8.7.1 Bathing

Around half of mothers bathed their baby two or three times a week (48%). This was fairly evenly distributed across the three study arms. Twelve parents (14%) bathed their baby daily; the majority of these were in the no oil group (n=7). Table 6.39 illustrates the bathing frequency by study arm.

<table>
<thead>
<tr>
<th>Number of baths</th>
<th>Olive oil (n=38) N (%)</th>
<th>Sunflower oil (n=38) N (%)</th>
<th>No oil (n=39) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 (11)</td>
<td>2 (7)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>2</td>
<td>5 (18)</td>
<td>9 (30)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>3</td>
<td>10 (36)</td>
<td>7 (23)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>4</td>
<td>5 (18)</td>
<td>7 (23)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>5</td>
<td>3 (11)</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>7</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>7 (23)</td>
</tr>
</tbody>
</table>

Table 6.39: Bathing frequency

Mothers were asked what bathing aids they used. A list was provided to select from which included a flannel, baby sponge, family sponge, hand only or a specified other. The various frequencies are illustrated in table 6.40. The most popular method was by hand, followed by use of a baby sponge. The types of ‘other’ aids included use of cotton wool or a muslin cloth.

6.8.7.2 Moisturising

Mothers were asked to disclose if they had used anything other than the treatment they were allocated to moisturise their baby’s skin. Of twenty two mothers who answered yes,
most were from the sunflower oil group (n=4 olive oil; n=11 sunflower oil; n=7 no oil). The
moisturisers which had been used included olive oil, J & J Baby Oil, Vaseline, Oilatum and
J & J Baby Lotion. Six mothers (29%) reported using the moisturiser daily; with eleven
mothers using a moisturiser on their baby less than three times a week. All mothers were
aware to avoid the three study treatment areas with other skincare products and
compliance is discussed in part one of this chapter, section 6.6.5.

<table>
<thead>
<tr>
<th>Bathing aid</th>
<th>Olive oil (n=38) N (%)</th>
<th>Sunflower oil (n=38) N (%)</th>
<th>No oil (n=39) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flannel</td>
<td>8 (29)</td>
<td>11 (37)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Baby sponge</td>
<td>10 (36)</td>
<td>10 (33)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Family sponge</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hand only</td>
<td>12 (43)</td>
<td>10 (33)</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (11)</td>
<td>7 (23)</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>

Table 6.40: Bathing aids used

6.8.7.3 Use of washing detergent

Mothers were asked whether they used biological or non-biological washing detergent.
The majority of mothers (85%) reported using non-biological detergent (n=24 olive oil;
n=26 sunflower oil; n=26 no oil). This is shown to be evenly distributed across the three
study groups.

6.8.8 Views about the treatment

Women reported that the allocated treatment helped their baby’s dry skin adequately
(83% overall; n=19 olive oil; n=26 sunflower oil; n=9 no oil). The response to this question
in the no oil group was evenly split (50% helped/50% did not help). The majority of women
felt that the treatment made no difference to how the baby smelled (94% overall; n=25
olive oil; n=28 sunflower oil; n=31 no oil). A high proportion of women reported that the
routine of applying the treatment made no difference to how close they felt to their baby
(80% overall; n=17 olive oil; n=25 sunflower oil; n=28 no oil) and even though a high
proportion of these were in the no oil group, it is evident that a similar proportion were
from the sunflower oil group. Overall 19% did feel closer to their baby and expectedly this
was least reported in the no oil group. When asked about whether the treatment was good
or bad for their baby’s skin, 52% felt that it made no difference (n=9 olive oil; n=11
sunflower oil; n=25 no oil) and 45% felt that it was good (n=14 olive oil; n=19 sunflower oil;
n=6 no oil). In relation to the state of dryness of the skin, 54% felt that the treatment made
the skin less dry (n=18 olive oil; n=22 sunflower oil; n=5 no oil), and 43% felt it made no difference (n=6 olive oil; n=6 sunflower oil; n=24 no oil). Parents were asked whether the baby liked the routine, and although 84% of babies evenly spread across the groups did not mind, only 13% actually liked it (n=3 olive oil; n=5 sunflower oil; n=3 no oil). When asked about convenience, 6% responded that being in the study was inconvenient (n=2 both oil groups; n=1 no oil group), and 59% felt that it made no difference to them (n=15 olive oil; n=12 sunflower oil; n=24 no oil). This was further addressed in the next question about how much time was involved where 3% from the oil groups felt that it interfered with their time, 76% felt that it made no difference (n=19 olive oil; n=19 sunflower oil; n=29 no oil) but 21% reported that they spent more quality time with their baby (n=5 olive oil; n=10 sunflower oil; n=3 no oil). With regards to establishing this as a treatment routine, 56% had no preference (n=10 olive oil; n=13 sunflower oil; n=24 no oil) but 32% would like the treatment to become routine (n=13 olive oil; n=11 sunflower oil; n=3 no oil). From those who wanted their treatment allocation to become routine the fewest were in the no oil group, implying that they may like to use oils on their baby’s skin.

6.8.9 Views about the equipment

Mothers were asked about what they thought of the equipment used to take the measurements on their baby’s skin. Out of a total of 69 responses to this question only two were negative. One of these was a concern about the length of time the assessments took which led to the baby becoming distressed and the other was a dislike of the D-Squame discs. The equipment used in the study was discussed in more detail in the qualitative interviews and this will be reported in part three of this chapter.

6.8.10 Views about the study

The majority of women stated that they would take part in the study if asked again (95%). Most women were happy with the quality of information provided (95%) but this was explored more deeply in the qualitative interviews, and is presented in part three. When asked about treatment allocation, 83% were extremely satisfied with the treatment group they were allocated to, and 14% were fairly satisfied. A high proportion of women would recommend the treatment that they were using to a friend (71%).
CHAPTER SIX PART THREE: Qualitative data results

6.9 Overview

This part of the chapter presents the results of the nested qualitative study which comprised 20 in-depth semi-structured interviews with eighteen mothers and two couples; 14 face-to-face and 6 by telephone, representing all three treatment groups. All interviews were conducted by the researcher in the participant’s home between five weeks and six months after birth. Data also included written descriptions of positive and negative aspects of the study from the follow-up questionnaires where these two questions had been answered (n=90). The interviews aimed to explore the views and experiences of mothers in connection with the acceptability of having a newborn baby in a pilot RCT, practicality and convenience, treatment allocation, protocol compliance and information provision (appendix 28).

6.10 Results

Data were managed in NVivo 10 (QSR International Pty Ltd., Australia) and analysed using Framework Analysis encompassing the five stages of familiarisation, creating the thematic framework, indexing, charting, and mapping and interpretation (Ritchie and Spencer 1994). The process is presented in detail in chapter four, part two.

6.10.1 Characteristics of the sample

A purposive sample was recruited for interview, selecting participants from within the trial sample. All three study arms were represented with additional regard to those who had provided answers in the open-text parts of the study questionnaire that were of particular interest for deeper exploration. A total of 25 women were approached, and 20 agreed to be interviewed (recruitment rate 80%). All of the women in the sunflower oil group and the no oil group who were approached agreed to be interviewed, but eleven women had to be approached in the olive oil group to gain the consent of six who were interviewed. The characteristics of the interview sample are presented in table 6.41. The participants included ten women and two couples of White British background, four women of White European background and four women of Asian background. More women were in the age group 21 to 30 years (n=13), with the remainder being 31 to 40 years (n=7). Eight of the babies had a family history of atopic eczema, whilst twelve did not. This was the first baby born to eleven of the mothers; the remaining nine were mothers for the second time.

Qualitative data collected by the study questionnaire (two open-text questions) represent the views of the whole trial sample, for which baseline characteristics can be viewed in tables 6.2 and 6.3 in the first part of this chapter. Where quotations are used to illustrate
findings, data were identified using pseudonyms which the participants chose themselves, and questionnaire data were identified by study number.

<table>
<thead>
<tr>
<th>Pseudonym</th>
<th>Gender</th>
<th>Age</th>
<th>Ethnicity</th>
<th>Family history of atopic eczema</th>
<th>Parity</th>
<th>Phone or Face-to-Face</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aisha</td>
<td>Female</td>
<td>31-40</td>
<td>Pakistani</td>
<td>Yes</td>
<td>2</td>
<td>Face</td>
</tr>
<tr>
<td>Elaine</td>
<td>Female</td>
<td>21-30</td>
<td>White British</td>
<td>Yes</td>
<td>2</td>
<td>Face</td>
</tr>
<tr>
<td>Ila</td>
<td>Female</td>
<td>21-30</td>
<td>Indian</td>
<td>Yes</td>
<td>2</td>
<td>Face</td>
</tr>
<tr>
<td>Indiana</td>
<td>Female</td>
<td>21-30</td>
<td>White British</td>
<td>Yes</td>
<td>2</td>
<td>Face</td>
</tr>
<tr>
<td>Jane</td>
<td>Female</td>
<td>21-30</td>
<td>White British</td>
<td>Yes</td>
<td>1</td>
<td>Face</td>
</tr>
<tr>
<td>Jill</td>
<td>Female</td>
<td>21-30</td>
<td>White British</td>
<td>No</td>
<td>2</td>
<td>Phone</td>
</tr>
<tr>
<td>Lydia</td>
<td>Female</td>
<td>31-40</td>
<td>White British</td>
<td>No</td>
<td>1</td>
<td>Face</td>
</tr>
<tr>
<td>Margaret</td>
<td>Female</td>
<td>21-30</td>
<td>White Other</td>
<td>No</td>
<td>1</td>
<td>Phone</td>
</tr>
<tr>
<td>Maureen</td>
<td>Female</td>
<td>31-40</td>
<td>White British</td>
<td>No</td>
<td>2</td>
<td>Face</td>
</tr>
<tr>
<td>Meg</td>
<td>Female</td>
<td>31-40</td>
<td>White Other</td>
<td>No</td>
<td>1</td>
<td>Phone</td>
</tr>
<tr>
<td>Nicole</td>
<td>Female</td>
<td>21-30</td>
<td>White British</td>
<td>Yes</td>
<td>1</td>
<td>Phone</td>
</tr>
<tr>
<td>Olivia</td>
<td>Female</td>
<td>31-40</td>
<td>White Other</td>
<td>No</td>
<td>2</td>
<td>Face</td>
</tr>
<tr>
<td>Rachel</td>
<td>Female</td>
<td>21-30</td>
<td>White British</td>
<td>No</td>
<td>2</td>
<td>Phone</td>
</tr>
<tr>
<td>Salma</td>
<td>Female</td>
<td>21-30</td>
<td>Indian</td>
<td>No</td>
<td>2</td>
<td>Face</td>
</tr>
<tr>
<td>Samantha</td>
<td>Female</td>
<td>31-40</td>
<td>White Other</td>
<td>No</td>
<td>1</td>
<td>Face</td>
</tr>
<tr>
<td>Sarah</td>
<td>Female</td>
<td>21-30</td>
<td>White British</td>
<td>Yes</td>
<td>1</td>
<td>Phone</td>
</tr>
<tr>
<td>Ted and Barbara</td>
<td>Couple</td>
<td>21-30</td>
<td>White British</td>
<td>No</td>
<td>1</td>
<td>Face</td>
</tr>
<tr>
<td>Tom and Marie</td>
<td>Couple</td>
<td>21-30</td>
<td>White British</td>
<td>No</td>
<td>1</td>
<td>Face</td>
</tr>
<tr>
<td>Tori</td>
<td>Female</td>
<td>31-40</td>
<td>White British</td>
<td>Yes</td>
<td>1</td>
<td>Face</td>
</tr>
<tr>
<td>Zaynad</td>
<td>Female</td>
<td>21-30</td>
<td>Pakistani</td>
<td>No</td>
<td>1</td>
<td>Phone</td>
</tr>
</tbody>
</table>

Table 6.41: Characteristics of qualitative sample by pseudonym

6.10.2 Familiarisation

Figure 6.4 shows the first draft of how the codes fit together within the initial themes. As illustrated, the pseudonym of the participant was recorded next to each code so that commonality of the various issues could be immediately visualised. The codes and the initial analytical framework were discussed and agreed with the Primary Supervisor for the purpose of consistency and rigour.
6.10.3 Constructing the thematic framework

Themes were identified which linked particular codes together to group the data. Figure 6.5 illustrates the first grouping of data. Figures 6.6 and 6.7 illustrate the development of the thematic framework. In view of the nature of the research question under exploration it was evident that the themes remained very close to the topic guide. The nodes were hierarchical in nature and the complete hierarchical analytical framework can be viewed in appendix 43.

6.10.4 Indexing

Once all of the data had been indexed, the thematic network comprised three main themes, with 10 main sub-themes, 18 minor sub-themes and 95 emergent analytical themes.

6.10.5 Charting

Once the data had been fully indexed, each theme generated a chart or matrix. The matrix for one of the themes, altruism, is illustrated in appendix 44.
Figure 6.5: First draft of the developing thematic framework

Figure 6.6: Second draft of the developing thematic framework
6.10.6 Mapping and interpretation

The themes at the mapping stage remained similar to those developed in the thematic network and are illustrated in table 6.42.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub-themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptability</td>
<td>Timing</td>
</tr>
<tr>
<td></td>
<td>Rationale for participation</td>
</tr>
<tr>
<td></td>
<td>Pre-conceptions of skincare</td>
</tr>
<tr>
<td>Treatment and Assessment</td>
<td>Group Allocation</td>
</tr>
<tr>
<td></td>
<td>Compliance</td>
</tr>
<tr>
<td></td>
<td>Equipment</td>
</tr>
<tr>
<td>Communication</td>
<td>Type: verbal, visual, written</td>
</tr>
<tr>
<td></td>
<td>Influence of others</td>
</tr>
</tbody>
</table>

Table 6.42: Themes and sub-themes

During the final part of the mapping and interpretation phase, the matrices for each theme were reconsidered and interpreted in a rigorous manner to establish patterns of association within the data in addition to differences. The themes from the charting phase were refined from ‘acceptability’, ‘treatment and assessment’ and ‘communication’ to become the three main overarching themes for the qualitative study: ‘influences on participation’, ‘perceptions of the intervention’ and ‘building a trusting rapport’.

These three themes encompassed all of the influential factors emergent from the data provided by the participants as illustrated in table 6.43. Data remained true to the individual participant data by encompassing quotations within summary text and defined by pseudonym. The final overarching themes were agreed within the wider research team.
In keeping with the process of framework analysis, all of the information in the final framework matrix can be visualised against each previous stage of the analysis demonstrating efficient organisation and transparency, together with a decision trail for how the final themes eventually emerged from the original interview topic guide (appendix 28). Full details of how the original participant data mapped with the final study themes is illustrated in table 6.44. In summary, when data analysis was complete, three overarching themes emerged: ‘influences on participation’, ‘perceptions of the intervention’ and ‘building a trusting rapport’, with nine influential descriptors (table 6.43). Each of these will now be presented.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Influential factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influences on participation</td>
<td>Rationale: altruism, minimal burden, awareness of atopic eczema</td>
</tr>
<tr>
<td></td>
<td>Timing: recruitment, assessment, duration, routine</td>
</tr>
<tr>
<td></td>
<td>Pre-conceptions of skincare: regimes, ideas, beliefs</td>
</tr>
<tr>
<td>Perceptions of the intervention</td>
<td>Treatment allocation</td>
</tr>
<tr>
<td></td>
<td>Protocol compliance</td>
</tr>
<tr>
<td></td>
<td>Equipment</td>
</tr>
<tr>
<td>Building a trusting rapport</td>
<td>Communication</td>
</tr>
<tr>
<td></td>
<td>Influence of others</td>
</tr>
<tr>
<td></td>
<td>Setting</td>
</tr>
</tbody>
</table>

Table 6.43: Final themes and underlying influential factors following mapping and interpretation phase of analysis

6.11 Reporting of main themes

The aims of the qualitative study were to assess acceptability of the trial to new parents, and to explore the feasibility of the trial processes, parameters and management from the maternal perspective. It was intended that only mothers would participate but in two cases their partners also contributed to the interview. Both fathers consented to allow their data to be used in dissemination and both also chose pseudonyms to assure their anonymity, as did all of the mothers. Interview questions were designed to address the aims of the study. Due to the nature of these aims and consequent interview topics, the themes to be discussed closely reflect the topic schedule.

6.11.1 Influences on participation

Participation was influenced by the mother’s perceptions, ideas and beliefs about research participation, the timing of the various study processes, and awareness of and family history of atopic eczema. This theme as a whole generated the most data from the mothers, and the sub-theme of participating for mainly altruistic reasons was supported by the most data from both the interviews and the questionnaire open-text responses.
Influences on participation

### Rationale for participation

**Altruism:**

- Interviews: Ila, Indiana, Jane, Jill, Lydia, Maureen, Nicole, Rachel, Samantha, Ted and Barbara, Tom and Marie, Tori, Zaynad, Aisha, Elaine, Meg, Salma, Margaret, Olivia

**Minimal burden:**

- Interviews: Elaine, Ila, Indiana, Jane, Lydia, Maureen, Salma, Ted and Barbara, Tom and Marie, Tori, Zaynad, Jill, Nicole
- Questionnaires: 014 / 015 / 016 / 035 / 041 / 051 / 074 / 088 / 106

**Awareness of atopic eczema:**

- Interviews: Elaine, Tori, Zaynad, Aisha, Ila, Indiana, Meg, Olivia
- Questionnaires: 063 / 089 / 108

### Timing

**Recruitment:**

- Interviews: Aisha, Elaine, Jill, Samantha, Tom and Marie, Lydia, Maureen, Nicole, Olivia, Salma, Tori

**Duration of assessment / study:**

- Interviews: Aisha, Ila, Indiana, Lydia, Margaret, Salma, Ted and Barbara, Tom and Marie, Tori, Zaynad, Jane, Maureen, Nicole, Olivia, Jill, Elaine, Samantha, Meg, Rachel
- Questionnaires: 059

**Establishing a routine:**

- Interviews: Elaine, Zaynad, Tom and Marie, Maureen, Nicole, Samantha, Ila, Olivia, Jane, Jill, Ted and Barbara, Indiana, Margaret, Rachel, Salma, Tori
- Questionnaires: 012 / 015 / 066 / 076 / 081

### Pre-conceptions of skincare

**Regimes:**

- Interviews: Jane, Ted and Barbara, Jill, Elaine, Ila, Indiana, Olivia, Samantha, Nicole
- Questionnaires: 099

**Ideas and Beliefs:**

- Interviews: Aisha, Jane, Ila, Jill, Salma, Tori
- Questionnaires: 001 / 078 / 081 / 092

### Perceptions of the intervention

**Treatment allocation**

- Interviews: Elaine, Tom and Marie, Indiana, Lydia, Maureen, Nicole, Olivia, Tori, Meg, Sarah, Zaynad, Ila, Jane, Jill, Salma, Aisha, Rachel, Ted and Barbara
- Questionnaires: 011 / 013 / 038 / 077

**Protocol compliance**

- Interviews: Indiana, Lydia, Olivia, Samantha, Tom and Marie, Aisha, Jane, Maureen, Meg, Rachel, Sarah, Tori, Zaynad, Jill, Nicole, Ila, Salma
- Questionnaires: 002 / 008 / 010 / 016 / 028 / 071 / 092 / 093 / 097 / 109 / 110 / 112

**Equipment**

- Interviews: Elaine, Jill, Margaret, Maureen, Rachel, Ted and Barbara, Aisha, Ila, Indiana, Jane, Lydia, Meg, Salma, Zaynad, Tom and Marie, Tori, Nicole, Samantha
- Questionnaires: 047 / 052 / 097

### Building a trusting rapport

**Communication**

- Interviews: Elaine, Indiana, Lydia, Maureen, Meg, Rachel, Salma, Samantha, Ted and Barbara, Tori, Zaynad, Jill, Nicole, Tom and Marie, Ila, Aisha, Jane, Margaret, Olivia, Sarah
- Questionnaires: 032 / 074 / 099 / 107

**Influence of others**

- Interviews: Lydia, Meg, Nicole, Samantha, Ted and Barbara, Tom and Marie, Elaine, Jane, Maureen, Jill, Tori, Ila, Zaynad, Aisha
- Questionnaires: 032 / 076 / 087 / 097 / 099 / 108

**Setting**

- Interviews: Lydia, Nicole, Margaret, Tom and Marie, Zaynad

Table 6.44: Mapping of original data to main themes

6.11.1.1 Rationale for participation

6.11.1.1.i Altruism

Mothers were generally very positive about allowing their newborn baby to participate in the trial. There was an overwhelming feeling that it was important that research is conducted in order for knowledge to advance.

“... if nobody does it then you never find anything out.” Marie
Many of the mothers wanted to take part so that there would be a benefit to future babies and children, even though they would not benefit personally. This reason was often connected with a family history or awareness of others with atopic eczema.

"…why I took part is because my other two children have got eczema, so if … the study can help future children, even if they’re not mine … then yeah, why not …"

_Aisha_

The desire to take part was often related to the awareness of the prevalence of atopic eczema and how badly it affected many of the families.

" … we were actually happy that you were doing it because I thought actually, we used to speak about it, thinking it needs to be done … someone needs to do something about this, to find out why kids these days get more eczema."

_Ila_

Mothers wished to take part so that they had early access to the study results as it was a topic area that they were interested in, due to a family history of dry skin or atopic eczema.

“I was curious … whether … the oil makes a difference or not … my … first daughter’s skin was very, very dry as well when she was born … the midwife did tell me to put olive oil on her and I did see improvement. So, I was interested in this study, because I wanted to know … did it really work or is it just because … she’s growing and her skin is changing? So, yes, it would be interesting to know the results.”

_Salma_

6.11.1.1.ii Minimal burden

Mothers were generally positive in their responses when discussing the burden of being in the trial. Many mothers suggested that the protocol was not overly onerous compared to other trials that they had experienced in pregnancy. There were many comments suggesting that the OBSeRvE study was easy to follow and comply with, did not take up much time or detract from their daily activities.

"It wasn’t time consuming or anything like that. You have to remember … what areas you could touch or couldn’t touch. Other than that there was no problems or anything like that. It’s quite easy to do.”

_Jane_

Mothers were given a supermarket voucher at the end of the follow-up assessment to say thank you for their time, and travel expenses were reimbursed. Some mothers mentioned this and were very appreciative. Most of these mothers qualified their statement saying that they would have participated without the voucher, apart from Salma who suggested
that she wanted to make sure that she followed all of our instructions to ensure that she 'earned' the voucher.

“Well, erm, it helped me to do the, er, you know, the study properly, because, you know, I, erm, I wanted to feel like I've earned those vouchers, so it helped me to remember that I know I've got to do this everyday …” Salma

6.11.1.1.iii Awareness of atopic eczema

For many mothers their personal family history of atopic eczema, awareness of friends and family with the condition, or awareness of the prevalence of the condition were reasons that mothers gave for taking part in the research which were also altruistic in their desire to help others.

“My family all suffer with dry skin so will help to see if this will benefit everyone.” Questionnaire 063

Some mothers reflected on the debilitating nature of the condition of atopic eczema and the impact on the child.

“… having kids with skin problems, you're like constantly … trying one cream. Then it's another. One helps for maybe a few weeks and then it don't help anymore. Then you go to your GP for another one … you can't use normal products … for a kid to go through that, it's just horrible. And you don't know what to use, and you don't know what it's causing. So, that was, for me, the main thing to, you know, to do it [take part].” Aisha

6.11.1.2 Timing

6.11.1.2.i Recruitment

The effect of the birth was a major theme mentioned by mothers. The effects of the birth had an impact on many other aspects of the study including consent, commitment, and information provision which will be covered in other sections of these results. Mothers suggested that the timing of recruitment (within 72 hours of birth) was not the best time for women even though they understood that it was necessary for the study. Some women said that their mind at that time was not functioning properly, or that they were very fatigued.

“I think maybe my brain wasn't, like, 100% after giving birth! [laughs]” Samantha
This was also recognised by partners in the interview. This was supported by the number of partners who brought the baby for the baseline assessment leaving mothers to rest on the ward, together with other interview data which highlights the mother’s reliance on others to make a decision to participate.

“I also think it depends how the mother’s birth has been, how coherent the mother is at the time.”

Tom

6.11.1.2.ii Duration of assessment / study

The researcher was very open about how long the assessments would take (approximately 45 minutes), which meant that parents were prepared for this. This probably encouraged the positive comments in the data. Some mothers suggested that they were pleased to have something else to do.

“I think particularly sort of, ‘cause you’re in hospital, and you’re so flipping bored. The thought of having your mind on something else for 40 minutes is really good!”

Tori

There was some discussion over the four week duration of the study so that mothers’ opinions of a longer study duration could be explored to inform future study design. Some mothers felt that they would have been prepared to participate if the study was longer in duration.

“In the name of science [laugh], I probably could have done it for six months!”

Ila

More mothers felt that four weeks was long enough and that a longer duration may have affected their adherence to the protocol or may have affected their decision to participate in the trial.

“Yes, I think 28 days … felt like enough, yes. I remember, sort of, feeling a little bit relieved it was coming to an end.”

Maureen

“… if I was a brand new Mum on the ward and I’d been asked to do an eight week study, I’d probably think, I can’t think past next week.”

Lydia

6.11.1.2.iii Establishing a routine

Many mothers felt that being in the study helped them to more quickly develop a routine with their baby. Some also suggested that it helped them to get to know their baby’s likes and dislikes in relation to touch and massage.
“… it actually helped me to get into a bit more of a routine, er, with bathing and stuff like that, getting him ready.”  

Indiana

Some mothers had continued to follow the same routine beyond the end of the study treatment period.

“Today we still do it morning and night”  

Olivia

6.11.1.3 Pre-conceptions of skincare

Many mothers suggested that they had a skincare strategy in mind prior to having their baby, but were happy to put this aside for the sake of research.

“"Oh, it would have been fine because we understand that it was for the research so it wouldn’t have really bothered me. But, obviously, we got the best group for us, like personal choice.”  

Barbara

Some mothers felt that it was acceptable to go against their pre-conceived ideas because the study only involved three small areas of the baby (left forearm, abdomen, left thigh), so they could continue to use their choice of products on the rest of the baby’s body.

“… we weren’t going to be using any other products, erm, initially on his skin … and because it was only in a few small areas, erm, it didn’t really cause us any concern.”  

Nicole

Having pre-conceived ideas for skincare was particularly noticeable amongst multiparous women who may have followed the same skincare strategy for the new baby as they had for previous children, but they were willing to put this aside for the research.

“… well because my daughter’s got eczema, you know, and it could have been caused by something I’ve used or because, you know, I’ve slopped all sorts on her skin when she was the same age as he is now …”  

Elaine

One reported belief was mentioned by Salma after the end of the recorded interview, and was recorded in field notes. Salma advised that the Muslim teachings of the Prophet Mohammed encourage using olive oil with mustard seeds, honey and turmeric for skin conditions and general health. The olive tree is a blessed tree in Islam. The qualitative data did not generate any common themes on cultural and religious beliefs, but eight women did decline to take part because of their cultural background being incompatible with a change in their traditional baby skincare practices.
6.11.2 Perceptions of the intervention

This theme encompassed mothers’ views and experiences of their baby's treatment allocation and the process of randomisation, their adherence to the protocol with regard to study treatment use and other product use, and their perceptions of the equipment used in the study for testing the outcome measures.

6.11.2.1 Treatment allocation

There were no issues raised from mothers pertaining to the process of randomisation, in terms of allocation or understanding of the process. The researcher took time to explain the process during the information provision phase, and those who did not want to be allocated to a particular treatment regime by chance declined to take part at this point.

Once allocated to an intervention group, mothers remained blind to which oil they had, labelled only X and Y. Some mothers disclosed that they had thought about what oil they had been allocated to but decided it was best not to know. The reasons for this were two-fold: some mothers felt that they would inadvertently tell the researcher which oil they had if they knew, as it had been strongly emphasised to them that the researcher needed to remain blind to what group they were in.

“I would have liked to have known but … if I did know I probably would have slipped up.” *Elaine*

Other mothers preferred not to know as they suggested that they may have researched more about the oil and not felt confident in using it.

“It was probably best that we didn’t know … I would’ve still put it on her because you wouldn’t give me something that would’ve harmed her; it was only a bit of oil.” *Marie*

The emphasis that mothers put on agreeing to participate because it was a study that would not harm the baby probably required further interrogation by the researcher, but this was not taken further. It was made clear to mothers during the information provision phase that it was unclear if these oils were good for, or harmful to, baby skin, and that the use of some oils may be connected to the development of atopic eczema. The researcher perceived from the interviews that mothers felt that the oils were not harmful to babies. Mothers had obviously digested the information about the possible connection with atopic eczema, but it is unclear whether they had disregarded the connection with harm. Mothers appeared unconcerned about the oils being harmful and yet many were looking for them to cause a reaction to the baby’s skin.
“I wanted to be in one of the oil groups, ‘cause I wanted to see if he’d react to anything on his skin.”

Tori

Many mothers suggested that being in one of the intervention groups made them feel as though they were doing something in the study.

“I like that I was actually taking part … in the study. I know that … you have a control group who … don’t get anything and they are still part of the study because you have to have that control group but I, I liked that I was actually doing something.”

Lydia

This resonated with a perception that being in the no oil group was the easy option.

“… I remember joking with my partner that it would have been good to have been in the no oil group because then you don’t have to do anything…”

Jill

6.11.2.2 Protocol compliance

This was the only theme where there was some consensus of negative responses. This mainly revolved around the protocol instruction to leave the baby undressed for approximately ten to fifteen minutes following application of oil, and the awkwardness of trying to avoid the study areas (left forearm, abdomen, left thigh) when bathing the baby.

The delay in cares following application of the oils was mentioned by a number of mothers in the questionnaire. Some mothers suggested that the baby did not like being undressed and became distressed. Others were concerned about getting oil on the baby’s clothes, and the remaining comments reflected the additional time to get ready.

“It didn’t take too much out of the day … towards the end I was thinking ‘oh [big sigh], I just want to put her clothes on’, and I had to oil her.”

Marie

“… putting, er, the oil on is quite a messy thing and having to wait for it to soak in is … a bit messy. If there’s any way, I don’t know, if, if you, if there was a, a sticker with the oil in, you could put on [like a nicotine patch]”

Lydia

Bathing the baby generated an increased response from mothers. Mothers had been advised to use water only to bathe the baby, but that if products were used they should avoid the study areas. Mothers found it very difficult to comply with this, although the majority did comply, mainly due to the limited duration of the study.

“I have felt slightly restricted about what I apply to my child’s skin. However this has not really bothered me as it was only for 4 weeks.”

Questionnaire 093
Two mothers suggested that this issue could be solved with the provision of a control cleanser in the study.

“…maybe if you had a control soap where you … say you wash your baby in this control soap only … and everyone uses the same, then I think that might be a bit more easy to keep it going for a longer time.”  

Ila

Some mothers reported that protocol compliance was made slightly more difficult by family involvement, with family members putting products on to the baby’s skin without the mother’s knowledge, the baby having dry skin and mothers wanting to treat this, and attending baby massage classes and being encouraged to use oil.

6.11.2.3 Equipment

The main comments about the equipment used for assessing the baby’s skin concerned the non-invasive nature of the probes which did not harm or cause distress to the baby. Mothers were not overwhelmed by the number of probes being used, but this feeling may have been minimised by the full explanation for each probe given by the researcher during the assessment.

“I suppose I was quite surprised because I actually didn't realise … what, sort of, tests you were doing but, you know, I thought it … looked very modern and [laughing] … you were obviously not distressing to the baby at all. You explained absolutely everything beforehand. You told me what everything was and what was going on his skin. So, … I felt like I had all the information I needed.”  

Maureen

Many of the mothers were intrigued with the science of the probes, and were impressed with the technology. They suggested that this was reassuring.

“I was very impressed … you were working with this kind of equipment, so it made me even more … confident in you, or in the [study]”  

Meg

Some of the equipment was specifically mentioned: the bottles were an issue for some mothers and the D-Squame discs for others. Plastic bottles were chosen for safety reasons but mothers experienced some issues with the quality of the bottle. Some advised that the bottles were too light so they were easy to knock over, and some said that the lid was an issue.

“…I was in the oil group and, erm, the containers that the oil was in were quite … I actually over tightened mine so it cracked.”  

Jill
One mother did not like the redness caused to the baby’s skin from the D-Squame disc. Others said that they were happy with the discs as the researcher always stuck one on the parent first so that they were reassured that they would not harm the baby.

6.11.3 Building a trusting rapport

This theme encompassed the relationship developed between the researcher and the participants, and the study information provided to participants verbally, visually and in written form. It also reflected on the influence of others and the setting in relation to the decision-making process and study participation.

6.11.3.1 Communication

All participants were provided with a direct mobile telephone number for the researcher and told that they could contact her anytime. None of the participants took advantage of this service. The researcher did contact each participant by phone on a weekly basis, and one adverse reaction was detected by this method. This participant was happy with the speed of the contact when this occurred.

“... I don’t even think he [dermatologist] was in the country at the time, so it was amazing ... how quickly it was, you know, it was put a stop to really ...”

Elaine

Most mothers felt that a weekly phone call was the optimal frequency for contact with the researcher.

"I got a phone call every week ... when you've got a newborn baby ... any more you would have been like, ‘ooh stop hassling me’ [laughs], any less and you would have been like, ‘oh well, no-one’s getting in touch with me’.

Indiana

Mothers suggested that a mixed approach to communication was best. They liked the personal direct contact of the researcher talking to them about the study on the ward, followed up with an information leaflet that they could peruse in their own time.

“If you’re going to give out the leaflets for it I think it should be once you’ve been and spoke to the parents about it ... then given them the leaflet after it so then it’s fresh in their mind and they can flick through it then.”

Ted

Nearly all of the mothers discussed the usefulness and memory-stimulating nature of the laminated photographic diagram of the baby which had the study areas highlighted (chapter 4; figure 4.1). They placed the importance of this visual information higher than the participant information leaflet (appendix 13). Mothers kept the diagram by the baby
changing area and this helped them to remember to do the treatment applications, and which side (left or right) of the baby they should be treating or avoiding.

"... I, kind of, used to, like, make sure she was in the same, the exact same position as the baby [in the picture] so I could definitely make sure it was in the right place because you can easily get the wrong side if you… [are] feeling tired…"

_Jill_

Most of the mothers were content that the participant information leaflet covered everything and was comprehensive and easy to understand. Conversely they also suggested it was slightly too long although they appreciated all of the information was necessary. Some suggested that more pictures or bullet-pointed information may be more beneficial to aid understanding for women who have just given birth and may be fatigued. Many mothers suggested that they relied on their partners to digest the information and help them to make a decision on whether to participate or not.

"I understand that you’ve obviously got to put certain information in it to, you know, cover everything … but whether it could be reduced or condensed so that it could just be, you know, like visual or even a bit more easy to look through considering the circumstances of the women that you’re approaching."

_Nicole_

Nearly all of the mothers interviewed suggested that they did not remember seeing the summary participant information leaflet which was given out antenatally (appendix 12). The leaflet was in a pack of leaflets given out during pregnancy and even though it was a professionally produced colour leaflet, it was not recalled.

6.11.3.2 Influence of others

Mothers stated that they had confidence in the researcher and the research team associated with handling a newborn baby and managing the equipment. Some mothers liked having a midwife leading the research. Many participants described the team as very professional.

"I liked the fact that it was a midwife. I wouldn’t, it wouldn’t have stopped me from doing the research, but … it fills you with … more confidence."

_Marie_

There were usually two researchers in the clinical room (researcher and research technician) and mothers felt that this gave them more confidence in the whole assessment process.
“I liked the fact that there were two people there, so there was one person who was taking the results and there was one person who, well, maybe it was my assumption, but there was one person that, if my baby was reaching for a probe or something that they would be able to stop them. … that made me feel more comfortable about everything really.”  

Lydia

Some mothers discussed the conflicting advice that they received about skincare from family, friends and health professionals. They felt that the study would help to provide evidence so that health professionals could all give out the same advice, and parents would have the evidence to stand up to family recommendations.

“The midwives at the hospital didn’t seem to be all for or all against. But mostly parents and grandparents and health visitors seem to, like to give you all their information.”  

Jane

Partners appeared to play a substantial role in this study. It has already been mentioned that women relied on their partner to digest the written study information and take part in the decision-making regarding whether to participate.

“…I was, erm, a bit delirious really … having to digest complicated information on my own without my partner there was probably, you know, you just, kind of, need that reassurance and a second opinion from a member of the family or your partner just to, you know, confirm what you’re thinking.”  

Nicole

Although numbers were not recorded by the researcher, many partners brought the baby for the baseline assessment and the researcher would suggest that this was probably in the region of approximately 70% of the assessments. They did this mainly to allow the mothers to get more rest. Many of the partners also took ownership for the treatment applications, as they had been so involved at the decision-making stage and for the baseline assessment.

“…he would sort of come home and say ‘have you done it?’, and I’d be like ‘yeah, yeah I’ve done it’ …[and partner said] ’where did you put some?’ [laughing]. So I’d sometimes forget, but because he’d been to it [baseline assessment] …it was quite useful actually that he went instead of me…”  

Tori

6.11.3.3 Setting

The hospital was a teaching hospital with a dedicated Maternal and Fetal Health Research Centre. This was important to mothers. Some said that this was the reason why they chose to give birth at this hospital.
“I felt fairly confident because we were in the hospital. We obviously knew that it was a safe thing to do, erm, and it was just, kind of, perfect because we were in the hospital.”  

Nicole

However, being a research hospital also meant that it was a very busy hospital, which caused problems for some participants relating to parking, for example. Even though travel and parking expenses were reimbursed this could not recompense participants for the difficulty in finding a parking space.

“I think the only problem with the hospital is sometimes the parking. ’Cos the actual hospital is pleasant, it’s a lovely hospital unit, easy to get around, a nice quiet area where the research is…”

Tom

6.12 Conclusion

This study has encompassed quantitative and qualitative methods to obtain a variety of data in the form of clinical trial data, questionnaire and in-depth interview data. The quantitative data has provided proof of concept that olive oil and sunflower oil have an effect on newborn skin barrier function. This data also informs the researcher’s understanding of the optimal methods for future research design and current maternal preferences for newborn skincare. The qualitative data has provided an understanding of the parental perspective of having a baby participating in a skincare trial, including what aspects of the study are acceptable. The combination of the two approaches has provided evidence to inform future study design. Further observational and mechanistic research is necessary before a definitive trial is conducted, and the quantitative and qualitative pilot data which has been generated has helped to inform how best this might be achieved. This will be discussed in detail in the next chapter.
CHAPTER SEVEN: DISCUSSION

7.1 Introduction to the chapter

This chapter examines the findings of the OBSeRvE study in greater detail to critically analyse the research conducted in terms of the findings, methodological strengths and limitations, and future clinical and research recommendations. A key consideration in this discussion is how the research informs future research; this is important given that this was a pilot trial. Findings are contextualised within the existing body of research.

This was a pilot study and as such, was not powered to determine statistically significant differences in outcome variables tested. The study aims were to establish proof of concept that topical oils had some effect on baby skin barrier function, and to investigate optimal trial parameters and processes. These aims are the emphasis of this chapter. The challenges of recruitment and retention are also discussed, together with the benefits of conducting pilot studies before the decision to proceed with a definitive trial.

Reflexivity is incorporated, and the dialogue evolves from a combination of the findings from the quantitative and qualitative components of the study. The anticipated result of this work was the generation of data that would inform a definitive randomised controlled trial, but findings have indicated that this is not the optimal next step. The choice of methodology and designs for future research in this field are reflected upon in the final part of the chapter.

7.2 Aims and objectives of the study

The primary aims were to assess the feasibility of testing the hypothesis that the regular application of topical sunflower oil, when compared to topical olive oil or no oil, improved the skin barrier function of newborn term babies, to consider the optimal parameters and processes for a definitive trial and to consider the acceptability of such a trial to mothers. The research question arose from a clinically-based issue: the traditional practices of recommending and using topical oils on newborn baby skin. The evidence to support these practices does not exist. Clinical guidelines are required to support practice that only does good for babies, and does not cause harm (Higgins and Green 2009). The high prevalence of atopic eczema amongst children aged between 2 years and 15 years is a growing concern (Gupta et al. 2004). This is the first study that the researcher is aware of, to investigate and compare the impact of olive oil and sunflower oil on newborn term baby skin barrier function. These are the two most commonly recommended and used oils on newborn babies in the UK (Cooke et al. 2011). The existing research in this area considers oils in different populations and different settings (discussed in chapter two). A pilot RCT with a nested qualitative component was designed and implemented at a large
teaching hospital in the North West of England to address this gap in the evidence, comparing these two oils against a control group using no oil to assess the feasibility and acceptability of the protocol, outcome measures and interventions.

7.3 Originality

The originality of this research is evident in the population, the findings, and the implications of the findings. The literature review (chapter two) demonstrated the dearth of studies addressing newborn term babies. There were no studies that investigated and compared the effects of olive oil and sunflower oil, the two most commonly recommended oils in the UK, on newborn term baby skin. OBSēRVē has filled this gap in the evidence, and a first Cochrane review of the evidence is currently in progress.

OBSēRVē has also generated a substantial neonatal dataset of biophysical skin measurements at birth and 4 weeks for babies using topical sunflower oil, olive oil or no oil, including a novel measurement of the lipid lamellae structure using Attenuated Total Reflectance Fourier Transform Infra-Red (ATR-FTIR) spectroscopy. This outcome measure is ethical for a baby population as it can detect changes in the skin profile before any effects are visible clinically. The results from this outcome measure are also novel when compared to the existing evidence base. The finding that both topical olive oil and sunflower oil may impede the development of the skin barrier function from birth was a completely novel finding when data analysis was completed in October 2014, and the researcher was unblinded to group allocation on 4th November 2014. Shortly after, a small German study of a preterm population (Kanti et al. 2014; n=22) was published, which supported the OBSēRVē results also finding that sunflower oil adversely affected the skin barrier function. The clinical implications of the findings from the OBSēRVē study are that there must be a change in midwifery practice so that these topical oils are no longer recommended or used; until further research is available that supports the use of a topical oil for baby skincare.

7.4 Methodology

Post-positivism is the underlying philosophical perspective for this study. This stance provides not only the required objectivity for quantitative data collected in a randomised controlled trial, but also the complementary qualitative data which reflects the meaning, understanding and experiences of mothers of babies participating in the study. The qualitative data were analysed using Framework Analysis which fits with the philosophical stance of post-positivism due to its organised and methodical approach. Post-positivism provided the basis with which to consider the research through both quantitative and qualitative lenses, providing an additional dimension to the assessment of feasibility for
future research. This has worked well in the OBSerVe study. Challenges faced in the trial, such as recruitment and retention, have been enlightened by the qualitative data so that future studies can address the resolution of these issues at the design stage. The qualitative data will inform the choice of equipment for a future study such as the optimal oil container. The qualitative data also suggests that information provision should be made more visual; taking into account a mother’s needs immediately following the birth of her baby. None of these issues would have been exposed in a quantitative study alone.

7.4.1 Study design

The combination of the randomised controlled trial with the qualitative study has resulted in a wealth of data to inform future research design. By utilising both approaches, the researcher has gained a fuller understanding of what is required, and what constitutes an acceptable study design for mothers to permit their babies to participate in. The barriers and facilitators, particularly for recruitment and retention of the mother and baby population, have also been highlighted enabling solutions to be considered.

The qualitative component became even more important at the realisation that loss to follow-up was higher than anticipated. The decision was taken to increase the number of qualitative interviews to realise more data and extract more meaning as to why retention in the study was so difficult. The recruitment and retention challenges experienced by the researcher particularly highlighted the importance of using both quantitative and qualitative approaches when assessing feasibility, as the qualitative data provided understanding of issues that are important to participants in a clinical trial (Pope et al. 2002). Using the complex intervention framework exploratory and development phase (Medical Research Council 2008) encouraged the addition of the qualitative component at the design stage, and this has proved invaluable in providing understanding of the barriers and perceived benefits of participating in the research. This will contribute to robust future research design.

The discussion in this chapter integrates the qualitative interpretation with the quantitative findings to ensure that the processes are fully explained from both the researcher’s and participant’s perspectives. The researcher was solely responsible for collecting all of the data, both quantitative and qualitative. To ensure rigour and credibility of the findings, data analysis was ratified by other experts within the research team including a statistician for the trial data, experts in skin barrier function and infrared spectroscopy for the primary outcome data, and an expert in qualitative data analysis for the interview data. Quality of the methodological aspect of the study was a priority. Reporting has been transparent in all processes, including clear detail of the methods and processes (chapter four), and
discussion of all of the outcome variables documented in the study protocol and the Clinical Trial Registry. The role of the researcher in the study processes was integrated throughout this discussion chapter to ensure that reflexivity was included and transparent. Any ethical issues were also incorporated within the relevant parts of the discussion.

7.5 Discussion of the feasibility of the study
7.5.1 Recruitment and retention

This section discusses the challenges of recruiting newborn babies to a randomised controlled trial. Although many of the issues were anticipated, with strategies learnt from previous research incorporated into the study design, there were also some unforeseen challenges. The target population included term babies (>37th weeks gestation) born in St. Mary’s Hospital in Greater Manchester, North West England.

7.5.1.1 Eligibility
7.5.1.1.i Screening

There were 4085 mother and baby pairs assessed for eligibility; 2886 were excluded at the first phase of screening. The recruitment period, commencing on 11th September 2013 and ending on 20th June 2014, was a total of 40 weeks, giving an eligibility assessment rate of 102 patients per week or 34 per day during which recruitment was performed. This is the most accurate figure that can be provided. The screening was conducted by the clinical midwives on the postnatal wards each recruitment day from study commencement to 2nd February 2014, but the researcher cannot be confident that during this period the midwives always confirmed all of the eligible mother and baby pairs on the ward. At times, clinical midwives gave the impression that it was a considerable effort to determine eligibility. Although this was not often stated in so many words, the researcher perceived that there may have been eligible mother and baby pairs who were not given the opportunity to participate. This was confirmed for 91 mother and baby pairs where the clinical midwives actually stated that they were “too busy” to assess their caseload for eligibility. Lack of time has been suggested by clinicians as a significant barrier to recruitment in previous studies (Tooher et al. 2008). Conversely, some clinical midwives conducting the eligibility screening had suggested that a mother and baby were eligible, but when the researcher approached the women, subsequently found them to be ineligible.

When it became apparent that recruitment was not as successful as anticipated, an ethical amendment was submitted to amend the screening procedure so that this could be conducted by the researcher. This amendment was approved and became effective from
2nd February 2014. The revised screening process permitted the researcher to identify eligible women from the hospital in-patient software (BedMan) rather than asking the clinical team to do this. The researcher then approached the clinical midwife with a list of identified eligible mother and baby pairs in order to confirm if there was any reason they should not be approached. The new screening process reduced the burden of time on the clinical team. Enhanced recruitment is significantly associated with having a dedicated clinical trial manager (McDonald et al. 2006). The process became more efficient and the researcher became confident that all eligible mother and baby pairs were given the opportunity to participate.

The volume of mother and baby pairs passing through the two busy postnatal wards of St. Mary’s hospital, being a large tertiary hospital, meant that there were many potential participants. However, it also meant that the time taken for the researcher to screen the in-patients each day took capacity away from other aspects of the study such as recruitment and assessments. This was an issue due to the nature of the doctoral study where a lone researcher was conducting all aspects of the study. In a definitive study, a research team would need to include sufficient capacity to overcome this problem. One researcher recruiting and one conducting assessments, and both screening, could be a potential solution.

7.5.1.1.ii Age of baby

One of the original inclusion criteria was for babies to be recruited within 48 hours of birth. This criterion was put in place in order to reduce the risk of babies being bathed prior to baseline assessment. When an interim assessment of recruitment was conducted, the researcher noted that even with a 48 hour restriction in place, some babies had already been bathed. An ethical amendment was submitted to extend the eligibility to include babies within 72 hours of birth, as this was deemed to have little effect on outcome data, but it increased the number of babies eligible to take part in the study. This ethical amendment was effective from 2nd February 2014.

7.5.1.1.iii Room availability

An additional reason why the extension from 48 hours of age to 72 hours of age made such a difference was linked to the availability of the research assessment room. The room allocated at the hospital for the study was on the 5th floor in the Maternal and Fetal Health Research Centre, a purpose-built research facility. As St. Mary’s Hospital is a teaching and research hospital, the Research Centre is heavily used by many different research studies. When the original study fellowship application was submitted there had been an understanding that the room would be available every day. When the funding and necessary approvals were in place, the room was, in reality, only available on alternate
days (Monday, Wednesday and Friday). The availability of a research room would need to be considered at the study design stage for future studies, and contractual negotiations may be required to secure the room. Mothers were approached about participating in the study, and some asked if they could have the baseline assessment on the following day when they were more rested, but this could not be accommodated due to the room not being available. By extending the eligibility to allow babies up to 72 hours old to take part, mothers that were still in the hospital on the next but one day, could postpone their baseline assessment until they felt more ready.

7.5.1.1.iv Jaundice

Another challenge pertaining to the eligibility criteria was the exclusion of babies with neonatal jaundice. Jaundice is reported to affect approximately 60% of term and 80% of preterm babies within the first week of life, and if breast-fed can still affect a baby at one month old (National Institute for Health and Care Excellence 2010). This prevalence explains the high number of ineligible babies for recruitment. Neonatal jaundice is often a physiological issue but prolonged neonatal jaundice may be indicative of an underlying liver disorder (Shortland et al. 2008). There is a strong association between the incidence of neonatal jaundice and being of low birthweight (<2500 grams) or of Oriental origin, and a negative association with being of white or black descent (Linn et al. 1985). Other reports suggest that incidence is higher in babies of East Asian, American Indian and Greek origin (Shortland et al. 2008) and that there is a three-fold increased risk for babies of East Asian origin (Setia et al. 2002). The increased prevalence of jaundice for these babies may mean that the exclusion criteria may have caused a higher than proportionate loss of eligible babies from this particular group. On further investigation this was not the case: the mothers of East Asian origin made up 14.8% of the OBSeRvE sample and this compares well to the recorded number of East Asian mothers having their babies at St. Mary’s hospital, being 15% (Central Manchester NHS Foundation Trust 2014). Jaundice occurs when bilirubin accumulates in the blood and surrounding tissue and this may be affected by prematurity, bruising, cephalhaematoma, polycythaemia, delayed passage of meconium and breast-feeding (Shortland et al. 2008). The level of serum bilirubin is usually highest around day five following birth (Shortland et al. 2008).

The treatment for neonatal jaundice is phototherapy; bilirubin molecules absorb light which triggers three processes: configurational isomerism, structural isomerism and photo-oxidation which all contribute to the excretion of bilirubin (Shortland et al. 2008). Where the baby was undergoing phototherapy treatment or the midwife advised that treatment would likely be prescribed, babies were not included in the OBSeRvE study. This decision was taken at the study design stage before recruitment commenced, as babies would not be able to use topical oils on the skin whilst being treated under a
phototherapy light unit. Phototherapy would also delay discharge from the hospital and study treatment commencement. During a review of recruitment at the end of the study, the OBSerVe Trial Steering Committee agreed that it should not be necessary to exclude babies undergoing phototherapy treatment from future studies; the duration of phototherapy treatment is short and trial treatment could cease during phototherapy and (re)commence after phototherapy had ended. This would substantially increase the number of babies eligible for recruitment to the study.

7.5.1.1.v Gestational age

The Trial Steering Committee also discussed a change to the inclusion criteria to incorporate a reduction of the eligible gestational age at birth to $35^{+0}$ weeks as these babies are often well babies who are cared for clinically on the normal postnatal wards. Neonatal jaundice has been shown to have a higher prevalence of severity at 35 to 37 weeks of gestation (Sarici et al. 2004), so may be more of an issue. However, in general, this change in eligibility would positively affect the numbers of babies eligible.

7.5.1.2 Recruitment

Of the 1199 mother and baby pairs who were eligible to be approached, 318 declined. Women did not need to give a reason for declining to participate but, where this was offered, it was documented by the researcher to contribute towards the data for feasibility. Almost half of the women did not give a reason (n=158). Of those who gave a reason for non-participation (n=160), some had pre-conceived ideas about skincare regime and wanted to use specific products (n=34) or did not want to use products (n=21); some felt it was too much to commit to with a new baby (n=67) or could not come back for the follow-up appointment (n=30). In eight cases, mothers reported that the family would not support them. These were generally women from Asian cultures where the grandmother was the matriarch of the family and determined the care regime of the baby. New mothers felt that they would not be able to oppose the grandmother’s opinion if they were randomised to a treatment group that would not comply with the family traditional practice. Previous research has suggested that agreement to participate is influenced by other family members’ opinions (Qiu et al. 2013;Ross et al. 1999). This may be an issue that affects recruitment and retention of women from minority ethnic cultures in future research, where specific interventions are required.

7.5.1.2.i Group allocation

Mothers appeared to understand the concept of randomisation when the researcher clarified comprehension during the information provision and consent process. This was also supported by the qualitative data. Some women declined to participate as they had
specific ideas for how they wanted to care for their baby’s skin. They did not want to be allocated to a group that would not permit them to follow the regime they had chosen for their baby. Similar issues have been found in previous studies (Baker et al. 2005; Ross et al. 1999). Some women were happy with any treatment group even if they had pre-conceived skincare ideas, stating that it was only for four weeks and that they could return to what products they wanted to use after the study had ended. Other women suggested that because the study treatment areas were only three small areas of the baby’s body, they could use alternative products on the rest of the body so that was acceptable. In all cases it was important to emphasise to parents to wash their hands after using different products to maintain the protocol adherence on the three study sites.

7.5.1.2.ii Timing

The timing of recruitment was a much discussed issue for mothers. One of the qualitative themes was “just had a baby” which encompassed mothers being tired, not being able to concentrate, relying on their partner or family members to digest the study information, or not feeling well enough to bring the baby for assessment. Timing did not only affect the initial recruitment; some women suggested that committing to four weeks for a study when it was their first baby was quite overwhelming. The researcher had anticipated that it would be women with other young children who may have found it more difficult to commit to the time necessary, but this was not the case. As these mothers had previous experience of a new baby they could anticipate whether they would have the time to devote to a study, compared to new mothers who were overwhelmed with their new situation. Previous research has found similar issues with a mother and baby population (Cartwright et al. 2011; Baker et al. 2005; Mason et al. 2000). OBSeRvE had a substantial number of mothers who gave this as a reason for not participating (n=67), and it is likely that this number was much higher as the timing of recruitment probably also affected a substantial number of those who did not give a reason for non-participation (n=158). It is not anticipated that this challenge can be easily resolved, but what can help is encouraging fathers to engage in the research. During the OBSeRvE pilot, many of the babies were brought for their first assessments by the father. In the qualitative interviews two of the fathers took part with their partners and mentioned taking ownership of the treatment regime whilst the mother was recovering from the birth. More emphasis could be made of this possibility with partners and this may encourage participation.

7.5.1.2.iii Other reasons

There were a further 766 mother and baby pairs who were not recruited for other reasons: some were discharged before they had sufficient time to consider the study information (n=78); for five potential participants there was no randomisation midwife available as the potential to recruit fell outside her working hours; there was insufficient time to arrange an
interpreter for 19 mothers; for several it was not possible to obtain permission from the clinical midwife to approach the mothers (n=91); or some babies were unable to leave the postnatal ward as they were cold or poor feeders (n=52). For most of those who were excluded for other reasons, these reasons were logistical (n=521): mothers were asleep, feeding, had visitors, were being provided with clinical care by the midwife, hearing screener, paediatrician, anaesthetist, obstetrician or breast-feeding support (n=274); some mothers stated that they had not had sufficient time to consider participation (n=71); or the researcher was unable to return in time to recruit due to the length of time needed for assessments (n=176).

Some of these challenges will naturally occur with a new mother and baby population. There is routinely a steady turnover on the postnatal ward; women may be discharged home before they have had time to consider participation (Watson et al. 2008). An attempt to overcome this issue was made by giving out a study leaflet antenatally. All pregnant women at St. Mary’s hospital are given a package of information leaflets between 20 and 28 weeks gestation and the OBSeRvE study leaflet was included. The leaflet (appendix 12) was professionally produced in colour to attract attention, using a high quality 130 grams per square metre paper in a tri-fold format. The leaflet incorporated a response slip which could be returned to the named midwife if the woman was interested in further information and/or participation. Only six response slips were returned. Of these, two were recruited, three gave birth and/or were discharged on a non-recruitment day, and one response was received after the end of the recruitment period. When mothers were questioned during the qualitative interviews, most did not recall seeing the leaflet; some suggested that the volume of leaflets given out in pregnancy was so large that many leaflets were not read. This resonates with the existing literature with suggestions of women suffering from information overload, not reading the patient information leaflet or relying on the verbal information given or a family member reading the information (Smyth et al. 2012; Golec et al. 2004; Mason et al. 2000).

7.5.1.2.iv Antenatal classes

The researcher attempted, on a number of occasions, to attend the Parent Education classes to speak to parents-to-be about the study, but was advised that there was insufficient time in the programme to allow a researcher into the timetable, even for five minutes. The potential to recruit women from these classes was high as they were a captive audience approximately two to seven weeks from giving birth. Negotiation with the Parent Education team should be made earlier in future studies to gain access to this population, and this method of recruitment should be incorporated in the ethics application. If some women could be recruited at these classes, in addition to recruitment on the postnatal wards, the recruitment rate would improve. Women who attend the
Parent Education classes may fit a specific population. Previous studies have found that the majority of attenders at antenatal classes are those in their first pregnancy, and those with a higher level of education; women with a degree were eight times more likely to attend than women with a minimum level of education (Fabian et al. 2004; Spinelli et al. 2003). Young women, single women, those from ethnic minority groups and those of lower socio-economic status are more unlikely to attend (Fabian et al. 2004; Schott and Priest 2002; Cliff and Deery 1997). Any bias regarding type of participant due to recruitment from antenatal classes could be balanced by ensuring that all other eligible women were approached on the postnatal ward during the recruitment period. However, if a large proportion of the total sample were women recruited from antenatal classes, additional analyses could be conducted to explore whether this had any effect on retention, protocol violation or outcomes. Approaching some women antenatally in the Parent Education classes makes the process more efficient as it saves the time spent approaching these same women postnatally on the wards after childbirth and waiting for them to consider participation.

7.5.1.2. v Randomisation staff

The lack of a randomisation midwife could be overcome by using a computer-generated 24-hour randomisation service, rather than a service which is only manned between the hours of 9.00am and 5.00pm on working days (Monday to Friday). One of the reasons that this service was chosen surrounded the safety procedures in using the equipment. The ATR-FTIR spectroscopy required liquid and dry nitrogen to operate it. Due to the cryogenic safety requirements it was only safe to use the spectroscopy equipment when the research department was fully manned so that personnel were available in the event of a cryogenic emergency. This eliminated the possibility of working out of hours and at weekends, hence the randomisation service chosen for the pilot study was suitable. Only five potential participants were lost at times when the research midwife was working a different shift pattern than the randomisation service. In a future study, the technology is available to have a bespoke portable ATR-FTIR device which would not require the use of nitrogen (appendix 48). A 24-hour, seven days a week randomisation service could therefore be used; assessments could be conducted at the bedside and consequently recruitment would benefit from addressing several of the challenges faced in the pilot study:

- clinical room only being available alternate days
- only three days of the week available for recruitment
- lack of portability of the equipment
- lack of randomisation midwife
- lack of capacity to arrange an interpreter
• babies needing to leave the ward for assessments
• restricted visible presence on the ward due to conducting assessments

A fully online randomisation service would have to be carefully assessed for its proven reliability, accessibility and the ability to randomise according to the required study design, such as with stratification or unequal group sizes. Use of such a service would have to be discussed with a Clinical Trials Unit, who may wish to oversee the running of a randomised study and may have their own randomisation service.

7.5.1.2.vi Clinical staff

Clinical midwives being too busy to give the researcher permission to approach potential participants was frustrating and not simple to address. There appeared to be an ethos that clinical care was the only priority, and research was not a priority when the ward was busy or short-staffed. Health professionals do not always consider research to be important or relevant (Abraham et al. 2006; Fayter et al. 2006; Somkin et al. 2005). The researcher was present on some shifts where the midwife could not be found, no matter how long the researcher waited or searched. On other occasions the midwife said that they were too busy; this was either a final decision or they asked the researcher to return later. On one occasion the midwife shift coordinator told the researcher not to approach the midwives during that shift. This left the researcher unable to recruit that day. The researcher attempted to overcome these issues by making midwives aware of the research from the outset by attending shift meetings, having individual meetings with all ward managers and shift leaders, putting up posters in the communal areas, updating ward and community midwives throughout the study and keeping the channels of communication open. Good channels of communication with clinicians have been shown to be important in making recruitment as successful as possible (Watson et al. 2008; Youngblood et al. 2005). Some midwives were open to research and were extremely helpful throughout the study; other midwives were quite obstructive and would not even examine their caseload shift notes before saying that they had no-one eligible. The researcher spent more time engaging with these midwives to attempt to ensure that they were aware of what the study was, and the importance of giving every eligible woman the opportunity to choose whether or not to take part (Watson et al. 2008). As the researcher is a midwife, this may have helped with the communication and relationship-building, and could potentially be more of a challenge for a non-midwife researcher. Although it took some time to build a rapport with these midwives, eventually an understanding ensued. This may help other research studies’ in the future as the clinical team have a better understanding of the reasons for research.
The logistical reasons for non-recruitment were under-estimated. The researcher, as a midwife, was aware of the busy nature of a postnatal ward, but the difficulty of seeing women between their other visitors was worse than anticipated. The number of women lost to recruitment for this reason was very high (n=274), and a dedicated recruitment midwife may help to overcome this as they would not need to leave the ward environment to conduct assessments. This would enable them to have a presence on the ward and see women when they became available. The researcher’s time was limited as some of the day had to be spent conducting assessments. As each assessment took approximately 45 to 60 minutes of the researcher’s time, this minimised the time that could be spent on the ward recruiting. The effect of this is highlighted from the additional number of women lost as the researcher was unable to return to them before the end of the working day (n=176). Again a dedicated recruitment midwife, working alongside a dedicated assessor, could improve the recruitment rate.

There has been a growth in the number of studies considering barriers and facilitators to recruitment over the past decade. One common theme throughout the literature is that altruism plays a major part in participant decisions on whether or not to participate in research trials (Barnett and Jones 2015; Brumatti et al. 2013; Tooher et al. 2008; Sammons et al. 2007; Canvin and Jacoby 2006; Baker et al. 2005; Hoehn et al. 2005; van Stuijvenberg et al. 1998); this has not changed from earlier research (Ross et al. 1999). The OBSeRvE interview data also highlighted an overwhelming sense of altruism; wanting to help others in the future and contribute to progress in clinical research. The OBSeRvE data highlights that this reasoning for mother and baby pairs to participate in research still exists and will likely continue to exist for future research. It is unlikely that the recruitment rate for a future study in this area would therefore be any worse, and by addressing the challenges discussed in this chapter is likely to substantially improve.

There did appear to be a recruitment dichotomy with altruism on one side balanced against self-protection on the other. Mothers were happy for their baby to participate as there was no perceived harm, the tests were non-invasive and the procedures involved were unlikely to cause the baby to become distressed. Other studies have also determined that the perceived risk to a baby was an important consideration for parents when agreeing to participate (Kenyon et al. 2006; Snowdon et al. 2006; Burgess et al. 2003; Mason et al. 2000). A baby may be considered as a higher priority than a mother when it comes to making decisions about research, due to a mother’s duty of care to her child (Rodger et al. 2003), but conversely some research has shown that children and
their parents are willing to put the child at some risk in research for the benefit of others (Wendler and Jenkins 2008). Interestingly, some mothers who were interviewed reported that they wanted to see if the study oil caused the baby’s skin to react, but they did not appear to be concerned about the harmful element of the reaction, only if the reaction would occur. This was a surprise to the researcher as the implication from the OBSeseRvE qualitative data and from previous literature (Baker et al. 2005) is that participants wish to protect their babies from harm. None of the reasons given by participants for declining to participate involved concern about harm, even though the researcher had been completely honest in the verbal and written information during the recruitment phase that there was some concern that some oils may be harmful to baby skin.

The trial was deemed to be acceptable by all of those interviewed, and the negative elements were not sufficient for mothers to say that they would decline if asked again to participate. Some mothers were unenthusiastic about the ‘messiness’ of the oils, the awkwardness of bathing and the delays with baby care, but were still happy to take part, to do so again and to remain in the trial for a longer duration. This provided another dichotomy in the data between finding the trial to be acceptable, against the burdensome elements of participation. A previous study also found that practical inconvenience was an issue for mothers but that reimbursement of expenses could negate this (Baker et al. 2005). Some of the mothers who were interviewed did mention the value to them of receiving vouchers to thank them for taking part and reimbursement of travel expenses. However, they emphasised that the vouchers were not the reason they consented to take part. It was quite difficult for the researcher to assess whether the vouchers were regarded as an incentive rather than a ‘thank you’. The emphatic denial given by mothers that the vouchers were the reason for participation may have been justification to override the possible embarrassment felt by mothers for stating their happiness with the vouchers. Only one mother went so far as to say that knowing that she was receiving the vouchers at the end of the study made her feel dutiful in following the protocol instructions, so that she felt as though she was ‘earning’ the vouchers.

7.5.1.3 Retention

Of 115 mother and baby pairs recruited, 23 did not return for the follow-up assessment at 4 weeks (completion rate 80%). The original target sample was 100 babies to allow data collection on 30 babies per study arm and 10% loss to follow-up. This was deemed to be a reasonable sample size for a pilot study to assess feasibility of trial processes and parameters to inform a definitive study (Lancaster et al. 2004). During an interim assessment of recruitment in December 2013 (three months after study commencement) it was evident that there was a higher than anticipated loss to follow-up. The target sample
was then increased to 120. This was necessary as the ATR-FTIR spectroscopy data were novel and sufficient data were required to ensure that evaluation of this outcome measure could be properly assessed.

7.5.1.3.i Direct contact

The researcher had a number of strategies in place to reduce attrition. Direct contact to the researcher was available, giving participants a mobile number which they were advised could be used 24 hours a day, seven days a week. The date and time of the follow-up assessment was given to the participants on the contact number sticker. The researcher would telephone the participant weekly, and during the phone call on the third week, the date and time of the follow-up assessment would be confirmed with the participant. On the morning of the assessment a text message would be sent as a reminder. If the participant did not attend the follow-up assessment, the researcher would phone the participant to reschedule the appointment within five days. Even with these strategies in place, 23 participants were lost to follow-up. The follow-up questionnaire was sent out to all participants lost to follow-up in order to add further depth to the qualitative data, but only one of these was returned and did not give any further information to explain why the participant had withdrawn. The researcher was available at any time for the study participants, and this was emphasised to them. Only a minority of the participants used the mobile number to contact the researcher; one to withdraw and the remaining few to clarify or change appointments.

The participants were aware that the researcher was also a midwife. The researcher had expected that there may be several calls of a midwifery care nature, but this did not occur. Having a 24 hours a day, seven days a week available contact number for participants is potentially open to abuse; however this was not the case, which highlights the understanding of participants in the study. Previous research showed that parents appreciate having on-call access to the researcher (van Stuijvenberg et al. 1998). When one of the interviewed participants was questioned about the availability and use of the mobile contact, it was evident that they regarded the researcher as a researcher. Although they made various comments acknowledging her midwifery status, they did not use the phone number for midwifery-related issues. Previous research has suggested that participants appreciate the extra care and attention of health professionals when participating in a study (Baker et al. 2005; Morley et al. 2005; van Stuijvenberg et al. 1998), but OBSeRvE has shown that this facility is utilised respectfully and contact is made only when necessary. This is important for future studies where it may be difficult to convince study personnel to be on-call for phone contact out of hours. Knowing that the study participants were highly responsible in how they used the midwife’s availability should
encourage future research personnel to do the same with some confidence. This also highlights that it does not require the phone contact to be a clinician in a future study.

Existing research suggests that having a personal approach to the study in the form of a dedicated clinical trial manager and direct contact to that researcher will help recruitment and retention (Gul and Ali 2010; Watson et al. 2008; Ross et al. 1999; van Stuijvenberg et al. 1998). Recruitment and retention in the OBSerV E study may have been far worse without a dedicated researcher who was driven to ensuring a successful study. A recruitment rate of 11.1% and completion rate of 80% were not as good as anticipated. There were some aspects of the pilot study which could be adjusted to improve these rates but it would be impossible to improve the direct contact aspect of the study. It would be important to address this aspect in future study design as mothers did report that they liked the facility to contact a known person, and they felt that the researcher cared about the research which gave them confidence in the study. As a future study would likely incorporate multiple centres it would be important to ensure that thorough training was provided for study personnel, that the lead researcher was carefully chosen with the right balance of clinical experience and approachability, and that each individual site research team was engaged in the study (Tooher et al. 2008; Ross et al. 1999).

7.5.1.3.ii Timing and commitment

When the reasons for withdrawal were analysed, there were no real patterns apart from the timing of recruitment. Six mothers who withdrew advised that being in the study was “too much”. Although this is a small number, it was 26% of the total loss to follow-up and the level of commitment was also a common theme in the reasons given for non-participation and in the qualitative data. There were 67 women who said that they did not wish to participate in the study as it was too much to commit to. In the qualitative interviews, women said that the timing of recruitment made decision-making difficult. They described having just had a baby as overwhelming and that they had to rely on their partner or family to help to make the decision to participate and fulfil the instructions of the study. Other research with a mother and baby population found similar challenges. The study by Baker et al (2005) suggested that women wanted an individualised approach to recruitment taking into account the timing, researcher manner, status and method of communication, allowing for sensitivity to their maternity status. This is a supportive argument for having a midwife as the researcher in this type of study.

Other research has suggested that the confidence of the researcher giving the information is more important than timing or the information itself, although information should be given as soon as possible so that parents have sufficient time to digest the information and make an informed decision (DeMauro et al. 2014; Cartwright et al. 2011). The ability
for the researcher to establish a rapport is also considered important (DeMauro et al. 2014), and a feeling of trust in the researcher is an important element when deciding to participate (Smyth et al. 2012; Mason et al. 2000). Overall, it is generally considered acceptable to approach new mothers with regard to entering their baby into a trial (Barnett and Jones 2015; Shilling et al. 2011).

Three of those who said that they wanted to withdraw from the study, as it was too much of a commitment, were due to return for follow-up in December. December was the follow-up month where most of the loss to follow-up occurred (n=8). With hindsight, December may be a difficult month for a mother and baby population, particularly if they have other young children. There were 53 multiparous women (46%) in the sample. There are often many activities for young families around the Christmas period, and school-aged children are on holiday so mothers are caring for all of the family at home, confirmed in the qualitative interview data. This may impact on the time that they have available to participate in research. This challenge may also relate to other major seasonal celebrations such as Eid. Future studies should incorporate strategies to address this challenge at the design stage, as the researcher has been unable to determine any existing research in this area.

Loss to follow-up was lowest in the no oil group (n=4). The researcher considered that this may have been because there was no treatment regime to follow. In the qualitative data, women in the no oil group found their allocation “easy”, and women in the oil groups thought that being in the no oil group may have been the “easy option”, but women in the oil groups conversely liked the “routine” of applying oil.

7.5.1.3.iii Study duration

The four week study duration was discussed in the interviews and was generally reported to be acceptable to participants. Some mothers said that they would have been happy to stay in the study for longer, but others suggested that it was a relief when it was over. This was particularly related to bathing: trying to avoid the study areas and wanting to use cleansing products. Protocol adherence did worsen in week four of the study which may imply that the duration was too long. Previous research has found a similar drop in compliance in week four and suggested that an earlier data collection point may be appropriate (Lavender et al. 2011). Some mechanistic work would be required to assess what changes in skin barrier function could be seen in the biophysical measurements from baseline to three weeks compared to four weeks to ensure that this is a valid assessment time-point for a future study. An alternative option may be the inclusion of a control cleanser in the study. However, if a good cleanser was provided, this may mask the effect of the oils and if a poor cleanser was provided, this could have a negative effect on the
skin that could overwhelm the effects of the oils. Again, mechanistic work would be required to investigate the possibility of offering a control cleanser in a future trial.

7.5.1.3.iv Home visits

Two home follow-up visits were conducted. Home visits were only offered to those who could not return for follow-up assessment in the final phase of the study so that the feasibility of home visits could be assessed. A decision was taken not to offer more home visits to increase retention, due to the requirement to collect ATR-FTIR spectroscopy data at follow-up for which the equipment was not portable. As has been mentioned previously, the use of a bespoke portable ATR-FTIR device (appendix 48) would undoubtedly enhance recruitment and retention. This would allow baseline assessment to take place at the bedside on the postnatal ward and home visits could be offered as a choice at follow-up. The availability of home visits reduced attrition rates in a previous pilot trial (Lavender et al. 2011). The loss to follow-up in the OBSeRvE pilot study compared quite favourably to the levels before home visits were introduced in this previous pilot study (20% vs. 58%; Lavender et al. 2011). Loss to follow-up of less than 10% would be preferable; this was achieved in a definitive trial when home visits were offered (Lavender et al. 2012).

Home visits are not the optimal choice of design when considering the time taken for each aspect of the study. The assessment conducted in the clinical room at the hospital took approximately 45 to 60 minutes when every aspect of the researcher’s time was taken into account. This at least doubled when a home visit was undertaken, and could be more depending on the location of the visit. When the setting for recruitment is a large tertiary hospital, the catchment area for mothers attending that hospital is substantial. Women having their babies at St. Mary’s hospital can live as far as 25 miles away and the routes to their homes can involve motorways and busy traffic, taking up time that a researcher could be using for recruitment and assessments in the hospital environment.

The risks of unsettling the equipment are also greater when the equipment is moved, adding to the time spent setting up the equipment on arrival at the mother’s home. This increases the assessment time as the equipment requires re-calibration; for example the AquaFlux for TEWL measurement requires 15 to 30 minutes to set up (Imhof et al. 2014; du Plessis et al. 2013). Ambient conditions are also different although TEWL readings using the AquaFlux closed chamber technology are reported to be fairly stable when conducted in different environments (Imhof et al. 2014). This additional time to set up and calibrate the equipment also affected the time burden on the mother and baby, although this was minimised by the omission of the ATR-FTIR assessment. In summary, the offer of home visits, although providing one solution to high attrition also brings some disadvantages which need to be considered at the study design stage.
7.5.2 Data collection

Data were collected using case report forms (CRFs), questionnaires and interviews. CRFs were used to capture baseline information about eligibility, allocation to intervention groups or control group, baseline demographic information about the mother and the baby, baseline and follow-up measurement data, and information about adverse events, withdrawals and protocol deviations (appendices 14-18, 20, 22-25, 37-38, 40, 42).

7.5.2.1 Case Report Form (CRF) data

CRFs were completed as fully as possible. Where data were missed this was due to withdrawal from the study or equipment failure. As the researcher was the chief investigator for the study and was responsible for collecting the data, there was a personal feeling of ownership for the study which meant that data were collected under all circumstances apart from the ones mentioned above. There was no independent verification of data collection relating to adherence to the protocol, but the study was audited by The University of Manchester Ethics Team in July 2014 (appendix 45). The audit was carried out in accordance with The University of Manchester ethical guidelines to obtain reasonable assurance on the adequacy and effectiveness of the governance, risk management, and control processes. The audit included reviewing on a test basis project data and source documentation to ensure that this was complete and well-organised. The audit report recommended three actions for the management and quality of study documents: dating and signing any corrections where these were missing on study documents, creating a document management system to indicate current versions, and crossing and dating older versions of documents to indicate that they had been superseded. None of the audit findings were considered a serious breach, meaning that they did not represent a risk to patient safety or the integrity of the scientific data. The actions were addressed and the subsequent audit of the amendments was approved in September 2014.

During the analysis, three improvements were suggested for data collection forms for a future study: 1) the addition of water birth in the mode of birth question as this may have had some effect on baseline measurements; 2) the addition of a protocol compliance yes/no box to the follow-up questionnaire; and 3) condensing data collection form 1 into less parts to facilitate easier and more efficient data input.

One other issue that arose with the CRFs was the order in which the data for the baseline and follow-up assessments were recorded. The researcher used a CRF from a previous baby skincare trial (Lavender et al. 2012) as a template for the OBSSeRvE study. When conducting the assessment, it became evident that there was an optimal measurement order for OBSSeRvE but this was not the same as the order on the CRF for recording the
data. This caused some initial confusion and also some mistakes to be made when recording the results such as writing the results for the left forearm in the boxes on the CRF for abdomen. The optimal order for baseline and follow-up assessment is suggested in revised CRFs (appendices 46-47). The ordering of the data recorded on the CRFs was also an issue when inputting data to IBM SPSS Statistics. Some CRFs were not in the most logical order for data input and the complete SPSS dataset did not list the variables in the optimal order for conducting the data analyses. Initially the researcher reflected on this issue and believed that it would be best to order the CRF to allow easier data input and analysis; however, with hindsight and further reflection on the trial as a whole, it is more important to ensure that the assessment process involving the baby is the priority so that the baby does not become distressed. The other CRFs (appendices 16-18) should be carefully considered so that these are optimally designed for data input purposes, but the baseline and follow-up assessment CRFs must be designed with the baby in mind. Data may be reordered later within IBM SPSS Statistics before detailed analysis to simplify the analysis process.

If a larger study was conducted, it would most likely be a multi-centre study which would require members of staff at the individual sites to be involved in recruitment and data collection, rather than the chief investigator. The use of multiple staff to collect the data would require a high standard of training to ensure that all staff were able to understand the protocol, CRFs and the study requirements, together with independent verification of protocol adherence. The training should be centralised to ensure standardisation, and this could also act as a networking event where study personnel from different sites can meet. The gatekeepers at the various settings would need to be engaged by the research team to commit to and support the research and encourage staff to engage too. Regular meetings with staff at the various settings, with telephone support in between, should be maintained so that staff feel a part of the research and will approach the chief investigator with any issues before they become a problem.

The challenges faced during data collection were mainly due to the probes being very sensitive to movement, and the participants (babies) being very mobile with their arms and legs. This did not result in missing data as the desire to obtain the measurement was high. The easiest measurements to conduct were those on the abdomen. Another challenge was the time taken to complete the assessments at each visit, and the risk of the baby becoming distressed approximately two thirds of the way through. In the majority of cases, babies were either asleep or awake and calm for approximately the first 25 minutes of the session. After that, in those babies that became unsettled, there was some pressure to complete the assessment as quickly as possible. This pressure arose for a number of reasons: some parents did not like the baby to be distressed, the TEWL
measurement was impossible to obtain if the baby was crying, and finally if it was getting
towards the end of the day, the knowledge that the randomisation midwife needed to see
the parents before she finished her shift. In the latter case, the researcher in some cases
had to leave the assessment room mid-assessment, allowing the randomisation midwife
to come in to the assessment room, discuss the randomisation and the allocated
intervention. If the participant was in a treatment group, the midwife hid the oil bottles so
that the researcher remained blinded when they returned to the room to complete the
assessment. This became very complicated and was described astutely as “very cloak
and dagger” by some participants. The researcher was never unblinded to treatment
allocation during these circumstances, so the process was considered successful, but
would need to be addressed for future assessor-blinded studies.

Finally, it was difficult, although not impossible, for one person to complete the
assessments. The assessments were more efficient when two of the team were present:
the researcher and the research technician. The TEWL assessment will always be
sensitive to baby movement; the only solution is to stop a baby from moving around,
which is inappropriate. Having two members of the study team present meant that one
could hold the baby in the correct position for the probes whilst also comforting the baby.
Even in these circumstances, TEWL was almost impossible to obtain if the baby was
unsettled. The need for two assessors would not be necessary if the equipment became
portable and could be used at the bedside and at home; the probe could be taken to the
baby rather than the baby to the probe. This would have the added advantage of not
needing to disturb the baby when sleeping. An alternative would be not to include a
measurement such as TEWL if there was no clear evidence that it was essential for the
study.

7.5.2.2 Questionnaire data

For the questionnaire, there were no challenges in obtaining the follow-up data for all of
the 92 mothers and babies who returned for follow-up. It was more difficult to have
complete datasets for the weekly telephone questionnaires, as it was sometimes difficult
to reach participants, despite many attempts. Some mothers changed their mobile
telephone number after the birth, and some reported that they had run out of credit so
were unable to use their phone. The issues with the mobile phone were more evident
amongst the younger mothers. Where it was known, the researcher would email instead
or use other telephone numbers that the participant had disclosed in the baseline
demographic data. If the researcher was unable to contact the participant by phone, a
letter was sent out to remind the participant about the follow-up appointment. The use of a
variety of methods to contact participants has been shown to improve data collection and
to reduce attrition (Chen et al. 2011; Chen et al. 2008; Robinson et al. 2007; Cotter et al. 2005).

There were two issues that emerged related to the questionnaire. Firstly, many parents queried what the question phrased “What are your views on the measurements taken on your baby?” meant. This question sought to explore parents’ feelings about the equipment and probes being used on their baby and would need to be rephrased in a future study, perhaps to “What are your views on the equipment used to take the measurements on your baby?” Secondly, the follow-up questionnaire incorporated a question assessing what products babies had used but omitted to clarify that this referred to the previous week, that is, since the last weekly telephone questionnaire. It is possible that some parents completed this section for the whole study period, which may have skewed understanding of protocol adherence in week four of the study. Finally, an option of “don’t know” should have been included for the question: “What type of washing powder do you use to wash your baby’s clothes?” The options provided were “biological” and “non-biological” and it appeared that some parents were not sure what these terms meant, or which category their product came within. It is important to ensure that there is no ambiguity of questions in a questionnaire (Fan and Yan 2010; Kelley et al. 2003; Fowler 1992); a factor to be resolved in future studies. Fortunately, mothers always completed the questionnaires in the presence of the researcher and were able to clarify what was meant by the question. It is likely that, had this not been the case, questions would have been omitted by the participant or there would have been a diversity of meaning in the answers.

7.5.2.3 Interview data

The only challenge in obtaining the interview data was that some telephone interviews were conducted (n=6). This approach made it difficult to respond to the woman’s body language as this could not be visualised, and for the participant to be encouraged through the researcher’s body language (Knox and Burkard 2009; Garbett and McCormack 2001; Rubin and Rubin 1995). The researcher also found it more difficult to avoid asking closed questions and not to talk over the participant. This experience was contrary to some literature which suggests that an interviewer may be more likely to interrupt the participant in a face-to-face interview (Carr and Worth 2001). The researcher conducted all of the interviews, and was the main point of contact for the participants for all of the study components. This may have introduced some bias, as participants may have felt under pressure to say what they thought the researcher wanted to hear. Social desirability bias has been shown to be worse in telephone interviews than face-to-face interviews (Tourangeau and Yan 2007). The researcher tried to mitigate this by being open and honest from the start of the process. Honesty and transparency were encouraged; the
researcher made it clear to participants from the outset that any protocol violations would be recorded to allow the most trustworthy results to be obtained. The researcher wanted to instil trust in the participants and to be approachable to participants. The rapport built with the participants was felt to be successful. In addition, the type of qualitative data being collected was not sensitive but rather aimed to inform and improve design of future work. In these circumstances, the researcher felt that there was no reason for participants to hide their views and experiences; however, this cannot be known for certain.

There may have been some recall bias as some interviews were conducted up to six months after participating in the trial. However, there did not appear to be any differences between the data generated from the interviews held later and those which were held in the immediate months following participation in the trial. Recall is generally considered fairly reliable up to six months after an event, particularly for topics as important to participants as childbirth (Bowling 2009).

For the weekly telephone questionnaires and the follow-up questionnaire, mothers were self-reporting without any visual confirmation of the report by the research team (such as rash), which is a limitation of the study (Polit and Beck 2004). Social desirability bias may also have been an issue, as mothers were self-reporting directly to the researcher and may have felt obligated to respond in a way they felt was expected (Bowling 2009). This issue was minimised by emphasising the need for transparency to the mothers at recruitment, during the baseline and follow-up assessments and during the initial conversation during the weekly questionnaire phone calls. These conversations were held to ensure that participants were aware that this would help to provide more trustworthy results, and to create a rapport where participants felt able to converse easily whilst providing anonymity with use of a pseudonym (Polit and Beck 2004).

7.5.2.4 Equipment

The most difficult tool to use was the AquaFlux for the TEWL measurement. The AquaFlux works via a closed chamber system; the closure of the chamber occurs when the opening is sealed horizontally against the baby’s body surface. As babies are active when awake, the TEWL measurement was often disturbed when the chamber became unsealed due to a movement and had to be restarted. The TEWL measurement also reacted to babies who were crying and this may be due to increased activity or temperature. A previous study demonstrated that TEWL values increased by 37% during activity compared to those measurements taken at rest, and increased after remaining constant once a body temperature of 37.1ºC was reached, with no sweating observed under either a state of activity or increased temperature (Hammarlund et al. 1979). A previous study found no difference in TEWL when the analysis was adjusted for neonatal
state (Lavender et al. 2013), but the numbers of crying babies in the OBSERvE sample were too small to draw any conclusions. TEWL measurements were repeated when the baby became settled or missed altogether if they could not be settled. The measurement itself took approximately 30 to 40 seconds under the optimal conditions, so this proved to be the most difficult and time-consuming measure.

Methods used to alleviate this situation for all measurements included allowing mums as much time as they needed to settle the baby, keeping the baby as wrapped as possible so that they were not cold or disturbed, and encouraging mums to feed their baby during the assessment if necessary. The assessments proved to be easily conducted if a mother fed her baby whilst taking the measurements, but some mums were unhappy to allow the researcher to conduct the measurements when the baby was breast-feeding. As the research technician was male, he often had to leave the room if mothers needed to breast-feed, leaving the researcher to take the measurements alone. This worked well in the majority of cases, although the assessments proved to be more difficult and time-consuming as the researcher had to look after the equipment (cleansing and resetting) and complete the CRF at the same time as taking the measurements. Having a second person to share the assessment duties made the process more streamlined and efficient, but the gender of the team should be considered for future studies to allow the privacy required of new mothers learning to breast-feed.

The other challenge was equipment failure. This occurred twice for the ATR-FTIR and an engineer needed to be called. ATR-FTIR data was only missed for three participants; only one of these was due to equipment failure and was on one of the first days of the study (the other two were home visits). For the first engineer call-out, it appears the ATR-FTIR may have been unsettled by the move from Sheffield to Manchester. This issue could be remedied by ensuring that the machine arrives early enough to settle before the start of the study. For the second call, the equipment had experienced intermittent failures but nothing was found to need replacement or repair. The pH meters had to be repaired during the study, but it was possible to borrow a replacement from The University of Sheffield for the remainder of the study data collection period. The touchpad for the TEWL laptop ceased to work, but a wired mouse purchase solved this. On the final day of data collection, the liquid-crystal display (LCD) screen on the base unit for the Mexameter® readings ceased to work. The unit had been transported for a home visit on the previous assessment day and it is possible that the transportation of the unit may have caused the damage. This should be considered if a future study offers home visits.
7.5.2.5 Time

The burden of time for each participant per assessment was at least 45 minutes. Apart from the actual measurement, time was spent walking to and from the postnatal ward to the clinical assessment room and also included a conditioning time so that all babies were settled to the same ambient conditions. This sometimes caused annoyance to the clinical team who may have needed to conduct some aspect of care whilst the mother and baby were not at the bedside. The researcher routinely confirmed with the midwife that they did not need the mother and baby for the duration that they would be away from the ward. The researcher also left a laminated sheet on the bed of the participant advising what time they would return, together with the phone number of the clinical room so that midwives could call the mum back to the ward if necessary. In all but two cases where the babies needed to be fed, the return time was achieved. In those two cases, the clinical midwives were pleased that the babies had received a good feed and this outweighed the frustration with the delay in return to the ward.

The qualitative data suggest that parents were happy with the duration of the assessment. They suggested it was a ‘break’ from the ward, a ‘change of scenery’ and ‘something to do’. None of the parents indicated that it was too long and suggested that even when the baby became unsettled they felt that they were not under pressure for time. This was due to the researcher providing that reassurance and showing patience during the assessment to obtain the measurements whilst the baby was calm; the assessment was halted if the baby needed to be settled by the parents. It should be noted that the research team felt under pressure as it was obvious that the longer an assessment took, the higher the risk of not having time to recruit another participant that day. It was necessary to ensure that a complete set of data was collected from each baby and therefore time was prioritised to the baby being assessed. Recruitment was the priority when there was no baby in the assessment room and data collection was the priority when there was.

Often the father brought the baby for the assessment so that the mother could have a rest. After several fathers had done this, the researcher started to encourage it as there were multiple benefits. Firstly, mothers could rest and did not have the worry of walking to the research room when they had recently given birth. Secondly, fathers were very ‘hands on’ in the assessment room, and probably felt useful. This meant that often the research technician was not needed to hold the baby for assessments. Finally, the time spent conducting the assessments was reduced as the father was fit to walk at normal pace to the clinical room and the researcher was not having to observe the mother for any signs of fatigue, illness or other effects of the birth.
Working in a two-person team had several benefits. Firstly, the assessment time was reduced as the researcher could relay the results to the technician to complete the CRF. The technician could cleanse and reset the probes, and complete the D-Squame disc storage whilst the researcher gave advice or booked the follow-up appointment. It was particularly difficult to conduct the hydration, pH and erythema measurements alone, where three consecutive measurements were necessary. Secondly, the baby had to be held for the assessments. The layout of the clinical room was not perfect as there was nowhere to place the baby for the ATR-FTIR measurement, for example. The probe was very fragile and could not be over-flexed which meant that the baby needed to be at a certain height. Not all babies were in the most modern cots. Older cots were not height-adjustable. The more modern cots which could be adjusted for height were not sufficiently high enough at full extension for the ATR-FTIR probe to reach. It was impossible to hold the baby and take the measurement at the same time with only one pair of hands, due to needing to also press ‘start’ on the laptop and clean the probe of skin surface residues after each measurement. This was made easier if the father had brought the baby for the assessment as they were willing to hold the baby and there was no danger to them in doing so (they were not suffering any after effects of the birth). Conversely, it was not possible to ask mothers who brought their babies to do the same as there was a risk of fainting due to fatigue or the effects of childbirth. This was a constant worry for the researcher away from the ward environment.

The researcher, as chief investigator with overall responsibility for the safety aspects of the study, had ensured that the research technician and randomisation midwives all had maternal and neonatal/paediatric resuscitation training and that the necessary resuscitation equipment was included on the emergency trolley. If future studies of this type are conducted where assessments take place away from the postnatal ward environment it is crucial to ensure that these matters are considered and addressed. Alternatively, a fully height-adjustable cot would need to be purchased. This would be less expensive than employing a second researcher to help with the assessments. However, parents reported that they liked having more than one person working with the baby and the equipment, as this made them more confident that the baby would not come to any harm.

For all of these challenges, portable equipment that can be transported on a trolley around the postnatal ward with assessments being conducted at the bedside would be a viable solution.
7.5.3 Protocol violations

The researcher believed that the no oil group would find it most difficult to adhere to the protocol due to the request not to use any products on their baby, but in reality this group achieved the highest protocol adherence rate. Protocol adherence for alternative product avoidance was worse in week four of the treatment period in comparison to other weeks. This also occurred in a previous baby skincare pilot randomised controlled trial (Lavender et al. 2011) which suggested that a primary endpoint prior to four weeks may be beneficial providing it is clinically acceptable. The first follow-up assessment could be conducted at three weeks in a future study, but adherence to the protocol may still remain an issue. One solution could include the provision of a control cleanser for all treatment groups, but this may still be problematic. If a good cleanser was used, the effects of the oils may be masked. If a poor cleanser was used, the negative effects could overwhelm the effect of the oils. Some parents in the qualitative interviews suggested the possibility of a control cleanser. Mechanistic work would be required to assess the effects of a control cleanser on skin barrier function and on the oils before incorporating this into a future study design.

The self-reporting aspect of protocol adherence may affect researcher confidence that the participants inform the researcher about all protocol violations. The researcher built up a good rapport with the participants and was transparent at the outset that all information would be valuable to achieve the most trustworthy results. The researcher was confident that participants disclosed their protocol violations. Questions were asked in a matter-of-fact way, without judgement.

The parents themselves faced a number of challenges which were disclosed in the qualitative interview data: the study interfered with bathing and other cares, the oils were messy and the bottles were fragile, and they wanted to treat their baby's dry skin.

7.5.3.1 Bathing and cares

Bathing was an issue for parents. In the instructions given to parents at the start of the treatment period, water only for bathing was advised and if they wanted to use a product they were asked to avoid letting the product come into contact with the three study treatment sites. Parents suggested that this was a difficult request. They wanted to be able to bathe their baby with a cleansing product. This again raises the issue of incorporating a control cleanser into the study design; mechanistic work would be necessary to evaluate the effect of such a product on the outcome measures, but if all of the study arms were using the same cleanser in the same way this should eliminate any confounding.
Parents also suggested that the instruction of letting the intervention oil absorb for ten to fifteen minutes after application was a burden for two reasons: they either wanted to get the baby dressed as quickly as possible or the baby was unhappy being undressed and this distressed the parents. This could be solved if the oil could be present on a type of ‘patch’, as suggested by one of the participants, but the adhesive and material of the patch would need to be investigated so that it did not cause harm to a newborn baby’s skin. Furthermore, the use of a patch would not be very pragmatic in the real-world.

7.5.3.2 Oils and their containers

Topical oils are commonly used by parents in the UK, so the suggestion that application was ‘messy’ was unexpected. Only two of the participants suggested this, but it was discussed in great detail, indicating its importance. It is reasonable to assume that if it was possible to apply the oil in a less ‘messy’ way then future studies should consider this.

The suggestion of a ‘patch’ was a novel one if such an intervention could be produced at a reasonable cost, was not harmful to the baby, and occlusion did not affect the results. However, it is not really pragmatic and the material impact would necessitate investigation. The intervention should really be delivered in the same way it is applied in daily living, so it is probably more important to look at what can be improved about the containers. Plastic bottles with a dropper lid were chosen for safety reasons. The glass samples which had been considered were sturdier and no more expensive, but the plastic ones were chosen so that the possibility of broken glass was not a concern. Unfortunately choosing a much lighter bottle increased the chance of knocking the oil over. One of the participants suggested the use of the ‘rubber bungs’ used in liquid baby analgesia bottles, so that if the bottle did fall over there would be no spillage. This would be a suitable option for a future study, but the weight of the rubber bung may result in a plastic bottle overbalancing on a frequent basis which may also be an annoyance for parents. An integrated dropper may be the solution, rather than a lid with a pipette which has to be unscrewed.

7.5.3.3 Desire to treat dry skin

The questionnaire data showed that 56% of women had no preference for using topical oils routinely (n=10 olive oil; n=13 sunflower oil; n=24 no oil) but 32% would like the treatment they were allocated to become routine (n=13 olive oil; n=11 sunflower oil; n=3 no oil). Few women in the no oil group wanted their allocation to be routine, implying that the no oil group as a whole would like to use oils on their baby’s skin. In the weekly question about skin concerns, all of the concerns surrounded the issue of dry skin.
However, although there was a desire to use something on the skin, the no oil group was the most adherent to the protocol and some participants mentioned that being in the no oil group had shown them that they did not need products as the skin had improved on its own.

For all of the challenges discussed it is likely that there will always be some protocol violations with a new mother and baby population. It is important to establish a good rapport with the participants so that protocol violations are disclosed and can then be accommodated in any analysis.

7.5.4 Safety reporting

All adverse events, serious adverse events, and adverse reactions were documented as specified in the study protocol. No serious adverse reactions or suspected unexpected serious adverse reactions were reported during the study. One adverse reaction was diagnosed during the study; treatment was stopped. Photographs were sent electronically to the on-call dermatologist who diagnosed a folliculitic reaction to the oil and advised the parent to stop using the oil. The researcher became aware that the participant was in one of the oil groups during the discussions of the reaction, but not which oil. The participant attended the follow-up appointment at which point the rash had substantially diminished. The experience of this adverse reaction highlighted the success of the on-call dermatologist system. The dermatologist was not in the UK when the reaction was discovered but the whole process of taking a history, obtaining photographs, communicating with the dermatologist, receiving a diagnosis and stopping the treatment was completed within three hours. The participant was very pleased with the service, and for feasibility purposes it was proven to be successful.

Interestingly, participants did not appear to be concerned that topical oils may have the potential for harm, but were more interested in whether the oils they were allocated would cause a reaction to the baby’s skin. Many of the mothers mentioned this in the qualitative interviews.

7.5.5 Outcome measures

This trial has generated one of the largest neonatal datasets of novel information provided by the use of infrared spectroscopy. From an ethical perspective, ATR-FTIR is advantageous for a neonatal population as it provides a method which can detect changes in the molecular composition of the stratum corneum non-invasively before those changes are visible clinically. The spectra generated a plethora of data measurements which may be of interest for future studies: lipids, bulk water, sebum, carboxylate and
sulphates. Challenges which arose with the ATR-FTIR equipment included its size, the need for liquid and dry nitrogen to operate the equipment, and location of the equipment. As the equipment was not portable, mothers had to leave the postnatal ward to have the baby’s baseline assessment conducted in a research room on a different floor and return to the hospital with their four week old baby for follow-up assessment. The OBSeRvE study found that ATR-FTIR spectroscopy is suitable as an outcome measure, but would require the equipment to be perfected and validated to be included as a primary outcome. The ATR-FTIR equipment is available in a smaller, portable, handheld device that would not need liquid or dry nitrogen to operate (appendix 48). This is currently quite heavy in its cordless form, but could be easily adapted for a newborn population. This would enable assessments to be conducted at the bedside or at home, and this would help to improve recruitment and retention.

Prior to data analysis, a macro had to be devised to convert the graphical spectra data into numerical data. Standardised software would be required to work concurrently with the ATR-FTIR device to produce the numerical data directly from taking the assessment. This data could then be immediately transferred into any analytical software package such as IBM SPSS Statistics.

TEWL is a validated measure of skin barrier function (Fluhr et al. 2006). Although our data did not show any significant differences in TEWL between groups, it was not powered to detect this and would require a larger sample size. TEWL would still be recommended as an included outcome measure for a larger study as it has been shown previously to detect changes in skin barrier function with the use of topical oils (Correa et al. 2014; Danby et al. 2013; Jiang et al. 2000; Sinha and Kaur 2000). The AquaFlux was found to be extremely sensitive to movement and was therefore difficult to use in a newborn baby population. If the baby became distressed this increased the TEWL measurement which then required repeating. As the TEWL measurement took at least 30-40 seconds, a necessary repeat measurement added time to an already long assessment time for the baby.

The doctoral study did not include any health economics analysis but the equipment did incur a number of costs. The ATR-FTIR was rented from The University of Sheffield at a cost of £16,400 for a twelve-month period. This amount included transportation costs and a maintenance agreement with the manufacturer, ThermoFisher Scientific Inc. The liquid and dry nitrogen were not included in this amount, but were provided within the remit of the Maternal and Fetal Health Research Centre at St. Mary’s Hospital, Manchester. If a multi-centred study was conducted, any budget may need to include purchase of the ATR-FTIR equipment and associated operating expenses, including nitrogen. During the OBSeRvE study, the AquaFlux tools required servicing at a cost of £1,780, the Mexameter® needed a repair at a cost of £360 and the two skin pH meters® also needed
repair at a cost of £600. The University of Manchester owns two AquaFlux, one Corneometer®, two skin pH meters® and one Mexameter®, but if any other centres for a study were included there would be purchase costs involved in addition to allowance for maintenance. This would need to be taken into account for any funding application.

7.6 Proof of concept

The main focus of this study was to show proof of concept that using the defined topical olive oil and defined topical sunflower oil had an effect on baby skin barrier function, the magnitude of that effect, and to assess the feasibility of a definitive RCT investigating these specific defined topical oils versus no oil for newborn term babies. The hypothesis suggested that topical sunflower oil, when compared with no oil or topical olive oil, would have an effect on the skin barrier function of newborn term babies, having been based on the existing evidence base. This is the only trial known to the researcher to investigate and compare the effect of the two most commonly recommended topical oils in the UK on term baby skin barrier function. The ATR-FTIR data from the OBS_eRvE study provided evidence that these topical oils do have an effect on baby skin. Statistically significant differences in the structure of the lipid lamellae were found in both of the oil groups, compared to the no oil group. All of the study groups displayed an increased ordering of the lipids (improvement), both on the surface and within the stratum corneum, over the 4 weeks following birth, but this improvement was significantly less in the groups using the topical oils. This suggests that both the topical olive oil and sunflower oil used in this study may impede the development of the lamellar lipid structures of the permeability barrier from birth.

There are limitations of the ATR-FTIR methodology to discriminate between stratum corneum derived lipids, and those originating from the study interventions. Tape-stripping was employed to assay deeper stratum corneum layers but this technique is limited in babies due to moral and ethical considerations. It is common in dermatological studies to conduct tape-stripping at a frequency of 20 to 40 tapes (Löffler et al. 2004; Bashir et al. 2001; Dreher et al. 1998), but for a baby in the OBS_eRvE study this was reduced to three tapes for ethical reasons. The first tape-strips contain almost complete layers of corneocytes, with later ones having substantially less (Lademann et al. 2009). Substances which are usually located on the skin surface and in the upper layers of the stratum corneum can usually be assessed in studies taking only 5 to 10 tape-strips (Lademann et al. 2009). The decision to take three tape-strips for the OBS_eRvE newborn population therefore seems reasonable. The usual volume of 20 to 40 tape-strips would clearly damage a newborn baby’s skin which is much thinner than an adult’s skin (Stamatas et al. 2010). This pilot study was designed to inform future clinical trials on the topic; the limitation of the reduced tape-stripping for the oil/no oil comparison reported here may
mean that alternative non-invasive spectroscopic methods to assess the molecular composition of the neonatal stratum corneum require consideration against the ATR-FTIR measure. Nevertheless an important, clinically relevant effect of the oils may have been identified by the OBSeRvE study.

A reduction in the ordering of lipids throughout the stratum corneum is significantly associated with decreased skin barrier function (Damien and Boncheva 2010); which may increase the risk of developing atopic eczema. Moreover, skin barrier defects, displayed in the skin of atopic eczema patients, are characterized by reduced ordering of stratum corneum lipids determined using the same technique employed in this study (Higgs-Bayliss et al. 2014;Janssens et al. 2012). There was no significant change in skin barrier function evident between the two oil groups, but this pilot study was not powered to detect statistically or clinically important differences between groups; just overall patterns of differences. When a minimally invasive technique was used on adult volunteers (not suitable for the assessment of baby skin), there was a significant adverse effect of olive oil on the TEWL measurement (Danby et al. 2013). Free fatty acids, like oleic acid that accounts for the greatest proportion of the fatty acid components of olive oil triglycerides, are well-documented penetration enhancers that increase TEWL when applied topically to the skin (Correa et al. 2014;Jiang et al. 2000;Sinha and Kaur 2000). Triglycerides themselves do not penetrate the skin, which is demonstrated by the sudden decrease in lipid esters in the skin following tape-stripping. Lipases in the resident skin flora break down the triglycerides to release glycerol and free fatty acids such as linoleic acid and oleic acid (dos Santos Rodrigues et al. 2014;Sharma et al. 2014). Glycerol is an important moisturising factor (humectant) found in the stratum corneum. Increased levels of glycerol increase skin hydration (Choi et al. 2005). In the OBSeRvE study, both oil groups displayed improved skin hydration compared with the no oil group. The process of triglyceride lipolysis helps to elucidate why the topical oils appear to have a dual effect of hydrating the stratum corneum whilst also disrupting the lipid lamellae structure.

The types of fatty acids resulting from olive oil and sunflower seed oil are distinct, olive oil containing predominantly oleic acid and sunflower seed oil containing more linoleic acid. Previous research has implied that it is this differing content of oleic and linoleic acid that has been the overriding factor in the positive and negative effects of different oils on the skin barrier (Danby et al. 2013;Darmstadt et al. 2002). The OBSeRvE study found no significant differences in the effects of the two topical oils, but due to the limited sample size no conclusions can be drawn from this. Although the study has found statistically significant biological differences for the oil groups compared to the no oil group, the clinical importance of the difference is unknown and requires further investigation.
The OBSeRvE study provides important pilot data which investigates for the first time the impact of using the two most commonly recommended topical oils in the UK, olive oil and sunflower oil, on newborn term baby skin. These oils continue to be recommended by midwives, health visitors and other maternity service health professionals, for the prevention or treatment of baby dry skin or for baby massage. This practice is widespread (Cooke et al. 2011) aided by the common, but unfounded, belief that what is ‘natural’ is also ‘safe’ (Bedwell and Lavender 2012; Lavender et al. 2009). However, our pilot data has demonstrated that these oils may have an effect on skin barrier function. Future studies should concentrate on establishing clinical importance. This is absolutely necessary, particularly in view of the possible link between using these topical oils from birth and the increasing prevalence of atopic eczema in children aged 2 to 15 years (Gupta et al. 2004).

The study hypothesis stated that the regular application of topical sunflower oil, when compared to no oil or topical olive oil, had an effect on the skin barrier function of newborn term babies. The hypothesis was not supported by the generated data. The data showed that sunflower oil had a similar effect to olive oil on skin barrier function; both oils had a negative effect compared to the no oil group. The adverse effect of sunflower oil was an unexpected result in view of the existing literature which demonstrates beneficial effects of topical sunflower oil in adults (Danby et al. 2013) and preterm babies (Darmstadt et al. 2008; 2005; 2004). A recent study tested topical sunflower oil against no oil in a population of preterm babies (Kanti et al. 2014). This was a small sample (n=22), but this study also found that topical sunflower oil may impede skin barrier development, supporting the OBSeRvE study findings.

Both studies contrast with the work of Darmstadt (2008; 2005), who suggested that the positive effect of sunflower oil was linked to a barrier-enhancing effect. The positive effect found by Darmstadt may have more to do with the antimicrobial effect of sunflower oil. Unlike the Darmstadt population, the OBSeRvE term baby population were not faced with a significant fatal infection risk. The researcher suggests that whilst sunflower oil may not be a great barrier-enhancing topical agent, possibly the opposite, this does not detract from the very positive effect it has in situations where infection is a great risk. Darmstadt’s work was so positive in reducing infection and mortality in a high risk baby population that it must not be ignored. As the OBSeRvE study and Kanti’s study were not designed to determine the antimicrobial action of sunflower oil, it would be prudent to explore this in future research, in different populations and different resource settings.

7.7 Strengths and limitations of the research

The OBSeRvE study was a doctoral study. The chief investigator, as a doctoral student, was highly motivated to conduct a successful study. Future multi-centre studies may not incur the same level of commitment from study staff. It would be important to inform and
motivate staff by engaging staff from an early stage, establishing good communication strategies for targets and achievements, and maintaining direct and regular contact with the project coordinator.

The lack of a placebo oil meant that the study could not be double-blinded. This may have had an effect on the homogeneity of protocol adherence between the groups. It is unlikely that a placebo oil would ever be formulated, as all topical oils will have some effect on the skin. The only means therefore of improving compliance is to put more emphasis into the information provision phase to encourage parents to follow the study instructions to the best of their ability. It may be possible to determine a control cleanser for use by all of the study participants, but more mechanistic work would be necessary to ensure that this did not have the potential to affect the results.

The educational and career status of the mothers was not collected. This may have provided more depth of understanding to the qualitative component of the study when analysing the various viewpoints. It was evident from the data that some mothers were involved in science or knew about the various aspects of research and it would have been useful to assess whether this had skewed understanding of the data.

Although the study included funding to use an interpreter service, this proved to be impractical. At the beginning of the study, it was impossible to arrange an interpreter within the timescale of one recruitment day. As previously discussed, women had frequently been discharged before the next recruitment day. In the final phase of the study a telephone translation service was arranged, but in this phase there were no eligible non-English speaking women; this service could not be assessed for feasibility. With hindsight, although it is desirable to offer research studies to all eligible women, it would be very difficult to use a telephone translation service for the study assessment and explanation of the equipment used.

The study was not powered to detect statistically or clinically significant differences; however some statistically significant differences were found for a number of biological outcomes. The study has shown that both of the oils tested do have some effect on skin barrier function. We cannot be certain that no harm is taking place, therefore both olive oil and sunflower oil should not be recommended to parents to use on their babies until further research is undertaken. This is a novel and unexpected finding, as previous research has suggested that sunflower oil is beneficial to skin barrier function. The corroboration of the OBSeRvE findings by the recent German study (Kanti et al. 2014) justifies further investigation on a larger scale.

The combination of both quantitative and qualitative approaches has provided a depth to the feasibility aspect of the research which could not have been achieved by using a
single approach. The interwoven nature of the discussion incorporating both approaches has generated a much deeper and more meaningful understanding of the feasibility investigation. Future study design is informed by both clinical data and parents’ perspectives of the design, procedure or trial processes. One example of this is protocol compliance, where the ATR-FTIR data agreed with mothers’ self-reporting, subsequently illuminated by the questionnaire and interview data. Future studies can now consider the use of a different oil container and a control cleanser to ensure that the acceptability to parents is optimised. All outcomes indicated in the protocol and on the Clinical Trials Registry have been reported transparently, and sufficient robust data has been collected to enable a decision to be made about future study design.

Parents liked the personal touch to the study: that one dedicated researcher was the person providing the information, recruiting and taking consent, collecting data, conducting the weekly questionnaires and all of the assessments. Some women also remarked on having a direct phone number for the researcher in case of concern. Parents have suggested previously that they felt that their babies gained access to better or more care if they participated in research (Cartwright et al. 2011; Morley et al. 2005; van Stuijvenberg et al. 1998). Some women also feel ‘special’ (Baker et al. 2005; Lavender et al. 1999) or perceive an increased level of human contact (East and Colditz 1996). They appreciated the professional research ethos of the hospital and the professionalism of the study with regards to staff, setting, equipment and information. This should be incorporated as far as possible into future study design, however a larger study will require more study personnel particularly if this is multi-centred. Standardised training can help to ensure that all participants are given the same level of care and attention.

The OBSeRvE study has proven to be a good example of why it is important to conduct pilot work before embarking on a definitive trial. Pilot studies are the best way to assess the feasibility and potential rigour of all aspects of a definitive RCT, without going to the effort and expense of a much larger trial (Thabane et al. 2010; Arnold et al. 2009; Lancaster et al. 2004). Prior assessment of feasibility can help to ensure success of a study, by finding the optimal trial parameters and the solutions to challenging trial processes. The successful pilot acts as a ‘safeguard’ for researchers embarking on the definitive study, who can confidently progress knowing that parameters and processes have been pre-tested (Arnold et al. 2009). The Medical Research Council Complex Intervention Framework (2008) recommends development and piloting stages to ensure the fulfilment of robust research. A pilot study that concludes that a definitive trial is not feasible is a successful study, as it has prevented the conduct of a trial which would not have worked. It is important that researchers publish the findings of pilot studies to help other researchers make decisions about similar protocols at the design stage (van
Teijlingen et al. 2001). Although half of pilot studies report the need for further research, Lancaster et al (2004) found that less than 10% were followed up by a major study. It is the researcher’s aim to continue to conduct research to answer this research question.

When statistically significant results of potential harm occur in a pilot study, which is not powered for significance, the programme of research may be halted leaving an important question unanswered (Arnold et al. 2009). This could happen with the OBSeRvE study, which has found that the use of olive oil and sunflower oil on the skin of newborn term babies has a potentially negative effect on the development of skin barrier function. The study concludes that topical oils should not be recommended to parents for use on their babies until such time as the clinical significance of this finding is determined, but it is highly unlikely that a pilot study will change practice on a sufficiently large scale. Ethically it may prove difficult to obtain the necessary approvals for a future study due to the adverse findings of the pilot study, but equally it is unethical to allow parents to continue to use potentially harmful oils on babies without the appropriate evidence. It is important to emphasise the caution that is necessary in interpreting statistical results which are not powered to detect statistical or clinical significance. The research question should continue to be investigated until it reaches a significant conclusion (Arnold et al. 2009).

7.8 Evidence which has emerged since 2013

Since the literature review for this doctoral study was completed in 2013, three relevant studies have been conducted which sample term newborn babies. These three studies have been incorporated into the literature review in chapter two, which was updated in January 2015. They are discussed here to highlight the most recently published evidence in the field.

One of the published randomised studies originating in Europe investigated babies using topical almond oil (Roberta et al. 2014). The study compared newborns washed with water only (n=52) to newborns washed daily with liquid baby cleanser and moisturised with topical almond oil (n=42). The publication of this study does not clarify whether the study was powered, the level of protocol compliance or how homogenous the groups were, despite the requirements of the CONSORT statement (Moher et al. 2010). Contrary to findings from the OBSeRvE study, there was a statistically significant difference in TEWL between the groups at day ten with TEWL being higher in the intervention group. Only the intervention group used the cleansing agent which means that the specific effect of the oil alone cannot be determined. Using the cleansing agent may have negatively affected skin barrier function, resulting in higher TEWL values at follow-up. Roberta’s study concludes that cleansing and moisturising with oil may delay the natural maturation of skin barrier function which agrees with the findings of OBSeRvE, but the
methodological weaknesses of Roberta’s study reduce the impact of these results. The findings would have been of more value if the cleansing agent had not been incorporated in the intervention.

Another randomised controlled trial, conducted in Japan (Horimukai et al. 2014; n=118), addressed prevention of atopic eczema testing an intervention of daily application of 2e Douhet emulsion for 32 weeks. The intervention group and the control group were also both prescribed petroleum jelly to use. Another multi-centre randomised controlled trial, conducted in the UK and USA around the same time (Simpson et al. 2014; n=124), investigated a full-body emollient therapy for six months against no treatment. The emollient therapy could be chosen by the UK parents from sunflower seed oil, Doublebase gel or liquid paraffin 50% in white soft paraffin, and by US parents from the same sunflower seed oil, Cetaphil® cream or Aquaphor™ healing ointment. Both of these trials concluded that the use of a daily emollient therapy from birth reduces the incidence of atopic eczema in those with a family history of the condition. Both of these studies were prevention of eczema studies and only recruited babies at high risk of developing atopic eczema. The application of specific defined oils to the skin of newborn babies who are genetically predisposed to a defective skin barrier and atopic eczema may have different effects to those with no genetic predisposition to develop a defective skin barrier and atopic eczema. Topical oils are routinely recommended by health professionals to parents for use on the skin of their healthy newborn babies. It is not known what number of these healthy babies may go on to develop atopic eczema and whether the use of topical oils on the skin of healthy term newborns is linked to this condition. It is important to establish whether this link exists. Future studies should investigate the effects of defined oils on the skin of babies with and without a genetic predisposition to atopic eczema.

7.9 Recommendations for future research

The OBSeRvE study aimed to assess the feasibility of testing the hypothesis that the regular application of defined sunflower oil, compared to no oil or defined olive oil, had an effect on the skin barrier function of newborn term babies. The hypothesis was not supported by the data. Sunflower oil, expected to be better for skin barrier function, was found to have a similar negative effect on the skin to olive oil. OBSeRvE has found that olive oil and sunflower oil have the potential to adversely affect the development of the skin barrier. This adverse effect has the potential to increase the development of atopic eczema. It is impossible to draw any firm conclusions from this pilot data as the relationship between these findings and atopic eczema remains unclear. Future work must address clinical importance. Observational and mechanistic studies, in terms of the relevance of changes in lipid lamellae when topical oils are used from birth in babies with and without a genetic predisposition to atopic eczema, are required before possibly
embarking on a definitive RCT. Whether there is a link between the use of topical oils from birth and the development of atopic eczema needs to be investigated through a longitudinal observational study. This study should map the progress of skin adaptation and product use from birth to a time-point beyond the usual diagnosis of atopic eczema, which is not usually diagnosed before four to six months of age (Bieber 2008). Any future definitive RCT should be designed with biological and clinical outcomes to generate data which could support a change in clinical practice, if deemed necessary. The following research is recommended:

- A longitudinal observational study mapping the progress of babies from birth to just beyond diagnosis of atopic eczema is required. This would be different to current studies such as the BEEP study (Simpson et al. 2014) which is exploring prevention of atopic eczema. The recommended study would need to look at association, documenting the use of topical oils in babies genetically predisposed to atopic eczema and those who are not. Comparisons could be made between those babies using topical oils, and those not using oils, against the development of atopic eczema, in order to establish a link. It would not be realistic to expect parents to adhere to a protocol for the use or non-use of topical oil for such a lengthy period. It may not be considered ethical to do so either if the oils are damaging to the skin barrier. Parents would be free to choose to apply topical oils and this information would be recorded. Information would need to be captured regarding why they did so, from where the advice was received, which oils were used, what routine was involved including frequency of application and volume of oil, and what was the purpose of application. Data would also need to be collected recording the use of other skincare products. The OBSeRvE data detected some differences between ethnic groups but the Asian, Mixed and Black African groups were very small. Ethnicity would need to be monitored in a future study. The use of ATR-FTIR as an outcome measure would be recommended together with the validated measures included in OBSeRvE such as TEWL, stratum corneum hydration, skin surface pH and skin condition including erythema. These measures would be important to establish changes in the skin that may not be visible using techniques which are ethical in a newborn population. The primary outcome would be the diagnosis of atopic eczema. Diagnosis could be by a dermatologist or by monitoring primary care data through patient software. It would be important to establish a working definition for diagnosis of atopic eczema which was understood in the same way by all clinicians involved in the study to ensure that consistent results were obtained. The researcher feels that the observational study is the most important future work required following the findings from the OBSeRvE study, but acknowledges that this would require a substantial sample.
size to be followed up over a relatively long period of time, which is likely to be
economical. The rationale for this belief is the knowledge that, even with the
 completion of the OBServe study, midwives and health visitors are still
recommending topical oils for newborn dry skin or massage. This is a practice
which is ingrained and will be difficult to change. It is important to conduct research
which is able to establish any link between the use of the most commonly
recommended topical oils and atopic eczema if there is any hope of changing
clinical practice in the future.

- Further mechanistic work is required in order to validate ATR-FTIR as an outcome
measure. There is an increasing trend for the use of ATR-FTIR in dermatological
studies but the conversion of the spectra to numerical workable data is not
standardised. For example, even when the macro had been devised and provided
the numerical data, this had to be examined to ensure that it looked reasonable.
Results had been normalised using the Amide II variable, but this was not found to
be appropriate and the data had to be recalculated to normalise with the ~1800
wavenumber variable. This means that unless the analyst is experienced in
looking at the spectra and numerical data, and is able to identify any discrepancy,
then results will not be credible and could be flawed. If a bespoke portable device
is procured, then a working software package also needs to be devised so that
results are readily and accurately determined and the researcher can be confident
that they are valid. This could be part of the same or a separate study: one study
could standardise the outcome measures whilst another could develop the
handheld device.

- Further mechanistic work is required in order to determine an inexpensive optimal
formulation for newborn baby skin. Parents want to apply products on their baby’s
skin to prevent or treat dryness or for massage. If they are unable to obtain a
recommendation from a health professional it is likely that they will revert to
commercial formulations that will not have been rigorously tested on baby skin. It
is important that midwives and health visitors are able to recommend a product
that everyone, professional and public, is confident does not harm a baby’s skin
barrier function. At the present time 50:50 ointment (50% liquid paraffin/50% white
soft paraffin) may be the least harmful formulation to use on newborn skin (Cork
2015) but may not glide easily over the skin for massage for example. Adding an
emulsifier aids the gliding aspect of a formulation but the effect of the emulsifier
would also need to be investigated in mechanistic work.
- It is important that any future research considers the supply and use of any optimal formulation to both low resource and high resource settings. Baby massage is routine in some low resource settings in Africa and Asia, where the oils may be more toxic due to age and conditions and neonatal mortality due to infection is high, so this work is critical. Work to achieve the optimal formulation should concentrate on making this as inexpensive as possible so that it can be widely supplied to low resource settings. Research would then be required to establish the uptake of the new formulation and the effect on neonatal infection rates and mortality.

- Further research is required to determine the antimicrobial effect of linoleic acid in order to assess the reasons for the opposing findings between the work of Darmstadt (2008; 2005) and the OBSerVe (Cooke et al. 2013) and Kanti (2014) studies. Darmstadt's work was incredibly important for a high risk population as the reduction in neonatal infection and mortality was significant. It is important that there is no confusion regarding the conclusions of the OBSerVe study. Results from OBSerVe and Kanti do not overrule Darmstadt's work; there are other influential factors which need to be explored so that the evidence is clear. Any future study in this area needs to address the reasons for the opposing findings, and should concentrate on the antimicrobial nature of the high level of linoleic acid in sunflower oil.

- The OBSerVe study has highlighted that parents are also using commercial products to prevent and treat baby dry skin. These commercial products have not been rigorously tested in definitive randomised controlled trials, as they are not governed by medical research guidelines. The questionnaire data found that commercial baby oil (mineral) was as frequently used by parents as olive oil. It should be recommended to the manufacturer that an investigator-led randomised controlled trial should be considered to compare the effects of the oil against no treatment.

- The seasonal variation in recruitment of a mother and baby population should be explored to inform future study design. This would be a straight-forward secondary analysis which could collect recruitment trend data directly from identified study investigators who have conducted clinical trials with this population, and assess the differences in recruitment rates across the span of one year. This could inform researchers of the best times to set a recruitment period in order to reduce attrition.
Any future research must be disseminated to educate midwives, health visitors, other maternity service health professionals and baby massage instructors in order to engage the gatekeepers to new mothers and babies to change practice. Any change in practice must be evaluated to ensure that this has been successful and that care is evidence-based.

7.10 Implications for clinical practice

The OBSeRvE study has generated a valuable baseline dataset of newborn skin barrier biophysical measurements including the use of a novel technique. It has also provided informative data on optimal trial processes and parameters. As OBSeRvE was a pilot study, it was not able to provide data to establish a definitive link between the use of topical oils on baby skin from birth and the development of atopic eczema. Further, OBSeRvE was not designed to generate definitive answers on whether or not specific defined olive oil or sunflower oil should be used on babies’ skin. The data suggested that the skin of babies who used the oils in this trial may be better hydrated; however, the structure of the lipids in the skin barrier was negatively altered, the clinical importance of which is unknown at present. The clinical implications arising from the OBSeRvE study are therefore as follows:

- Given that health professionals should only recommend interventions if they have been proven to do more good than harm (Higgins and Green 2009), it would be difficult to support the use of topical sunflower oil or olive oil, based on the OBSeRvE data. Further research is required to inform future practice. Health professionals should cease to recommend or use topical oils on term newborn baby skin until this research takes place.

- OBSeRvE findings should be disseminated at local, national and international conferences for midwives, health visitors and dermatologists. The findings should be published in a professional peer-reviewed journal and summarised in other relevant professional journals. Health professionals should also be made aware of the Cochrane review “Topical oils for the prevention or treatment of dry skin in term infants”. A summary leaflet of current evidence in baby skincare should be circulated to hospital Trusts and parent associations such as the National Childbirth Trust, International Association of Infant Massage and the National Eczema Society.

- National clinical guidelines should be updated to ensure that health professionals are aware of the current evidence.
7.11 Conclusion

This chapter has discussed the feasibility and the results of the OBSeRvE pilot study. Data have been generated which inform future research and recommend a number of future studies. Until such research is conducted, the results which have emerged assessing proof of concept have indicated that using topical olive oil or sunflower oil on term newborn baby skin may adversely affect the skin barrier function. As health professionals should only recommend practices which are beneficial to babies, it is recommended that topical oils are not advised for use on term baby skin until such time as conclusive evidence is obtained to support this practice.

Data generated from the OBSeRvE study demonstrated that a definitive randomised controlled trial would not be the optimal immediate next step for this research and highlighted the value of conducting a pilot RCT. There are a number of directions that future research could take, possibly culminating in a definitive RCT once more exploratory and development work has taken place. Although data from the OBSeRvE study provided evidence of a biological effect on skin barrier function, a link between the use of topical oils from birth and the development of atopic eczema was not established, and the study was not adequately powered to do so. This potential link needs to be addressed in a future study to ensure that evidence emerges which supports good clinical practice. A longitudinal observational study which maps the development of atopic eczema against the use of topical oils from birth is required. Current longitudinal studies like the BEEP study (Simpson et al. 2014) are investigating prevention of atopic eczema, focusing on reducing the extent of atopic eczema in those children who are genetically predisposed to the condition. The study proposal emerging from OBSeRvE is more focused on the environmental causes of atopic eczema. If a clinical practice recommended by midwives, health visitors and other maternity service health professionals is found to be a cause of atopic eczema development then a change in practice must be implemented which has the potential to reduce prevalence in healthy babies.
CHAPTER EIGHT: PERSONAL REFLECTION

I hoped that this study would help me to answer a burning research question which emerged when I was a first year student midwife: I asked my mentor why she was advising a new mother to rub cooking oil on her baby? When I qualified as a midwife, I started to give out the same information whenever I came across a baby with dry skin, and my students therefore probably give out the same information that they learnt from me, to new mothers they are caring for as a qualified midwife, and subsequently passing on the information to their students. This same scenario is probably playing out across the country and has resulted in a widespread traditional ingrained midwifery practice. When I conducted a UK national survey of maternity and neonatal units (Cooke et al. 2011), the results confirmed this practice with 80% of midwives recommending olive oil and 20% recommending sunflower oil. I became aware that there was a school of thought attached to a possible link between the use of skincare products, including topical oils, from birth and the development of atopic eczema. It subsequently became very important to me to investigate this hypothesis and to work to change any clinical practice which may be causing harm to babies. When I became aware that the Professor of Midwifery had a Baby Skincare Programme of research in Manchester, it felt like my long-awaited opportunity to answer this question had arrived.

Through the application process of the National Institute for Health Research (NIHR) Doctoral Research Fellowship, I was able to develop a well thought out proposal before embarking on the doctoral period. The first six months of the doctorate were then used to further develop and refine this proposal and consider the existing literature more systematically. Many of the challenges faced would have been far more difficult had it not been for this refinement time. The study received praise from both the Research Ethics Committee and the University of Manchester study audit process for being well-designed and well-considered.

The opportunity to be the chief investigator of a randomised controlled trial has been a fantastic learning opportunity. I have learnt about the conduct of quantitative research for both the trial and questionnaire data, and I have built upon my knowledge of qualitative research with the opportunity to use a new method of qualitative analysis: Framework analysis (Ritchie and Spencer 1994).

There have been particular learning points which have developed my knowledge and understanding of research:
Firstly, I had not anticipated all of the challenges pertaining to recruitment and retention of participants. I put all of my effort into the study as I felt responsible for it; it was my doctoral study, I was the chief investigator and wanted it to be successful. Recruitment was still difficult. It was highlighted at one of the Trial Steering Committee meetings that although this effort was commendable, the results regarding recruitment and retention would be the best possible scenario. Recruitment staff in a definitive study that were not so committed to making the study work may not put in the same level of effort. I am aware that when the next study is designed it will be important to incorporate a training strategy for recruitment staff so that they feel confident in the study, and to build a team that feel ownership of the study so that there is a desire for it to succeed. The conclusion to this discussion was that a definitive randomised controlled trial may not be the optimal immediate next step for research in this topic area. This was disappointing as the direction for research was then unclear and could proceed in a number of ways. I learnt that even though a researcher may have pre-conceived ideas as to which direction research needs to take, an open mind must be maintained to other options. This challenge also made me realise the importance of conducting pilot studies to ensure that expensive definitive trials do not go ahead without pretesting study processes and parameters, and subsequently fail to achieve credible results.

Secondly, I learnt the importance of developing a good relationship with the gatekeepers at the hospital in order to make my research processes a success. I became well known on the wards and as I put the time in to get to know the ward midwives they became more helpful with recruitment and started to ask about skincare research. Some also began to ask about midwives leading research. This was important to me as one of my aims when applying for an NIHR Doctoral Research Fellowship was to be a role model for other midwives, heightening their awareness of the possibilities that exist to incorporate research into their career trajectory and helping them to realise the opportunities that exist for them to lead research. Midwives working clinically are arguably the most aware about clinical issues that need to be investigated to provide an up to date evidence base. It is imperative that more midwives lead patient-centred research to improve care for mothers, babies and their families.

Finally, the knowledge that new mothers are willing to allow their newborn babies to participate in a randomised controlled trial for reasons that they wish to benefit others in the future and allow knowledge to progress is a humbling experience. There was no personal gain, and my trial did require additional effort on their parts even though most said it was “easy” to do. I was still asking them to perform an intervention that was not essential, but, in reality, an extra task. This qualitative data, in addition to the knowledge that so many of the mothers had either personal knowledge or an awareness of atopic
eczema has highlighted again just what a prevalent issue this is, and that parents want to see a solution. This has deepened my desire to continue with research in this topic area. It was disappointing that the pilot study did not find a definitive RCT to be feasible, as that would have been a clear direction for me in the next phase of my career as a post-doctoral researcher. However, the pilot study was still successful as it generated a wealth of data that informs a number of directions the research could take. My belief is that the next phase of this work must be the longitudinal observational study outlined in the previous chapter. If there is a link between the use of topical oils from birth and the development of atopic eczema in healthy term babies, this will be the way to discover it.

My ambition in research is to generate evidence that can improve the care and well-being of mothers and their babies. We need to change potentially harmful practices that have become traditional, and conduct robust research to ensure that our care is evidence-based.
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Appendix 1

Publication:

Use of oil for baby skincare: A survey of UK maternity and neonatal units

Abstract
Olive oil is commonly recommended by health professionals to new parents for use in the prevention and treatment of the term baby’s dry skin, and for baby massage. There is no evidence to support this practice. The use of olive oil may be harmful to skin, affecting skin barrier function. This effect may be a contributory factor in the prevalence of childhood conditions such as atopic eczema. This paper discusses a national online audit of UK maternity hospitals (n = 67) and neonatal units (n = 33) performed between November 2010 and January 2011. Our findings confirm that oil use on babies’ skin is common practice. As the direct cost to the NHS for treatment of atopic eczema is high, it is imperative that further research in this area is performed, preferably in the form of a randomized controlled trial. Health professionals will then be in a position to provide accurate information to parents with regard to oil in baby skin care regimens.

Many health professionals recommend the use of olive oil in the prevention or treatment of dry skin in the term neonate (Lavender et al, 2009). This practice is not evidence based. There is a dearth of research in the area of skincare for neonates. Current clinical practice may affect skin barrier function and be a contributory factor in the prevalence of childhood conditions such as atopic eczema (also known as atopic dermatitis).

Anatomy of the skin
There are three compartments to the skin: the epidermis, the dermis and the hypodermis (subcutaneous layer). The epidermis (Figure 1) is composed of layers of closely packed keratinocytes at different stages of differentiation. New keratinocytes are formed in the basal layer (the stratum basale), and move upwards through the layers until they transition into corneocytes (terminally differentiated keratinocytes) at the transition between the stratum granulosum and stratum corneum (Candi et al, 2005). Mature corneocytes are shed from the surface, in a process termed desquamation, to balance cell division in the proliferative layer. The epidermis is the outermost compartment and the focus for the interaction of topical products. The layer of the epidermis exposed at the surface of the skin, referred to as the stratum corneum, acts as the ‘skin barrier’ to protect against the ingress of external pathogens, allergens and irritants (Figure 2). The skin barrier can be affected by genetic changes and environmental factors such as cleansing products or dust mites. In Figure 2, the wall (Panel A) represents the barrier to the loss of water and to the penetration of irritants/allergens. It is made up of bricks, representing the corneocytes, held together by iron rods, representing the corneodesmosomal junctions, and surrounded by mortar, representing the lipid lamellae (Elias, 1983; Cork et al, 2009). The rusting of the iron rods in the uppermost layers represents normal desquamation (corneocyte shedding), required to balance the generation of new cells in the basal layer of the epidermis. A defective skin barrier, represented by a broken wall with crumbling mortar, permits increased trans-epidermal water loss and is susceptible to bacterial invasion and the penetration of harmful irritants and allergens (Panel B).

Although skin anatomy at birth is well adapted to extra-uterine life, it continues to change during the first year of life (Stamatas et al, 2010). The skin barrier appears to undergo a period of further development and optimization during this time.
Differences between adult and neonatal skin

Neonatal skin is more vulnerable than adult skin as the stratum corneum is 30% thinner and the epidermis is 20% thinner in the neonate (Stamatas et al., 2010). This results in increased permeability and consequent dryness. Furthermore, as the neonate body surface to body weight ratio is higher than for adults, neonatal skin is more vulnerable to use of topical treatments (Nikolovski et al., 2008).

Neonatal skin contains less lipids, melanin and natural moisturizing factors than adults, which are associated with altered biophysical properties of the skin including an increased rate of trans-epidermal water loss and reduced stratum corneum hydration (Chiou and Blume-Peytavi, 2004; Nakagawa et al., 2004). Neonatal skin also exhibits an elevated surface pH, which may contribute to weakening of the skin barrier. High skin pH (low acidity) increases the activity of proteases that break down corneodesmosomes (supportive element of the stratum corneum) and inhibits the activity of enzymes required for lipid processing (Hachem et al., 2003).

The differences in structure and function of neonatal skin compared to adult skin suggest a greater vulnerability to negative environmental factors, including certain skincare products, and the subsequent development of skin conditions. In agreement with this the majority of cases of atopic eczema occur during the first year of life (Bieber, 2008). In order to prevent further weakening of the neonatal skin barrier the effect of topical skincare products must be determined to ensure only the use of those with positive effects.

Background

In the UK, prevalence of atopic eczema in children has increased substantially over the second part of the 20th century (Simpson et al., 2009). This may have been influenced by the increased use of topical treatments from birth. The application of olive oil is recommended by health professionals to new mothers for use on their term baby’s skin (Lavender et al., 2009); this can be to prevent/treat dryness or as part of massage.

Current research in this area is limited and conflicting, making it difficult to assess the effectiveness of this practice. There is evidence that oils containing high concentrations of oleic acid, in particular olive oil, may damage the skin barrier (Naik et al., 1995; Darmstadt et al., 2002; Jiang and Zhou, 2003). In mice the topical application of olive oil, mustard seed oil and soybean oil significantly inhibited the restoration of skin barrier function following experimentally induced damage (Darmstadt et al., 2002). In humans oleic acid was found to enhance penetration through the skin barrier (Jiang and Zhou, 2003).

In contrast, oils such as sunflower oil containing low levels of oleic acid and high levels of linoleic acid can enhance/repair the skin barrier (Darmstadt et al., 2002; 2004). A randomized controlled clinical trial investigating the effect of skin barrier therapy on neonatal mortality rates in preterm infants in Bangladesh reported that treatment with sunflower seed oil, containing low levels of oleic acid, significantly reduced mortality rates (Darmstadt et al., 2008). One of the mechanisms for the damaging effect of olive oil on the skin barrier is that it disrupts the ordered struc-
The differences in structure and function of neonatal skin compared to adult skin suggest a greater vulnerability to negative environmental factors, including certain skincare products, and the subsequent development of skin conditions.
The number of tertiary units, district general hospitals and neonatal units which responded to the survey was similar. There were a considerably smaller number of midwifery-led units/birth centres which responded (Figure 3). There were also fairly similar numbers of births per year in the ranges 1000–3000 births, 3000–5000 births and greater than 5000 births. There were a considerably smaller number of units with less than 1000 births (Figure 4).

Is oil stocked on units?
Some units \( (n=35, \text{36.5\%}) \) reported that they stocked oil for use by health professionals. This figure comprised 10 maternity wards and 12 neonatal units in England, 4 maternity wards in Scotland, 3 maternity wards in Wales and 2 neonatal units in Northern Ireland. Fewer units \( (n=27, \text{28.3\%}) \) reported that they stocked oil for use by parents. Of those supplying oil for parental use, 73.9\% \( (n=17) \) were neonatal units and 17.4\% \( (n=4) \) were maternity wards. The only types of oil that were stocked were olive oil and sunflower oil.

Which oil is recommended?
Over half \( (n=49, \text{52.1\%}) \) of maternity/neonatal units stated that they recommended the use of oil for baby skincare; the majority \( (n=40, \text{81.6\%}) \) of these units reported that they recommended olive oil for parental use on their babies (Figure 5), fewer \( (n=10, \text{20.4\%}) \) recommended sunflower oil and fewer still \( (n=6, \text{12.2\%}) \) recommended commercial baby oil (respondents were not asked which brand). It was clear from the results that some units recommended more than one type of oil. Other responses from maternity/neonatal units included ‘vegetable oil’, ‘grapeseed oil’, ‘cold-pressed high-quality organic vegetable oil’ and ‘cold compressed organic sunflower oil’.

Under what circumstances is the use of oil recommended?
Some units \( (n=10, \text{20.4\%}) \) reported that oil was recommended for the prevention of dry skin (Figure 6). The majority \( (n=44, \text{89.8\%}) \) of units reported that it was recommended for the treatment of dry skin. Many \( (n=34, \text{69.4\%}) \) reported that it was recommended for use in baby massage. There were three other responses which included two units reporting use of oil in nappy cleansing and one which reported that oil was used as part of the development care plan, the Neonatal Individualized Developmental Care and Assessment Programme (NIDCAP) (Alis and Gibes, 1984) and massage.

The responses stated that information was given to parents in written form \( (n=4, \text{8.2\%}) \), in parent education classes \( (n=10, \text{22.4\%}) \) and verbally by midwives and neonatal nurses \( (n=34, \text{98\%}) \). It was clear from the results that some units provide information in more than one form. The advice given by health professionals to parents is reportedly based on research \( (n=17, \text{37.0\%}) \) and traditional practice \( (n=24, \text{52.2\%}) \). When asked for sources of evidence, responses given included NIDCAP, International Association of Infant Massage (IAIM) (McClure, 2001), research by Lack et al (2003) and BLISS, a support network for parents and health professionals caring for premature babies.

How much oil is recommended?
The majority of units \( (n=31, \text{64.6\%}) \) do not specify any particular amount of oil (Figure 7). Free text
responses included ‘a little’; ‘small amount on a cotton wool ball’; ‘just enough to thinly cover fingers of one hand’; ‘to suit babies’ individual needs’; and ‘sufficient for the skin’. Most units (n = 42, 87.5%) reported that they do not specify a length of time for use of oil. Of those that do, responses included ‘until skin no longer broken and healing’; ‘while skin is dry and infant is on neonatal unit’; ‘as required’; ‘if no improvement within 7 days, refer to GP’; and ‘for as long as baby massage used’. Baby massage is often performed well into the child’s first year, and therefore the usage of olive oil may be long-term for some babies.

**Discussion**

This survey was conducted to assess current clinical practice. Although response rates varied considerably across the UK, all potential respondents were contacted and reminded in the same way and at the same time. It is not clear, therefore, why some response rates were much better than others.

The survey found that olive oil is recommended to new parents by health professionals for their babies in spite of the dearth of evidence to support this practice. Less units stocked oil (olive oil and sunflower oil) for use by health professionals (36.5%) and/or parents (28.1%) in comparison to the number of units that reported recommending the use of olive oil (81.6%) for the treatment of dry skin (89.8%). The recommendations for the use of oil were mainly given verbally by midwives and neonatal nurses (98%). These results confirmed what the authors believed was occurring in clinical practice. Previous research has suggested that midwives and health visitors believe in the safety of olive oil (Lavender et al, 2009). It is not known whether this practice is good for, or harmful to, neonatal skin barrier function and consequently whether this practice is a contributory factor in the development of prevalent childhood skin conditions such as atopic eczema.

Most units do not specify an amount of oil to use or a length of time to use it. As health visitors and parents were not surveyed it is not possible to determine how long this practice may persist. Baby massage may be performed for more than a year. If the type of oil used is detrimental to skin barrier function, as skin continues to change during the first year of life (Stamatas et al, 2010), long-term use may have serious implications.

Respondents provided various sources of supporting evidence for their clinical practice. These are considered briefly here. None of the evidence suggested specifically recommends olive oil for baby skin care.
The landmark paper by Lack et al. (2003) regarding peanut oil, and also papers by Williams and Tate (2006), Isaksson and Bruze (1999) and Wong and King (2004) provide some evidence opposing the use of peanut and olive oil. Not only is there a complete absence of any evidence for the use of olive oil, some health professionals may be misquoting evidence as justification for using these oils.

**BLISS**
BLISS is a support network for parents and health professionals caring for premature babies. The authors were unable to find any evidence regarding the use of oil for baby skincare on the BLISS website. BLISS provides their support for NIDCAP but there is no specific information on the use of oil either on the website or within their downloadable publications. A helpline is offered for parents who require more information regarding baby massage. The authors contacted BLISS to ask what further information was provided to enquiries. They advised that they refer any enquiries to the IAIM.

**Research versus traditional practice**
It is important to consider what evidence counts in relation to research vs. traditional practice. Rycroft-Malone et al. (2004) suggested that effective clinical practice incorporates a broader evidence base informed by four sources of evidence: research, clinical experience, parental experience and information within a local context. They suggested that it is important to ensure that each source is as robust as possible, and the four aspects merged together in a sensible way in order to deliver effective, evidence-based, patient-centred care. Patients are entitled to receive care based on the best possible evidence. If that evidence does not exist, research studies are required to assess whether the current traditional clinical practice is in the best interests of the patient. In the case of baby skincare, traditional practice has been shown in this national survey to commonly recommend and use olive oil in the prevention/treatment of dry skin and for baby massage. This is in spite of the existing research performed in mice and adults that suggests that oil with a high oleic acid content is harmful to skin barrier function (Naik et al., 1995; Darmstadt et al., 2002; Jiang and Zhou, 2003). Existing traditional practice may have long-term consequences and should be investigated. Clinical experience, patient experience and local information can all be incorporated within the research design or better still within the Medical Research Council (MRC) Complex Intervention...
Framework (MRC, 2008) in the exploratory/development phases. User involvement is crucial to a robust study design and can include patient/clinician experience in a local, regional and/or national context.

There are difficulties in instigating a change in practice. Cultural and traditional beliefs within the health service can affect the way in which different types of evidence are acceptable (Stewart, 2001). A qualitative study of health professionals’ views of what evidence counts concluded that evidence that reinforces traditional practice will be adopted easily; conversely evidence that challenges existing beliefs will be difficult to instigate (Stewart, 2001). These barriers can be at different levels—the clinician; the organization; or at a regional or national policy level (Kalassian et al, 2002). These barriers can be lessened if clinicians are included at the design stage of the research study. They may then take ownership of the change.

Implications for future research and clinical practice

It is important to perform further research to investigate the effect of olive oil. This may provide the necessary evidence in order that health professionals can provide accurate information to new parents about baby skincare, rather than remain in confusion regarding which oil, if any, to recommend. It would also enable health professionals to provide consistent advice across the UK, rather than conflicting advice about whether or not to use oil and which oil to use.

Atopic eczema affects 31% of children (aged 2 to 15 years) in the UK (Gupta et al, 2004). Direct NHS costs for managing allergic disease including atopic eczema are estimated to be £100 billion per year (Gupta et al, 2004). The indirect costs to the NHS are unknown; atopic eczema accounts for 15–86% of parental sleep disruption, associated with resulting anxiety and depression (Meltzer and Moore, 2008). A research study has the potential to provide evidence that may reduce the prevalence of childhood skin diseases such as atopic eczema, and consequently reduce NHS treatment costs.

Limitations of survey

Any survey is limited by the number of people who want to respond. An analysis of 199 online surveys suggested an average response rate of 32.52% (Hamilton, 2009). The response rate in this survey was 31.15%, which is very similar to that reported. It is suggested that a mixed-mode strategy, such as a combination of web-based and mail, may provide a better response rate (Kaplowitz et al, 2004). However, the authors decided that as they wanted to complete the survey in a short timeframe, a web-based survey would be more efficient in achieving this. This decision was taken particularly as the survey data collection period of 2 November to 14 January coincided with the busiest time of the year for the mail service.

Health visitors and parents were not surveyed and therefore the average length of time for which the practice of using oil was continued could not be discovered. Length of usage may have implications for a worse outcome if olive oil does have a detrimental effect on skin barrier function.

Conclusions

This audit of UK maternity and neonatal units has shown that olive oil is recommended for use in baby skincare, even though this practice is not evidence-based. It is important that further research is performed, preferably in the form of a randomized controlled trial, to determine the effectiveness of this practice. This will either provide evidence to support our clinical practice, or evidence to support a change in practice. In either case, this trial is necessary to provide the best possible care for parents and their babies.

Acknowledgments: Figures 1 and 2 are reproduced with permission from the Academic Unit of Dermatology, The University of Sheffield Medical School.

Key points

- There is very little research in the area of neonatal skincare, particularly in relation to the use of oils
- Many health professionals recommend the use of olive oil in the prevention or treatment of neonatal dry skin, despite this not being evidence based
- The type and amount of oil recommended by health professionals varies, with olive oil being most frequently reported
- The triggers for recommending the use of oils are inconsistent
- Further research is required in this area, preferably in the form of a randomized controlled trial


Williams JD, Tate BJ (2006) Occupational allergic contact dermatitis from olive oil. Contact Dermatitis 55(4): 251–2

Appendix 2

Publication:

Topical oils for the prevention or treatment of dry skin in term infants (Protocol)

Cooke A, Victor S, Cork M, Lavender T

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2014, Issue 5

http://www.thecochranelibrary.com

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Topical oils for the prevention or treatment of dry skin in term infants (Protocol)
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Topical oils for the prevention or treatment of dry skin in term infants

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Editorial group: Cochrane Neonatal Group.


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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

We will assess the effect of the topical application of oils versus that of other topical oils, emollients, placebo or no treatment:

1. in the prevention of dry skin in term (≥ 37 weeks of gestation) newborn infants; and
2. in the treatment of dry skin in term (≥ 37 weeks of gestation) newborn infants.

BACKGROUND

Description of the condition

Dry skin is a common occurrence in the first few months of an infant’s life (Saijo 1991). Dry skin has been defined as “a cutaneous reaction pattern reflecting abnormal desquamation of diverse etiologies” (Madison 2003). In normal skin, corneocytes are shed from the skin in small enough quantities that they are not visible to the naked eye; however, in dry skin, the skin appearance becomes rough and flaky if this normal process is disturbed in any way. In an infant, this is a normal process of adaptation to life outside the uterus.

Atopic eczema (synonym atopic dermatitis) is an inflammatory skin condition characterised by dry and scaly skin, redness, blistering and itching. It affects up to 30% of children aged 2 to 15 years in the UK (Gupta 2004). Affected children are also predisposed to allergic asthma and allergic rhinitis (Gustafsson 2000). It is suggested that approximately 60% of sufferers develop atopic eczema in their first year of life (Bieber 2008). Prevalence has increased to this current level from approximately 5% of children in the 1940s (Taylor 1984). During that time the genetic structure of skin has not changed; however, the way that we care for an infant’s skin has changed, with an increase in use of soaps, other harsh detergents and oils (Cork 2009; Danby 2011a).

Infant skin is physiologically different to adult skin. The stratum corneum is 30% thinner and the epidermis is 20% thinner in-
fants than in adults (Stamatas 2010). This difference in skin structure results in increases in permeability and dryness in infant skin. Infant skin is also more vulnerable to the use of topical treatments, as the ratio of infant body surface to body weight is higher than that for adults; hence, the risk that such therapies will be absorbed through the skin is greater in infants than in adults (Nikoloski 2008). As the infant skin barrier continues to develop during the first year of life (Stamatas 2011), infants are vulnerable to this risk throughout this period. Infant skin is prone to an increased rate of transepidermal water loss (TEWL) and reduced stratum corneum hydration because it contains fewer lipids and natural moisturising factors, and less melanin than adult skin (Chiou 2004; Nakagawa 2004). Infants may also experience a weakening of the skin barrier due to their elevated skin surface pH. High skin surface pH (low acidity) results in increased activity of proteases, which breakdown cornodesmosomes (the supportive component of the stratum corneum), and hinders the activity of enzymes that are required for lipid processing (Hachem 2003; Cork 2009). These differences in both structure and function between infant and adult skin suggest that infant skin is more vulnerable to environmental factors, including infant skin care products. The use of some topical oils and emollients on infant skin may therefore contribute to the development of adverse skin conditions, including atopic eczema, whereas other topical oils may have a positive effect and prevent the development of this condition (Danby 2011a; Danby 2011b; Danby 2013).

Description of the intervention

Parents want to use skin products that make their infant look and smell nice (Lavender 2009; Furber 2012). The application of oil is commonly recommended by health professionals to new parents for use on their newborn infant’s skin (Lavender 2009; Cooke 2011), in order to prevent or treat dryness or for massage. The use of emollients is not commonly recommended; however, parents have the choice of a diverse range of emollient infant skin care products from numerous manufacturers. In a UK national survey (Cooke 2011), 52% of maternity and neonatal units recommended the use of oil; 82% of these units recommended olive oil to parents for use on their infant’s skin and 20% recommended sunflower oil. Health professionals, such as midwives and health visitors, believe these oils to be natural and, therefore, not harmful to infant skin (Lavender 2009). Infant skin conditions can cause parental anxiety (Adalar 2007). Parents will often adhere to advice given to them by health professionals with regard to the care of a newborn infant (Lavender 2009).

How the intervention might work

Some oils have been shown to have a positive effect on skin barrier function (Darmstadt 2004; Darmstadt 2008; Danby 2013), whereas others may impair this function (Naik 1995; Darmstadt 2002a; Jiang 2003; Danby 2013). Research has shown that olive oil of a certain composition (i.e. a high ratio of oleic acid to linoleic acid) may adversely affect skin barrier function in mice (Darmstadt 2002a; Jiang 2003) and adults (Naik 1995; Danby 2013). This composition of oil disrupts the lipid structure of the stratum corneum, and is a potential risk factor in the development or exacerbation of atopic eczema. Optimal sunflower oil (i.e. a high ratio of linoleic acid to oleic acid) has been shown in the same population to promote skin barrier repair (Darmstadt 2004; Darmstadt 2008; Danby 2013). The use of emollients or moisturisers is common in skin care regimens. They act by preventing water loss or by actively hydrating the skin (Elson 2011). The main reason to use emollients in skin care is to protect the integrity of the skin barrier. For healthy term infants, this is not clinically necessary; however, those infants at risk (such as those with a family history of atopic eczema) may benefit from the regular use of emollients (Frieden 2011). An oil is also an emollient that helps to prevent water loss and lubricates the skin.

Why it is important to do this review

Societal interest in ‘natural’ products is high (Allemann 2009), especially in parents of newborn infants (Cottingham 2007). There is a readiness among parents to use oil for infant skin care, and a readiness among maternity professionals to recommend it. There is a misconception that because a product is ‘natural’ it must be ‘safe’ (Lavender 2009; Bedwell 2012). Oils have been used in the cosmetic, pharmaceutical and perfumery industries for many years. Although oils are governed by guidelines for the testing and research of cosmetics (Council of the European Communities 1976), these are not as rigorous as those governing the use of medicines in humans (Department of Health 2004). This means that oils have been used as medicinal and homeopathic remedies for many years without any collection and analysis of toxicological data. The infant skin surface area in relation to body weight is high, and absorption is relative to the surface area exposed (Rutter 1987). Topical applications may cause irritation, damage or systemic effects through absorption of the oil in to the body. Infection is one of the leading causes of neonatal morbidity and mortality in low-resource countries (Darmstadt 2002a). The vulnerability of infant skin and the use of oils that may be harmful, combined with poor hygiene conditions, have the potential for increased hazards of infection. Nosocomial sepsis is more common in preterm infants, in whom the stratum corneum is not fully mature (Conner 2009) and the skin does not have the protective benefit of vernix (Yoshio 2003), than in term infants. Several studies (Darmstadt 2002b; Darmstadt 2004; Edwards 2004; Darmstadt 2005; Darmstadt 2008; Kiechl-Kohlendorfer 2008) and a Cochrane systematic review (Conner 2009) have considered...
topical applications for preterm infants, but no review has considered the evidence in term infants.

We know that 45% and 60% of atopic eczema cases occur in the first six months and year of life, respectively (Bieber 2008). This period of time is when midwives, maternity workers and other infant health professionals have the most influence with parents. Health professionals find it difficult to give evidence-based advice to new parents, as there is insufficient evidence to guide practice. It is therefore important to systematically review what evidence there is, to provide a high-quality basis for clinical practice and informed decision-making. Some oils are potentially harmful; however, others may provide some benefit. Given the rise in the prevalence of atopic eczema, it is timely to evaluate current evidence in order to provide the most appropriate advice for parents and health professionals.

This review will assess the effects of topical oils and emollients in the prevention or treatment of dry skin compared to the use of alternative oils and emollients or no treatment in term infants. The review will complement the body of work held in the Cochrane Database of Systematic Reviews, which includes reviews such as those investigating the prevention of infection in preterm infants (Conner 2009; Seliem 2009) and the prevention of napkin dermatitis in infants (Davies 2009).

A systematic review will provide:

1. an evidence base to inform parents and health professionals in their practice with healthy term newborn infants, rather than remain in confusion regarding which oil or emollient, if any, to recommend or use; and
2. highlight any area that requires further investigation.

**OBJECTIVES**

We will assess the effect of the topical application of oils versus that of other topical oils, emollients, placebo or no treatment:

1. in the prevention of dry skin in term (≥ 37 weeks of gestation) newborn infants; and
2. in the treatment of dry skin in term (≥ 37 weeks of gestation) newborn infants.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomised and quasi-randomised controlled trials (including cluster and parallel trials, and trials in which the infant serves as his/her own control) comparing the topical application of oils with the topical application of other oils, emollients or placebo, or with no treatment will be considered.

**Types of participants**

We will include newborn term (≥ 37 weeks of gestation) infants receiving the application of topical oils or emollients:

1. for the prevention of dry skin within the first 28 days following birth; or
2. for the treatment of dry skin within the first 28 days following birth.

There is no upper gestational age limit for eligibility.

For the purposes of this review, dry skin will be diagnosed using a validated skin assessment scoring tool (Lane 1993; Lund 2001) or skin surface hydration measurement tool (e.g. a Corneometer®), or by clinical observation by a midwifery, neonatal or dermatology health professional.

We will include infants with normal skin and infants with a family history of atopic eczema. Normal infant skin variations, such as erythema neonatorum, erythema toxicum or milia, will not be considered as skin disorders, and will therefore be included. A family history of atopic eczema will be defined as “at least one of mother, father or sibling who has a medical diagnosis of atopic eczema/atopic dermatitis and who is treated with topical steroidal treatment”. Infants diagnosed with an impairment of epidermal integrity, abnormal epidermis or dermis, such as collodion infant or congenital ichthyosis, will be excluded.

We will exclude newborn preterm (< 37 weeks of gestation at birth) infants, as this population has been included in another review (Seliem 2009).

**Types of interventions**

All of the stated interventions will be considered separately for both the prevention and treatment of dry skin.

**Intervention**

1. Application of topical oils, which may include any type of oil (such as olive oil, sunflower oil, coconut oil, grape seed oil, borage oil, evening primrose oil, other vegetable oil) compared with placebo or no topical applications
2. Application of topical emollients compared with placebo or no topical applications

**Other Interventions**

1. Intervention oil versus another topical oil
2. Intervention emollient versus another topical application (such as emollient, gel, cream, lotion or powder)
3. Intervention oil versus another topical application (such as emollient, gel, cream, lotion or powder)

It is expected that other products, such as soaps or bathing products, may be used on the infants in the trials. It is also expected that there will be variations in the dose, area, frequency and duration of application of the interventions. If there are substantial
differences across trials, data will not be pooled but reported separately. Where combinations of topical applications are applied, data from a combination of treatments will not be pooled with data for single treatments.

**Types of outcome measures**

Where appropriate, data will be pooled or, if necessary (and appropriate), dichotomised. Outcomes will be analysed at baseline and at further time points up to 28 days (e.g. 7, 14, 28 days).

**Primary outcomes**

1. Change in skin surface hydration, measured using a Corneometer® or similar validated tool, within 28 days following birth
2. Change in TEWL, measured using an Aquaflux, Tevameter® or similar validated tool, within 28 days following birth

**Secondary outcomes**

1. Change in skin assessment scores, measured using the Neonatal Skin Condition Score (Lund 2001) or the Skin Condition Grading Scale (Lane 1993) within 28 days following birth.
2. Systemic or cutaneous infection, confirmed by diagnosis more than 48 hours after birth, as determined by culture of swabs from a normally sterile skin site
3. Change in skin surface pH, measured using a Skin-pH-meter or similar validated tool, within 28 days following birth
4. Atopic eczema, confirmed by clinical diagnosis by a dermatologist
5. Clinical observations of adverse skin conditions (visible signs of skin barrier dysfunction such as erythema/rash), measured using a Mexameter® or similar validated tool, or documented clinical examination, within 28 days following birth
6. Maternal satisfaction with regard to using oils for infant skin care or condition of infant’s skin, as measured by questionnaire response
7. Other skin-related outcomes not identified a priori by the reviewers but reported by trial authors

**Searching other resources**

We will search for further studies in the reference lists of all identified articles. We will not apply language, start date or geographical restrictions. We will approach the clinical research departments of all major pharmaceutical and cosmetic companies to request access to their unpublished research (see Appendix 1). We will contact subject experts to identify ongoing, unpublished research. Abstracts presented at the annual meetings of the Society for Pediatric Research, the American Pediatric Society, and the European Society for Paediatric Research, and published in the journal Pediatric Research, will be handsearched. We will include trials presented in abstract form only if sufficient data are available from the abstract, or from contact with the author.

**Data collection and analysis**

We will use the standard methods of the Cochrane Neonatal Review Group.

**Selection of studies**

Two review authors (AC, TL) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third review author (SV or MC).

**Data extraction and management**

We will design a form for the extraction of data. For eligible studies, at least two review authors (AC, TL) will extract data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third review author (SV/MC). We will enter data into Review Manager (RevMan 2011) and check them for accuracy.

We will attempt to contact authors of the original reports to provide further details when information regarding the above is unclear.
Assessment of risk of bias in included studies

Two review authors (AC, TL) will independently assess the risk of bias in each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreement by discussion or by involving a third review author (SV/MC).

(1) Sequence generation (checking for possible selection bias)
For each included study we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:
• adequate (any truly random process, e.g. random number table; computer random number generator);
• inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
• unclear.

(2) Allocation concealment (checking for possible selection bias)
For each included study we will describe the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We will assess the methods as:
• adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
• inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
• unclear.

(3) Blinding (checking for possible performance bias)
We will describe for each included study the methods used, if any, to blind outcome assessors, participants and personnel from knowledge of which intervention a participant received. We will judge studies at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess the methods for blinding separately under the headings: participants, personnel and outcomes. We will assess the methods as:
• adequate;
• inadequate;
• unclear.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)
We will describe for each included study, and for each outcome or class of outcomes, the completeness of data, including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total numbers of randomised participants), reasons for attrition or exclusion, where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses that we undertake.
We will assess the methods as:
• adequate (where fewer than 20% of the data are missing);
• inadequate (where more than 20% of the data are missing);
• unclear.

(5) Selective reporting bias
We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:
• adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
• inadequate (where not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
• unclear.

(6) Other sources of bias
We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias as:
• yes;
• no;
• unclear.

(7) Overall risk of bias
We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias, and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through sensitivity analyses (see ‘Sensitivity analysis’).

Measures of treatment effect

Dichotomous data
We will present results as summary risk ratios and risk differences with 95% confidence intervals for dichotomous data. If statistically significant, we will present the number needed to treat for an additional beneficial or harmful outcome (NNTB/NNTH).

Continuous data
We will use the weighted mean difference for continuous data if outcomes are measured in the same way in all trials. We will use the standardised mean difference to combine data from trials that measure the same outcome using different methods. We will present these data with 95% confidence intervals.
Unit of analysis issues

Randomised trials where participant serves as own control

We will include these trials along with individually randomised trials. We will consider it reasonable to combine the results from both types of study if there is little heterogeneity between the study designs.

Cluster randomised trials

We will include cluster randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes by means of the methods described in the Cochrane Handbook for Systematic Reviews of Interventions, using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2011). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster randomised trials and individually randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and an interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will seek statistical advice for this part of the analysis.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect using sensitivity analyses. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis (i.e. we will attempt to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention). The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the I² statistic. We will identify heterogeneity using the following categories: less than 25%, no heterogeneity; 25% to 40%, low heterogeneity; 50% to 74%, moderate heterogeneity; and 75% or greater, high heterogeneity. We will explore substantial heterogeneity (≥ 75%), if identified, using subgroup analyses.

Assessment of reporting biases

Where we suspect reporting bias (see 'Selective reporting bias'), we will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results using sensitivity analyses.

We will create funnel plots using Review Manager version 5.2 (RevMan 2011) and assess the presence of publication bias by visual inspection of the plots for funnel plot asymmetry. Unfortunately, where the effect measure for dichotomous outcomes is the relative risk (or risk ratio), as is the case for potentially two of the outcomes in this review (skin assessment scores and maternal satisfaction), there is limited evidence to underpin the statistical assessment of funnel plot asymmetry (Higgins 2011). Therefore, we will limit our assessment of funnel plot asymmetry to a visual inspection only.

Data synthesis

Statistical analyses will be performed using the standard methods of the Cochrane Neonatal Review Group. Review Manager version 5.2 (RevMan 2011) will be used for meta-analyses. We will use fixed-effect meta-analyses for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect (i.e. where trials are examining the same intervention, and the trials' populations and methods are judged to be sufficiently similar). If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if we detect substantial statistical heterogeneity (see 'Assessment of heterogeneity'), we will attempt to explain the heterogeneity identified in the fixed-effect model based on differences in clinical, quality or other characteristics between studies.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses based on:

1. setting: high-income countries (gross national income (GNI) per capita $4036 or more) versus low-income countries (GNI per capita $4035 or less (World Bank 2012));
2. ethnicity: white versus black and minority ethnic;
3. family history of atopic eczema (“at least one of father, mother, or sibling, who has a medical diagnosis of atopic eczema and who has had topical steroid treatment”) versus no family history of atopic eczema.

For fixed-effect meta-analyses, we will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.

Sensitivity analysis

We will perform sensitivity analyses based on trial quality, separating high-quality trials from trials of lower quality. We will define high quality, for the purposes of this sensitivity analysis, as a trial having adequate allocation concealment and a 'reasonably
expected loss to follow up’ (classified as less than 10%). We will restrict sensitivity analyses to primary outcomes.

**REFERENCES**

Additional references

Adalat 2007

Allemann 2009

Bedwell 2012

Bieber 2008

Chiou 2004

Conner 2009

Cooke 2011

Cork 2009

Cottingham 2007

Council of the European Communities 1976

Danby 2011a

Danby 2011b

Danby 2013

Darmstadt 2002a

Darmstadt 2002b

Darmstadt 2004

Darmstadt 2005

Darmstadt 2008

Davies 2009

Deeks 2001
Topical oils for the prevention or treatment of dry skin in term infants (Protocol)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Stamatas 2010

Stamatas 2011

Taylor 1984
Taylor B, Wadsworth J, Wadsworth M, Peckham C.


World Bank 2012

Yoshio 2003

* Indicates the major publication for the study

### APPENDICES

**Appendix 1. Pharmaceutical and Cosmetic Companies approached to access unpublished research**

Johnson & Johnson  
Pfizer  
Roche  
GlaxoSmithKline  
Novartis  
Sanofi Aventis  
Astra Zeneca  
Abbott Laboratories  
Merck  
Bayer  
Eli Lilly  
Bristol-Myers Squibb  
Proctor & Gamble  
Boehringer  
Astellas Pharma Ltd  
Unilever  
L’Oreal  
Shiseido  
Estee Lauder  
Avon  
Beiersdorf  
Alberto-Culver  
Kao Corporation
CONTRIBUTIONS OF AUTHORS

Alison Cooke prepared the protocol.

All authors contributed to reviewing all sections of the protocol and reviewed the final version prior to submission.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK.
  Alison Cooke is funded by a National Institute for Health Research Doctoral Research Fellowship. This report is independent research supported by the National Institute for Health Research (Doctoral Research Fellowship DRF-2012-05-160). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.
  Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C.
Appendix 3: Protocol for Systematic Review

**Review title:** Topical oils and emollients for the prevention or treatment of dry skin in term infants.

**Authors:** Alison Cooke (AC), Suresh Victor (SV), Michael Cork (MC), Dame Tina Lavender (TL)

**Named Contact:** Alison Cooke

**Contact e-mail:** Alison.Cooke@manchester.ac.uk

**Organisational affiliation:** The University of Manchester

**Funding source/sponsors:** The lead reviewer is funded by a Doctoral Research Fellowship award from the National Institute for Health Research (DRF-2012-05-160)

**Conflicts of interests:** None

**Anticipated or actual start date:** 1st January 2013

**Stage of review:** Prospective

**Anticipated completion date:** 31st December 2013

**Review status:** Version 3, 28th June 2013
BACKGROUND

Dry skin is a common occurrence in the first few months of an infant’s life (Saijo and Tagami, 1991). Dry skin has been defined as “a cutaneous reaction pattern reflecting abnormal desquamation of diverse etiologies” (Madison, 2003 p236). In normal skin, corneocytes are shed from the skin in small enough quantities that they are not visible to the naked eye; however in dry skin the skin appearance becomes rough and flaky if this normal process is disturbed. In an infant this is a normal process of adaptation to life outside of the uterus, resulting from the change in environment from the wet surroundings of amniotic fluid in-utero, to the dry conditions of the atmosphere.

Atopic eczema (synonym atopic dermatitis) is an inflammatory skin condition characterised by dry and scaly skin, redness, blistering and itching. Allergic disease affects up to 30% of children aged 2 to 15 years in the UK (Gupta et al., 2004). Children affected with atopic eczema are also predisposed to allergic asthma and allergic rhinitis (Gustafsson et al., 2000), known as the ‘atopic march’. It is suggested that approximately 60% of sufferers develop atopic eczema in their first year of life (Bieber, 2008). Prevalence has increased to this current level from approximately 5% of children in the 1940s (Taylor et al., 1984). In that time the genetic structure of skin has not changed; however the way that we care for an infant’s skin has changed, including the increased use of soaps, other harsh detergents and oils (Danby and Cork, 2011, Cork et al., 2009).

Infant skin is physiologically different to adult skin; the stratum corneum is 30% thinner and the epidermis is 20% thinner (Stamatas et al., 2010); this difference in skin structure results in increased permeability and dryness. Infant skin is also more vulnerable to the use of topical treatments, as the ratio of infant body surface to body weight is higher than for adults (Nikolovski et al., 2008). The infant skin barrier continues to develop during the first year of life (Stamatas et al., 2011); infants are therefore more vulnerable not only at birth but throughout their first year.

Infant skin is prone to an increased rate of trans-epidermal water loss (TEWL) and reduced stratum corneum hydration due to differences from adult skin such as less lipids, melanin and natural moisturising factors (Chiou and Blume-Peytavi, 2004, Nakagawa et al., 2004). Infants may also experience a weakening of the skin
barrier due to their elevated skin surface pH. High skin surface pH (low acidity) results in increased activity of proteases which break down corneodesmosomes (supportive component of the stratum corneum) and hinders the activity of enzymes which are required for lipid processing (Cork et al., 2009, Hachem et al., 2003).

These differences between infant and adult skin in both structure and function suggest a greater vulnerability to environmental factors, including infant skincare products. The use of topical products may therefore contribute to the development of adverse skin conditions, including atopic eczema (Danby et al., 2013, Danby et al., 2011, Danby and Cork, 2011).

Parents want to use skin products to make their infant look and smell nice (Furber et al., 2012, Lavender et al., 2009). Infant skin conditions can cause parental anxiety (Adalat et al., 2007); parents will often adhere to advice given to them by health professionals with regard to care of a newborn infant (Lavender et al., 2009). Midwives and other health professionals commonly advise new parents to use olive oil to prevent or treat dry skin (Cooke et al., 2011). Skincare advice given to new parents by health professionals is likely to be based on traditional practice, personal experience and anecdotal evidence, due to a dearth of robust evidence. Importantly, the practice of using some topical oils and emollients on infant skin may contribute to the development of a wider public health issue: atopic eczema, while other oils may have a positive effect and prevent its development (Danby and Cork, 2011).

The application of oil is recommended by health professionals to new parents for use on their newborn infant’s skin (Cooke et al., 2011, Lavender et al., 2009), to prevent or treat dryness or for massage. The use of emollients is not commonly recommended, however parents have the choice of a diverse range of emollient infant skincare products from numerous manufacturers. In a recent UK national survey (Cooke et al., 2011), 52% of maternity and neonatal units recommended the use of oil; 82% of these units recommend olive oil to parents for use on their infant’s skin and 20% recommend sunflower oil. Health professionals, such as midwives and health visitors, believe these oils to be natural and therefore not harmful to infant skin (Lavender et al., 2009).
Some oils have been shown to have a positive effect on skin barrier function (Danby et al., 2013, Darmstadt et al., 2008, Darmstadt et al., 2004), compared to others that may impair this function (Danby et al., 2013, Jiang and Zhou, 2003, Darmstadt et al., 2002, Naik et al., 1995). Furthermore, this environmental factor of using topical oils and emollients may contribute to the development of childhood atopic eczema and related diseases (Cork et al., 2009). Research has shown that olive oil of certain compositions (high ratio of oleic acid to linoleic acid) may adversely affect skin barrier function in mice (Jiang and Zhou, 2003, Darmstadt et al., 2002) and adults (Danby et al., 2013, Naik et al., 1995). This composition of oil disrupts the lipid structure of the stratum corneum, and is a potential risk factor in the development or exacerbation of atopic eczema. Optimal sunflower oil (high ratio of linoleic acid to oleic acid) has been shown in the same population to promote skin barrier repair (Danby et al., 2013, Darmstadt et al., 2008, Darmstadt et al., 2004).

The use of emollients or moisturisers is common in skin care regimens. They act by preventing water loss, or actively hydrating the skin (Elson, 2011). The main reason to use emollients in skincare is to protect the integrity of the skin barrier. For healthy term infants, this is not clinically necessary; however those infants at risk (such as those with a family history of atopic eczema) may benefit from the regular use of emollients (Frieden et al., 2011).

**Why it is important to conduct this review**

Societal interest in ‘natural’ products is high (Allemann and Baumann, 2009), especially for parents of newborn infants (Cottingham and Winkler, 2007). There is a readiness amongst parents to use oil for infant skincare, and a readiness amongst maternity professionals to recommend it. There is a misconception that because a product is ‘natural’ it must be ‘safe’ (Bedwell and Lavender, 2012, Lavender et al., 2009). Oils have been used in the cosmetic, pharmaceutical and perfumery industries for many years. However, oils are governed by cosmetic guidelines for testing and research (Council of the European Communities, 1976) which are not as rigorous as those for medicines for human use (Department of Health, 2004). This means that oils have been used as medicinal and homeopathic remedies for many years without any collection and analysis of toxicological data. There may be a toxic effect on infant skin treated with topical oils; the infant skin surface area in relation to body weight is high and absorption is
relative to the surface area exposed (Rutter, 1987). Topical applications may cause irritation, damage or systemic effects through absorption of the oil into the body. There is some concern that some topical skin preparations may have carcinogenic properties (Sanchez-Prado et al., 2012, Cui et al., 2011); particularly if they contain a preservative such as Bronidox or Bronopol found in soap and gel in one study (Sanchez-Prado et al., 2012).

Infection is one of the leading causes of neonatal morbidity and mortality in low resource countries (Darmstadt et al., 2002). The vulnerability of infant skin, together with use of oils which may be harmful, combined with poor hygiene conditions, has the potential for increased hazards of infection. Nosocomial sepsis is more common in preterm infants where the stratum corneum is not fully mature (Conner et al., 2009), and skin does not have the protective benefit of vernix (Yoshio et al., 2003). There have been several studies (Kiechl-Kohlendorfer et al., 2008, Darmstadt et al., 2008, Darmstadt et al., 2005, Darmstadt et al., 2004, Edwards et al., 2004, Darmstadt and Saha, 2002), and a Cochrane systematic review (Conner et al., 2009), which have considered methods of preventing infection in preterm infants, but no systematic review of the evidence considering infection in term infants.

It is known that 45% of atopic eczema cases occur in the first six months of life, and 60% in the first year of life (Bieber, 2008). This period of time is when midwives, maternity workers and other maternity services health professionals have the most influence with parents. Health professionals may find it difficult to give evidence based advice to new parents due to the lack of a systematic review. It is important to provide a high quality basis for clinical practice and informed decision-making. Given the rise in the prevalence of atopic eczema, and the suggested link between the condition and environmental factors, it is timely to evaluate current evidence to provide the most appropriate advice for parents and health professionals. This review will assess the effects of topical oils and emollients in the prevention or treatment of infant dry skin, compared to use of alternative oils and emollients or no treatment.

A systematic review will provide:

1. An evidence base to inform parents and health professionals in their practice with healthy newborn term infants, and
2. Highlight any area that requires further investigation.

Review question

The quantitative component of this review will consider the following question:

What is the effect of using topical oils, emollients or no oil, in the prevention or treatment of dry skin in term infants?

The qualitative component of this review will consider the following question:

What are parents’ and health professionals’ experiences of using topical oils and emollients in the prevention or treatment of dry skin in their term infants?

Objectives

The objective of this review is to assess the effect of using oils and emollients for the prevention or treatment of infant dry skin.

Methods

The methods for the quantitative component of the review will be provided in Part One. The methods for the qualitative component will be provided in Part Two.
METHODS PART ONE

Criteria for considering studies for this review (quantitative)

Types of studies

The review will consider for inclusion non-randomised experimental and observational study designs including non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies.

Types of participants

Term infants (greater than or equal to 37+0 weeks of gestation and up to 28 days old) will be included.

Types of interventions

The review will consider studies that evaluate:

Intervention: Use of topical oils, emollients or no oil for dry skin

Exclusion Criteria

We will exclude newborn preterm infants (less than 37 weeks of gestation at birth).

Types of outcome measures

Primary outcomes

The primary outcome measures to be considered are as follows (as defined by study authors and measured within 28 days after birth):

1. Skin surface hydration
2. Trans-epidermal water loss (TEWL)

Secondary outcomes

The secondary outcomes to be considered will include (as defined by study authors and measured within 28 days after birth):

1. Validated skin assessment scores
2. Infection
3. Skin surface pH
4. Atopic eczema
5. Clinical observations of adverse skin conditions
6. Maternal satisfaction

Search strategy

Keywords and MeSH terms identified following a scoping search using the terms provided below, will be searched using the following three-step search strategy:

1. The databases to be searched include CINAHL, MEDLINE, EMBASE, BNI, Maternity and Infant Care and AMED. The search for unpublished studies will include the database SIGLE.

2. The reference lists of studies generated from the database search will be examined to find any further relevant studies. Pharmaceutical and cosmetic companies and prolific authors in the topic area will be contacted to access any unpublished research.

3. An electronic search of the journals British Journal of Obstetrics and Gynaecology, British Journal of Midwifery, Pediatrics, British Journal of Dermatology, and Journal of Obstetric, Gynecologic and Neonatal Nursing, for the last 3 years will take place to confirm that there are no obscure titles not found by the search terms.

Initial search terms will include:

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<tr>
<th>Population</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>oil* OR therap* OR treatment* OR oleic OR linoleic OR topical OR remed*</td>
</tr>
<tr>
<td>Comparison</td>
<td>emollient* OR cream* OR moistur* OR lubricant* OR powder*</td>
</tr>
<tr>
<td>Outcome</td>
<td>skin barrier* OR TEWL OR trans epidermal water loss OR skin hydration OR skin pH OR erythema OR rash* OR infection* OR skin assessment score* OR atopic eczema OR atopic dermatitis OR allerg* disease OR atopic march OR satisfaction OR AE OR AD OR dry skin OR xerosis OR ethnic*</td>
</tr>
</tbody>
</table>

Search using (P) AND (I OR C OR O)
(Booth et al., 2000)

There will be no restriction on start date, language or geographical location. Where research is only available as an abstract, attempts will be made to contact the study authors for the full data. If this is not successful, these studies will not be
included. Where there is no abstract but the title appears to fit the inclusion criteria, the full text will be obtained and reviewed to consider suitability for inclusion. Full text publications of all studies which fulfil the inclusion criteria will be obtained to take forward to quality assessment.

**Assessment of methodological quality**

Papers selected for further assessment will be reviewed by two review authors (AC and TL) independently for methodological validity prior to inclusion in the review. A standardised generic critical appraisal instrument suitable for all quantitative study designs and recommended by the Cochrane Collaboration (Higgins and Green, (Eds.) 2009) will be used (available from [http://www.ephpp.ca/tools.html](http://www.ephpp.ca/tools.html)). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (SV/MC).

**Data collection**

Data will be extracted from papers included in the review by two review authors (AC and TL) independently using a standardised data extraction tool from the Cochrane Collaboration (Cochrane Collaboration (HIV Review Group), 2013) which will be adapted by the review team. The form will be piloted to ensure consistency between authors. Any discrepancies will be resolved through discussion or, if necessary, will be discussed with a third author (SV/MC). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. We will attempt to contact study authors to provide further details if any of the information is missing or unclear.

**Data synthesis**

Where papers are appropriately similar with regard to participants, interventions and outcomes, where possible the data will be pooled in statistical meta-analysis. All results will be subject to double data entry. Effect sizes expressed as summary risk ratios (for dichotomous data) and mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also explored using subgroup analyses based on the different quantitative study designs included in this review. Where statistical pooling is not possible the findings will be presented
in narrative form including tables and figures to aid in data presentation where appropriate.
METHODS PART TWO

Criteria for considering studies for this review (qualitative)

Types of studies
The review will consider for inclusion studies that focus on qualitative data including, but not limited to, designs underpinned by phenomenology, grounded theory, ethnography, action research and feminist research. Mixed methods studies that include a qualitative element with sufficient data will also be considered.

Types of participants
The qualitative component of this review will consider studies that include:

1. Parents of term infants (greater than or equal to 37+0 weeks of gestation and up to 28 days old)
2. Health professionals caring for women and their term infants (greater than or equal to 37+0 weeks of gestation and up to 28 days old) in the postnatal period

Phenomena of Interest
This review will consider studies that explore parents’ and health professionals’ experiences of using topical oils and emollients on infants in the first 28 days after birth for the prevention or treatment of infant dry skin.

Exclusion Criteria
We will exclude parents of newborn preterm infants (less than 37 weeks of gestation at birth), and health professionals caring for a preterm infant population.

Search Strategy
Keywords and MeSH terms identified following a scoping search using the terms provided below, will be searched using the following three-step search strategy:

1. The databases to be searched include CINAHL, MEDLINE, EMBASE, BNI, Maternity and Infant Care and AMED. The search for unpublished studies will include the database SIGLE.
2. The reference lists of studies generated from database search to find any further relevant studies will be examined. Pharmaceutical and cosmetic companies and prolific authors in the topic area will be contacted to access any unpublished research.

3. An electronic search of the journals British Journal of Obstetrics and Gynaecology, British Journal of Midwifery, Pediatrics, British Journal of Dermatology, and Journal of Obstetric, Gynecologic and Neonatal Nursing, for the last 3 years will take place to confirm that there are no obscure titles not found by the search terms.

Initial search terms will include:

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<tr>
<th>Sample</th>
<th>infant* OR bab* OR neonat* OR newborn* OR term</th>
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<tr>
<td>Phenomenon of Interest</td>
<td>oil* OR emollient* OR oleic OR linoleic OR atopic eczema OR atopic dermatitis OR dry skin OR xerosis OR AE OR AD OR skin barrier OR TEWL OR trans epidermal water loss OR skin surface pH OR skin hydration OR maternal satisfaction OR infection* OR erythema OR rash* OR ethnic*</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>(Cooke et al., 2012)</td>
<td></td>
</tr>
</tbody>
</table>

There will be no restriction on start date, language or geographical location. Where research is only available as an abstract, attempts will be made to contact the study authors for the full data. If this is not successful, these studies will not be included. Where there is no abstract but the title appears to fit the inclusion criteria, the full text will be obtained and reviewed to consider suitability for inclusion.

**Assessment of methodological quality**

Papers selected for retrieval will be assessed by two independent reviewers (AC and TL) for methodological validity prior to inclusion in the review using the critical appraisal instrument developed by Walsh and Downe (2006), and the Grading System developed by Downe et al. (2009) based on the work by Lincoln and Guba.
(1985). The data extracted will include specific details about the phenomenon of interest, populations, study methods and methodology, significant to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (SV/MC). We will attempt to contact study authors to provide further details if any of the information is missing or unclear.

**Data analysis**

Qualitative research findings will be synthesised using the line of argument synthesis process of meta-ethnography (Noblit and Hare, 1988). This will involve the synthesis of findings to generate a new interpretation of the whole of the data that remains true to the individual studies. This will be conducted through assembling the findings (Level 1 findings), and categorising these findings on the basis of similarity in meaning (Level 2 findings). These categories will then be subjected to a meta-synthesis in order to produce a new interpretation (Level 3 findings) that can be used as a basis for evidence-based practice. Where a new interpretation is not possible the findings will be aggregated in narrative form.

**SYNTHESIS OF QUANTITATIVE AND QUALITATIVE DATA**

The findings from the quantitative and qualitative parts of the review will be synthesised narratively. Relationships in the data will be explored to provide an understanding of the effects of using topical oils and emollients in infant skincare and what the views and experiences of parents and health professionals are with regard to current skincare practice.

The framework used for this narrative synthesis will be structured using the guidance provided by Rodgers et al. (2006). By taking this structured approach, conclusions can be drawn from the data in a transparent way.
References


Contacts approached to confirm any unpublished research

Authors
Gary Darmstadt
Georgios Stamatas
Carolyn Lund
Natalie Garcia Bartels
Eric Simpson

Pharmaceutical Companies
Johnson & Johnson
Pfizer UK
Roche
GlaxoSmithKline
Novartis
Sanofi Aventis
Astra Zeneca
Abbott Laboratories
Merck
Bayer
Eli Lilly
Bristol-Myers Squibb
Proctor & Gamble UK
Boehringer
Astellas Pharma Ltd

Cosmetic Companies
Unilever
L’Oreal UK Ltd
Proctor & Gamble
Shiseido
Estee Lauder
Avon
Beiersdorf
Johnson & Johnson
Alberto-Culver
Kao Corporation
Gentle Beauty
### Appendix 5: Search Strategy Results

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<td>(epiderm$ adj barrier adj function).ti,ab</td>
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Total of search: 14,469 (inclusive of duplicates across databases)

Searches run 10\textsuperscript{th} April 2013 and updated 21\textsuperscript{st} January 2015

BNI = British Nursing Index
M&IC = Maternity and Infant Care
Appendix 6

Critical Appraisal Skills Programme

CASP Tool for appraising randomised controlled trials
11 questions to help you make sense of a trial

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a randomised controlled trial:

- Are the results of the trial valid? (Section A)
- What are the results? (Section B)
- Will the results help locally? (Section C)

The 11 questions on the following pages are designed to help you think about these issues systematically.

The first two questions are screening questions and can be answered quickly. If the answer to both is yes, it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a yes, no or can’t tell to most of the questions. A number of prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

There will not be time in the small groups to answer them all in detail!

These checklists were designed to be used as educational tools as part of a workshop

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(A) Are the results of the trial valid?

Screening Questions

1. Did the trial address a clearly focused issue?  
   - Yes  
   - Can’t tell  
   - No

Consider: An issue can be ‘focused’ in terms of:
- The population studied
- The intervention given
- The comparator given
- The outcomes considered

---

2. Was the assignment of patients to treatments randomised?  
   - Yes  
   - Can’t tell  
   - No

Consider:
- How was this carried out, some methods may produce broken allocation concealment
- Was the allocation concealed from researchers?

---

Is it worth continuing?
Detailed questions

3. Were patients, health workers and study personnel blinded?

Consider:
• Health workers could be; clinicians, nurses etc
• Study personnel – especially outcome assessors

4. Were the groups similar at the start of the trial?

Consider: Look at
• Other factors that might affect the outcome such as age, sex, social class, these may be called baseline characteristics

5. Aside from the experimental intervention, were the groups treated equally?
6. Were all of the patients who entered the trial properly accounted for at its conclusion?

Consider:
- Was the trial stopped early?
- Were patients analysed in the groups to which they were randomised?

(B) What are the results?

7. How large was the treatment effect?

Consider:
- What outcomes were measured?
- Is the primary outcome clearly specified?
- What results were found for each outcome?
- Is there evidence of selective reporting of outcomes?

8. How precise was the estimate of the treatment effect?

Consider:
- What are the confidence limits?
- Were they statistically significant?
(C) Will the results help locally?

9. Can the results be applied in your context?  
(or to the local population?)

Consider:

- Do you have reason to believe that your population of interest is different to that in the trial
- If so, in what way?

10. Were all clinically important outcomes considered?

Consider:

- Is there other information you would like to have seen?
- Was the need for this trial clearly described?

11. Are the benefits worth the harms and costs?

Consider:

- Even if this is not addressed by the trial, what do you think?
Appendix 7

Effective Public Health Practice Project

Tool for critical appraisal of multiple study designs
Component Ratings

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1. Very likely
2. Somewhat likely
3. Not likely
4. Can’t tell

(Q2) What percentage of selected individuals agreed to participate?

1. 80 - 100% agreement
2. 60 – 79% agreement
3. less than 60% agreement
4. Not applicable
5. Can’t tell

<table>
<thead>
<tr>
<th>RATE THIS SECTION</th>
<th>STRONG</th>
<th>MODERATE</th>
<th>WEAK</th>
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<tr>
<td>See dictionary</td>
<td>1</td>
<td>2</td>
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B) STUDY DESIGN

Indicate the study design

1. Randomized controlled trial
2. Controlled clinical trial
3. Cohort analytic (two group pre + post)
4. Case-control
5. Cohort (one group pre + post (before and after))
6. Interrupted time series
7. Other specify ______________________________________________________________________
8. Can’t tell

Was the study described as randomized? If NO, go to Component C.

No
Yes

If Yes, was the method of randomization described? (See dictionary)

No
Yes

If Yes, was the method appropriate? (See dictionary)

No
Yes

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<tbody>
<tr>
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</table>
C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?
1 Yes
2 No
3 Can’t tell

The following are examples of confounders:
1 Race
2 Sex
3 Marital status/family
4 Age
5 SES (income or class)
6 Education
7 Health status
8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?
1 80 – 100% (most)
2 60 – 79% (some)
3 Less than 60% (few or none)
4 Can’t Tell

RATE THIS SECTION
STRONG   MODERATE   WEAK
See dictionary
1 2 3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?
1 Yes
2 No
3 Can’t tell

(Q2) Were the study participants aware of the research question?
1 Yes
2 No
3 Can’t tell

RATE THIS SECTION
STRONG   MODERATE   WEAK
See dictionary
1 2 3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?
1 Yes
2 No
3 Can’t tell

(Q2) Were data collection tools shown to be reliable?
1 Yes
2 No
3 Can’t tell

RATE THIS SECTION
STRONG   MODERATE   WEAK
See dictionary
1 2 3
F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?
   1. Yes
   2. No
   3. Can’t tell
   4. Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).
   1. 80 -100%
   2. 60 - 79%
   3. less than 60%
   4. Can’t tell
   5. Not Applicable (i.e. Retrospective case-control)

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See dictionary

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?
   1. 80 -100%
   2. 60 - 79%
   3. less than 60%
   4. Can’t tell

(Q2) Was the consistency of the intervention measured?
   1. Yes
   2. No
   3. Can’t tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?
   4. Yes
   5. No
   6. Can’t tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)
   - community
   - organization/institution
   - practice/office
   - individual

(Q2) Indicate the unit of analysis (circle one)
   - community
   - organization/institution
   - practice/office
   - individual

(Q3) Are the statistical methods appropriate for the study design?
   1. Yes
   2. No
   3. Can’t tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?
   1. Yes
   2. No
   3. Can’t tell
GLOBAL RATING

COMPONENT RATINGS
Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

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GLOBAL RATING FOR THIS PAPER (circle one):

1 STRONG (no WEAK ratings)
2 MODERATE (one WEAK rating)
3 WEAK (two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1 Oversight
2 Differences in interpretation of criteria
3 Differences in interpretation of study

Final decision of both reviewers (circle one):

1 STRONG
2 MODERATE
3 WEAK
### QUANTITATIVE STUDIES (literature search April 2013)

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<tr>
<th>Author/date/country</th>
<th>Aims and objectives</th>
<th>Design</th>
<th>Participants</th>
<th>Setting</th>
<th>Sampling strategy and sample size</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Overall conclusion</th>
<th>Notes</th>
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<tr>
<td>Ahmed et al. (2007) Bangladesh</td>
<td>To gain insights into oil massage practices and acceptability of skin barrier-enhancing emollients in young, preterm neonates</td>
<td>Survey within RCT</td>
<td>PRETERM newborn (&lt;72 hours old) infants &lt;33 weeks gestation</td>
<td>Dhaka Shishu Hospital</td>
<td>Newborn infants admitted to special care nursery between Dec 1998 and Jul 2003 (n=497)</td>
<td>Daily massage with sunflower seed oil (n=159) or Aquaphor (n=157) or no treatment (control; n=181))</td>
<td>Skin scores (Lund et al. 2001) TEWL</td>
<td>Topical therapy with sunflower seed oil or Aquaphor was seen as superior to mustard oil by many families</td>
<td><em>same sample/study as paper 11, 12 &amp; 13</em></td>
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<tr>
<td>Brandon et al. (2010) USA</td>
<td>To evaluate the effects of No-Sting skin protectant and Aquaphor, a water-based emollient, on skin integrity and TEWL in premature infants</td>
<td>RCT</td>
<td>PRETERM newborn (&lt;48 hours old) infants &lt;33 weeks gestation</td>
<td>Duke University Hospital, North Carolina and Brenner Children’s Hospital, North Carolina</td>
<td>Newborn infants admitted over 18 month period to neonatal intensive care nurseries (n=69)</td>
<td>No-Sting protectant (one application within 48hrs of birth and one at 7 days) or Aquaphor twice daily for 2 weeks</td>
<td>TEWL</td>
<td>No-Sting protectant seems as effective as Aquaphor in decreasing TEWL and maintaining skin integrity</td>
<td>Compliance not reported</td>
</tr>
<tr>
<td>Danby et al. (2011) UK</td>
<td>To investigate the effect of aqueous cream BP on stratum corneum integrity and skin barrier function</td>
<td>Forearm controlled mechanistic study</td>
<td>ADULT volunteers with a predisposition to a defective skin barrier or with history of atopic dermatitis</td>
<td>Academic Unit of Dermatology Research</td>
<td>Volunteer study: predisposition to defective skin barrier (n=13), history atopic dermatitis (n=13)</td>
<td>Aqueous cream BP applied twice daily to volar side of one forearm for 4 weeks, other forearm untreated control. Those with history of atopic dermatitis untreated</td>
<td>Stratum corneum integrity and cohesion Intercornocyte cohesion Moisturisation Skin surface pH Erythema</td>
<td>Aqueous cream BP used as a leave-on emollient caused severe damage to the skin barrier in those with history of atopic dermatitis</td>
<td>Compliance measured by treatment diary but not reported</td>
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<tr>
<td>Danby et al. (2013) UK</td>
<td>To ascertain the effect of olive oil and sunflower seed oil on the biophysical properties of the skin</td>
<td>Two randomised forearm controlled mechanistic studies</td>
<td>ADULT volunteers with and without history of atopic dermatitis</td>
<td>Academic Unit of Dermatology Research</td>
<td>Volunteer study (n=19)</td>
<td>Cohort 1: six drops of olive oil to one forearm twice daily for 4 weeks, other forearm untreated control. Cohort 2: six drops of olive oil to one forearm and six drops of sunflower seed oil to the other twice daily for 4 weeks</td>
<td>TEWL post tape-stripping Transmission electron microscopy (TEM) Fatty acid profile measurements</td>
<td>Sunflower seed oil preserved integrity and improved hydration. Olive oil significantly damaged the skin barrier. The use of olive oil for treatment of infant dry skin and massage should be discouraged</td>
<td>Compliance not reported</td>
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<tr>
<td>Darmstadt et al. (2002) USA</td>
<td>To identify inexpensive, safe, vegetable oils available in developing countries that improved epidermal barrier function</td>
<td>Murine Mechanistic Study</td>
<td>MURINE study: barrier compromised male hairless mice, 6-8 weeks old</td>
<td>N/A</td>
<td>Not known</td>
<td>Single application of sunflower seed oil, olive oil, or soybean oil versus control (Aquaphor). Mustard oil tested separately with twice daily applications for 7 days</td>
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</table>

### Notes
- Compliance not reported
- Compliance measured by treatment diary but not reported
- Compliance not reported
- Considers rate of recovery of skin barrier, rather than damage by oils to skin barrier

### Risk of Bias
- High
- Moderate
- Moderate
- Moderate
- Unclear
### Appendix 8: Table of Study Characteristics

<table>
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<tr>
<td>Aims and objectives</td>
<td>To determine whether sunflower seed oil would improve skin condition and reduce the incidence of invasive bacterial infections in preterm infants</td>
<td>To ascertain whether topical application of emollients to enhance skin barrier function would prevent nosocomial infections</td>
<td>To ascertain whether topical application of emollients to enhance skin barrier function would improve survival rates</td>
<td>To ascertain whether topical application of emollients to enhance skin barrier function would prevent bacterial translocation</td>
<td>To determine whether prophylactic application of an emollient ointment would result in lower incidence of mortality and nosocomial sepsis</td>
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<tr>
<td>Design</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
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<td>Participants</td>
<td>PRETERM newborn (&lt;72 hours old) infants &lt;34 weeks gestation</td>
<td>PRETERM newborn (&lt;72 hours old) infants &lt;33 weeks gestation</td>
<td>PRETERM newborn (&lt;72 hours old) infants &lt;33 weeks gestation</td>
<td>PRETERM newborn (&lt;72 hours old) infants &lt;33 weeks gestation</td>
<td>PRETERM newborn (&lt;48 hours old) infants &lt;30 weeks gestation</td>
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<td>Setting</td>
<td>Kasr El-Aini neonatal intensive care unit, Cairo University</td>
<td>Dhaka Shishu Hospital</td>
<td>Dhaka Shishu Hospital</td>
<td>Dhaka Shishu Hospital</td>
<td>53 Neonatal Intensive Care Units in the Vermont Oxford Network</td>
</tr>
<tr>
<td>Sampling strategy and sample size</td>
<td>All infants admitted to unit (dates not declared) (n=103)</td>
<td>Newborn infants admitted to special care nursery between Dec 1998 and July 2003 (n=497)</td>
<td>Newborn infants admitted to special care nursery between Dec 1998 and July 2003 (n=497)</td>
<td>Newborn infants admitted to special care nursery between Dec 1998 and July 2003 (n=497)</td>
<td>Newborn infants admitted to Neonatal Intensive Care Units between Aug 1998 and March 2000 (n=1191)</td>
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<td>Intervention</td>
<td>Sunflower seed oil applied 3 times daily for 14 days then twice daily until 28 days or minimal to no use of emollients</td>
<td>Daily massage with sunflower seed oil (n=159) or Aquaphor (n=157) or no treatment (control; n=181)</td>
<td>Daily massage with sunflower seed oil (n=159) or Aquaphor (n=157) or no treatment (control; n=181)</td>
<td>Daily massage with sunflower seed oil (n=159) or Aquaphor (n=157) or no treatment (control; n=181)</td>
<td>Generalized application of ointment twice daily to day 14 or local application of ointment to site of injury (routine care)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Blood cultures</td>
<td>Nosocomial infections</td>
<td>Mortality</td>
<td>Skin scores (Lane &amp; Drost, 1993) Blood cultures</td>
<td>Mortality Nosocomial sepsis</td>
</tr>
<tr>
<td>Overall conclusion</td>
<td>Topical sunflower seed oil improved skin condition and reduced nosocomial infections</td>
<td>Sunflower seed oil provides protection against nosocomial infections in preterm very low birthweight infants</td>
<td>Topical therapy with skin barrier-enhancing emollients improved survival rates among preterm hospitalised infants</td>
<td>Topical therapy with sunflower seed oil reduced the passage of pathogens from the skin surface into the bloodstream of preterm infants</td>
<td>Prophylactic application of ointment did not lead to a difference in mortality or nosocomial sepsis in the first 28 days of life</td>
</tr>
<tr>
<td>Notes</td>
<td>ITT analysis Compliance high <em>same sample/study as paper 1, 12 &amp; 13</em></td>
<td>ITT analysis Compliance high <em>same sample/study as paper 1, 11 &amp; 13</em></td>
<td>ITT analysis Compliance high <em>same sample/study as paper 1, 11 &amp; 12</em></td>
<td>ITT analysis Compliance high <em>same sample/study as paper 1, 11 &amp; 12</em></td>
<td>ITT analysis Some non-compliance due to misunderstanding of protocol Infants in intervention group had better skin condition at day 14 but this was not an outcome</td>
</tr>
<tr>
<td>Risk of Bias</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
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</table>

*ITT* analysis refers to Intention-to-Treat analysis.
## Appendix 8: Table of Study Characteristics

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</thead>
<tbody>
<tr>
<td><strong>Aims and objectives</strong></td>
<td>To compare microbiologically the efficacy of olive oil use and keeping the umbilical stump dry</td>
<td>To compare the influence of three skin care regimens to bathing with water</td>
<td>To investigate the cutaneous effects of two different topical ointment therapies</td>
<td>To evaluate the effect of moisturizer therapy on neonates’ skin and skin bacterial colonization</td>
<td>To assess safety and compliance with daily application of a formula commencing in the neonatal period for the prevention of eczema</td>
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<tr>
<td><strong>Design</strong></td>
<td>Matched pair experimental study</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
<td>Non-controlled open label study</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td><strong>TERM</strong> newborn infants</td>
<td><strong>TERM</strong> (&gt;37 weeks gestation) newborn (&lt;48 hours old) infants</td>
<td><strong>PRETERM</strong> newborn (&lt;24 hours old) infants 25-36 weeks gestation</td>
<td><strong>PRETERM</strong> newborn (&lt;24 hours old) infants 29-36 weeks gestation</td>
<td>?TERM newborn infants (0-4 weeks of age) with family history of eczema</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>University hospital in Ankara, Turkey</td>
<td>Charité-Universitäts-medizin, Berlin and Clinic Dahme-Spreewald</td>
<td>Innsbrook Medical University</td>
<td>Neonatal Intensive Care Unit</td>
<td>Royal Women’s Hospital and the Royal Children’s Hospital, Melbourne</td>
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<td><strong>Sampling strategy and sample size</strong></td>
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<td>Newborn infants between Oct 2006 and May 2007 (n=64)</td>
<td>Newborn infants admitted to neonatal intensive care unit between Oct 2004 and Nov 2006 (n=173)</td>
<td>Strategy not declared (n=34)</td>
<td>Newborn infants between March and June 2010 (n=10)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>5 drops of olive oil was applied to the umbilical cords of neonates in the intervention group twice daily from immediately after birth until 2 days after separation of the cord</td>
<td>Four arms receiving twice weekly from day 7 to week 8 of life: 1) wash gel; 2) water and cream; 3) wash gel and cream; 4) water alone</td>
<td>Twice daily topical treatment for 4 weeks with water in oil cream (Bepanthen), olive oil cream or control group</td>
<td>Water-in-oil emollient cream twice daily for 16 days to no treatment</td>
<td>All infants applied EpiCeram to the full skin surface once daily, excluding hands and face, after bathing or at a regular time each day</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Skin cultures, Time for separation of cord, TEWL, Stratum corneum hydration, Skin pH, Sebum, Skin condition (Lund et al 2001) Microbiologic colonization</td>
<td>Skin scores (modified Lane &amp; Drost 1993)</td>
<td>TEWL (n=8), Skin scores, Fungal and bacterial cultures</td>
<td>Patient compliance, Adverse events, Clinical observations, TEWL, Skin pH, Skin hydration</td>
<td></td>
</tr>
<tr>
<td><strong>Overall conclusion</strong></td>
<td>Olive oil can be used in the umbilical cord care of neonates under appropriate conditions</td>
<td>Skin care regimens did not harm physiologic neonatal skin barrier adaptation within the first 8 weeks of life</td>
<td>Topical skin therapy lowers the risk of dermatitis. Olive oil cream was superior to water-in-oil emollient cream</td>
<td>Emollient cream moisturizer therapy of premature infants decreases dermatitis without changing the microbiological flora</td>
<td>Preliminary results support the safety and parental compliance with daily application of EpiCeram for the prevention of eczema</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Compliance not reported</td>
<td>Unclear if power calculation</td>
<td>44 participants unaccounted for in loss to follow up Compliance not reported</td>
<td>Unclear if power calculation</td>
<td>No control group</td>
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<td><strong>Risk of Bias</strong></td>
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## Appendix 8: Table of Study Characteristics

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<tbody>
<tr>
<td>Aims and objectives</td>
<td>To ascertain the effect of oleic acid, in vivo, in man</td>
<td>To demonstrate the efficacy of a colloidal oatmeal, skin protectant lotion in improving skin condition</td>
<td>To investigate the cutaneous and systemic effects of preservative free topical ointment therapy in premature infants</td>
<td>To determine the effects of repeated application of an occlusive ointment on the skin of very low birthweight infants</td>
<td>To investigate the penetration behaviour of four vegetable oils and of paraffin oil into the stratum corneum.</td>
</tr>
<tr>
<td>Design</td>
<td>Forearm controlled mechanistic study</td>
<td>Randomized, investigator-led study</td>
<td>RCT</td>
<td>RCT</td>
<td>Mechanistic study</td>
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<tr>
<td>Participants</td>
<td>ADULTS healthy, aged 25-50 years</td>
<td>ADULTS with moderate itch and severely dry skin, aged 18-55 years</td>
<td>PRETERM infants &lt; 33 weeks gestation &lt;96 hours old</td>
<td>PRETERM infants 26-30 weeks gestation, &lt;24 hours old</td>
<td>ADULT healthy volunteers, 25-50 years old (3 male/3 female)</td>
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<tr>
<td>Setting</td>
<td>Not declared</td>
<td>Not declared</td>
<td>Neonatal Intensive Care Unit</td>
<td>University of Maryland Medical Center</td>
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<td>Sampling strategy and sample size</td>
<td>Strategy not declared (n=8)</td>
<td>Strategy not declared (n=30)</td>
<td>Strategy not declared (n=60)</td>
<td>Strategy not declared (n=19)</td>
<td>Volunteer study (n=6)</td>
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<tr>
<td>Intervention</td>
<td>Solution of perdeuterated oleic acid in ethanol applied to inner ventral forearm, other arm treated with ethanol only (control)</td>
<td>Lotion applied twice daily for 7 days followed by 2 day regression period during which no lotion used</td>
<td>Topical Aquaphor twice daily for 2 weeks or no treatment (no treatment group included as-needed water-in-oil emollient)</td>
<td>Topical Aquaphor ointment twice daily for 2 weeks or to receive standard care</td>
<td>Jojoba oil, soybean oil, avocado oil, paraffin oil, almond oil and petroleum (control) were applied to the volar forearm in pre-marked areas</td>
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<tr>
<td>Outcomes</td>
<td>ATR spectroscopy</td>
<td>Clinical evaluations Skin moisturization Improvement in itching TEWL</td>
<td>TEWL Skin scores (Lane &amp; Drost 1993) Bacterial skin cultures Fluid requirements Patterns of weight gain/loss Blood cultures</td>
<td>Skin scores (Lane &amp; Drost 1993) Fluid requirements Skin bacterial colonization counts</td>
<td>Laser scanning microscopy TEWL</td>
</tr>
<tr>
<td>Overall conclusion</td>
<td>Oleic acid-induced skin penetration enhancement results from a mechanism involving both stratum corneum fluidization and phase separation.</td>
<td>Lotion demonstrated the quick efficacy in providing relief to patients with itchy, extra dry skin by providing moisturization, relieving itching, and improving the skin barrier</td>
<td>Aquaphor ointment decreased TEWL, decreased severity of dermatitis, decreased bacterial colonization of the skin, and incurred fewer positive cultures for microorganisms for preterms</td>
<td>Aquaphor ointment, used during first two weeks of life, improved skin condition in infants of 26-30 weeks gestation without changing skin bacterial flora</td>
<td>Oils only penetrated into the first upper layers of the stratum corneum. Decreased TEWL values indicate that the application of oils leads to a semi-occlusion of the skin surface, retaining moisture</td>
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<tr>
<td>Notes</td>
<td>Abstract only Not clear if there was a control group even though states randomized</td>
<td>Unclear if power calculation</td>
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<tbody>
<tr>
<td>Aims and objectives</td>
<td>To ascertain the waterproofing effect of a paraffin mixture (80% soft, 20% hard paraffin BP)</td>
<td>To investigate changes in normal skin after a 28 day application of Aqueous Cream BP</td>
<td>To evaluate the feasibility of optimizing skin barrier function from birth with daily full body emollient therapy to prevent onset of atopic dermatitis</td>
<td>To determine the feasibility of skin barrier protection as a novel atopic dermatitis prevention strategy</td>
<td>To study the transcutaneous absorption of traditionally massaged oil in newborns</td>
</tr>
<tr>
<td>Design</td>
<td>Observational</td>
<td>Mechanistic study</td>
<td>RCT</td>
<td>Mechanistic pilot study</td>
<td>RCT</td>
</tr>
<tr>
<td>Participants</td>
<td>PRETERM infants 26-30 weeks gestation, aged 1-4 days, nursed in incubators</td>
<td>ADULT healthy volunteers, females aged 23-29 years</td>
<td>TERM newborn infants to 6 months of age</td>
<td>TERM (&gt;37 weeks gestation) newborn infants at high risk of developing atopic dermatitis &lt;7 days old</td>
<td>TERM subset (&gt;37 weeks gestation) newborn infants &lt;3 days old</td>
</tr>
<tr>
<td>Setting</td>
<td>Not declared</td>
<td>Not declared</td>
<td>Multicentre: four centres in the UK and one in USA</td>
<td>Oregon Health and Science University, Portland</td>
<td>Tertiary care neonatal intensive care unit of a large teaching hospital</td>
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<tr>
<td>Sampling strategy and sample size</td>
<td>Strategy not declared (n=3-5)</td>
<td>Volunteer study (n=6)</td>
<td>Strategy not declared (n=124)</td>
<td>Pregnant mothers from November 2006 to November 2008 (n=22)</td>
<td>Strategy not declared (n=120)</td>
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<tr>
<td>Intervention</td>
<td>Paraffin generously applied to front of thigh of 26 week gestation infant, and to abdomen of 32 week gestation infant. Applied to most of infant’s skin (n=3) 26-30 week gestation</td>
<td>2ml Aqueous cream BP applied to the left and right mid volar forearm for 10 minutes twice daily for 28 days</td>
<td>Intervention group could choose between an ointment, cream, or sunflower oil (majority chose cream; 67.2%). Control group asked not to use routine emollients</td>
<td>All infants to apply Cetaphil cream once daily or more often to all body surfaces except diaper area and scalp. To be used immediately (within 3 minutes) after bathing</td>
<td>5ml of either safflower oil; coconut oil or no oil massaged 4 times daily for 5 days</td>
</tr>
<tr>
<td>Outcomes</td>
<td>TEWL</td>
<td>TEWL</td>
<td>Skin examination Skin barrier function</td>
<td>Incidence of skin related adverse events Incidence of atopic dermatitis Mean age at onset of dermatitis Compliance</td>
<td>Fatty acid profiles</td>
</tr>
<tr>
<td>Overall conclusion</td>
<td>Topical application of paraffin offers reduction in water loss and heat loss from the skin in preterm infants</td>
<td>The routine prescription of this preparation as a moisturizer in patients with atopic dermatitis is questioned.</td>
<td>While no significant differences were found between groups, a trend toward improved barrier function was seen in the emollient group. Emollient therapy from birth appears to be a safe and feasible approach for atopic dermatitis prevention</td>
<td>Skin barrier repair from birth represents a novel and feasible approach to atopic dermatitis prevention</td>
<td>Topically applied oil can be absorbed in neonates and is probably available for nutritional purposes</td>
</tr>
<tr>
<td>Notes</td>
<td>Not clear whether first 2 infants tested were also 2 of the 3 later infants tested or if total sample was 5.</td>
<td>No control group</td>
<td>Abstract only Author contacted for further information</td>
<td>No control group</td>
<td>Publication reports data for skin rashes, erythema and dermatitis was collected however these were not listed as outcomes. Author contacted for clarity</td>
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<tr>
<td>Risk of Bias</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
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<tbody>
<tr>
<td><strong>Aims and objectives</strong></td>
<td>Unclear</td>
<td>To assess the neurodevelopmental and biological effects of the simultaneous use of multimodal stimulation and the cutaneous application of vegetable oils</td>
<td>To investigate the effect of olive oil application to the skin flora colonization during the first two weeks of life in very low birthweight infants</td>
<td>To investigate the effects of oleic acid on the ultrastructure of stratum corneum lipids in rat skin</td>
<td>To produce baseline data which would inform decisions for the main trial design to investigate whether bathing with a specific cleansing product is superior to bathing with water alone</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>?non-randomised experimental study</td>
<td>RCT</td>
<td>RCT</td>
<td>Murine Mechanistic Study</td>
<td>Pilot RCT</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>?TERM newborns age and gestation unclear, with family history of atopic dermatitis</td>
<td>PRETERM infants 31-34 weeks gestation</td>
<td>Very low birthweight PRETERM infants</td>
<td>MURINE study: Hairless Wistar rats weighing 250-300g</td>
<td>TERM newborn infants &lt;24 hours old</td>
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<tr>
<td><strong>Setting</strong></td>
<td>Unclear</td>
<td>Tertiary referral centre, Poitou-Charentes region</td>
<td>Not declared</td>
<td>N/A</td>
<td>Teaching hospital in North West England</td>
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<tr>
<td><strong>Sampling strategy and sample size</strong></td>
<td>Strategy not declared (n=20)</td>
<td>Newborn infants admitted to Neonatal Intensive Care Unit between Sept 2002 and Dec 2004 (n=49)</td>
<td>Strategy not declared (n=35)</td>
<td>Not known</td>
<td>Newborn term infants born at the hospital between November 2008 and November 2009 (n=100)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Intervention group to use moisturizer (Locobase Repair) after bathing</td>
<td>Sensori-Tonico-Motor touch for 10 days with either sweet almond oil, ISI04 blended oil, placebo (normal saline), or no treatment (control)</td>
<td>Daily skin application of olive oil or routine skin care for first 2 weeks of life</td>
<td>Topical treatment with 10% oleic acid/propylene glycol for 2 hours</td>
<td>Infants bathed in water only (n=51) or with the baby wash product (n=49) approx. 3 times per week for 8 weeks</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>TEWL, Skin surface pH, Number of colonized S. aureus</td>
<td>Weight gain, Linear growth, Neurological maturation, Psychomotor development, Number of days of admission</td>
<td>Mortality, Nosocomial infections, Microflora</td>
<td>Structure of skin barrier, Epidermal barrier function, TEWL, Stratum corneum hydration, Skin surface pH, Clinical observations</td>
<td></td>
</tr>
<tr>
<td><strong>Overall conclusion</strong></td>
<td>Early intervention with moisturizer seemed to have an anti-bacterial effect. No other significant differences between the two groups</td>
<td>The combination of STM and cutaneous application of oils to healthy preterm babies resulted in enhanced weight gain and neurological development, and a shorter stay in hospital</td>
<td>Olive oil to the skin seems to be well tolerated by the premature infants and may act as a prebiotic in very low birthweight infants</td>
<td>Oleic acid might increase epidermal permeability through a mechanism involving the perturbation of stratum corneum bilayers and lacunae formation to enhance transdermal drug delivery</td>
<td>The decision to proceed with a superiority trial was inconsistent with the data, therefore a non-inferiority trial was recommended</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Abstract only</td>
<td>ITT analysis Improved moisturisation (p=0.001) and quicker recovery of dermatological conditions reported but not outcomes</td>
<td>Abstract only</td>
<td></td>
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<tr>
<td><strong>Risk of Bias</strong></td>
<td>Unclear</td>
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<tbody>
<tr>
<td><strong>Aims and objectives</strong></td>
<td>To examine the hypothesis that the use of a wash product formulated for newborn (&lt;1 month of age) bathing is not inferior to bathing with water alone</td>
<td>To examine the hypothesis that the use of a specially formulated cleansing wipe on the napkin area of newborn infants has an equivalent effect on skin hydration when compared with cotton wool and water</td>
<td>To explore the complexities of diaper area cleansing reported by women participating in an RCT to compare a baby wipe with cotton wool and water</td>
<td>To obtain baseline data on skin functional parameters about the influence of cleansing with baby wipes compared to cleansing with water</td>
<td>To compare the effects of two standard cleansing procedures on skin barrier function in newborns</td>
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<tr>
<td><strong>Design</strong></td>
<td>RCT</td>
<td>RCT</td>
<td>Mixed methods study (questionnaire and diaries)</td>
<td>Pilot RCT</td>
<td>RCT</td>
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<tr>
<td><strong>Participants</strong></td>
<td>TERM infants (&gt;37 weeks of gestation, &lt;48 hours old)</td>
<td>TERM infants (&gt;37 weeks of gestation, &lt;48 hours old)</td>
<td>TERM infants (&gt;37 weeks of gestation, &lt;48 hours old)</td>
<td>TERM infants (&gt;37 weeks of gestation, &lt;48 hours old)</td>
<td>TERM infants (&gt;37 weeks of gestation, &lt;48 hours old)</td>
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<tr>
<td><strong>Setting</strong></td>
<td>Teaching hospital in North West England</td>
<td>Large teaching hospital in North West England</td>
<td>Large teaching hospital in North West England</td>
<td>Charité-Universitäts-medizin, Berlin</td>
<td>Charité-Universitäts-medizin, Berlin</td>
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<tr>
<td><strong>Sampling strategy and sample size</strong></td>
<td>Healthy newborn infants born between February 2010 and March 2011 (n=307)</td>
<td>Healthy newborn infants born between February 2010 and October 2010 (n=280)</td>
<td>Healthy newborn infants born between February 2010 and October 2010 (n=280)</td>
<td>Healthy newborn infants born between May 2007 and October 2007 (n=44)</td>
<td>Healthy newborn infants born between October 2005 and April 2006 (n=57)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Bathing with wash product (Johnsons Baby Top-to-Toe Bath) (n=159) versus bathing in water alone (n=148), at least 3 times per week for 4 weeks</td>
<td>Cleansing with an alcohol free baby wipe (Johnsons Baby Skincare Fragrance Free Wipe) (n=140) or cotton wool and water (n=140) for 8 weeks</td>
<td>Cleansing with an alcohol free baby wipe (Johnsons Baby Skincare Fragrance Free Wipe) (n=140) or cotton wool and water (n=140) for 8 weeks</td>
<td>Cleansing with wipe (n=21) or water-moistened washcloth (n=23) for 4 weeks</td>
<td>Both groups used wet cotton washcloth and water twice weekly until day 7, then washing group continued with this care (n=28), and bathing group changed to bathing with water only (n=29) until 28 days</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>TEWL, Skin surface pH, Stratum corneum hydration, Clinical observations (Lund et al. 2001)</td>
<td>Skin surface hydration, Erythema, TEWL, Skin surface pH</td>
<td>Maternal views</td>
<td>TEWL, Skin hydration, Skin pH, IL-1α, Epidermal desquamation</td>
<td>TEWL, Skin pH, Skin hydration, Sebum, Skin condition (Lund et al. 2001)</td>
</tr>
<tr>
<td><strong>Overall conclusion</strong></td>
<td>No difference found between wash product and water alone. This provides reassurance to parents who choose to use the test wash product or other technically equivalent cleansers</td>
<td>Baby wipes had an equivalent effect on skin hydration when compared with cotton wool and water. These findings offer reassurance to parents who choose to use baby wipes</td>
<td>Women are faced with a complex environment regarding diaper area cleansing and need clear evidence-based guidance on effective diaper area cleansing</td>
<td>Neither of the two cleansing procedures harms skin barrier maturation within the first 4 weeks postpartum</td>
<td>Neither of the two skin care regimens harm the adaptation of the skin barrier in healthy neonates within the first 4 weeks of life</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Assessor blinded, non-inferiority trial, ITT analysis</td>
<td>Same study sample as 47</td>
<td>Same study sample as 46</td>
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<td><strong>Risk of Bias</strong></td>
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<td>Low</td>
<td>Moderate</td>
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<tbody>
<tr>
<td><strong>Aims and objectives</strong></td>
<td>To test the hypothesis that baby diaper wipes with emollient cleansers and a soft cloth would minimize skin compromise relative to cloth and water</td>
<td>To investigate the tolerance and mildness of a cleansing routine using a mild baby wash as compared to water only cleansing</td>
<td>To gain insights into the epidemiology, practice and perceptions regarding traditional oil massage of Bangladeshi infants</td>
<td>To explore traditional neonatal beliefs and care practices in low socioeconomic settlements</td>
<td>To explore home-based newborn care practices from the time of birth through the first 2 weeks of life</td>
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<tr>
<td><strong>Design</strong></td>
<td>RCT</td>
<td>Unclear</td>
<td>Questionnaire study</td>
<td>Mixed methods study (questionnaire, interviews and focus groups)</td>
<td>Large questionnaire study</td>
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<tr>
<td><strong>Participants</strong></td>
<td>TERM newborn infants &gt;38 weeks of gestation</td>
<td>?TERM infants (1 day old to 11.5 months old)</td>
<td>Primary caretaker</td>
<td>Mothers of recently delivered infants</td>
<td>Mothers of newborn infants</td>
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<tr>
<td><strong>Setting</strong></td>
<td>Regional Center for Newborn Care, Cincinnati Children's Hospital Medical Center</td>
<td>Not declared</td>
<td>Dhaka Shishu Hospital and Matlab Health Complex</td>
<td>Low socioeconomic settlements of Karachi</td>
<td>Sariahi District</td>
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<tr>
<td><strong>Sampling strategy and sample size</strong></td>
<td>Newborn infants born between November 2006 and January 2008 (n=33 term infants)</td>
<td>Strategy not declared (n=60)</td>
<td>Primary caretaker of patients who presented over a four week period (n=342)</td>
<td>Mothers between July and November 2000 (n=525)</td>
<td>Mothers of newborn infants between August 2002 and January 2006 (n=23,356)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Wipe A (Pampers Sensitive Wipes) with a product pH of 5.2, wipe B (Pampers Sensitive Wipes) with a product pH of 4.0, and control (4-ply rayon/polyester fabric and water), approx. 8 times daily, for 14 days</td>
<td>Twice daily for 14 days</td>
<td>Verbal questionnaire focussed on oil massage of their most recent liveborn child</td>
<td>Questionnaire (n=525), semi-structured interviews (n=15) and 5 focus group discussions</td>
<td>Questionnaire at day 1 and day 14 to assess essential newborn care practices</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>TEWL Rash/erythema Skin pH Skin condition</td>
<td>Clinical observations Skin hydration TEWL Skin pH Oxy-hemoglobin/deoxy-hemoglobin Parental views</td>
<td>Massage practice Total duration of oil massage therapy Type of oil used</td>
<td>Feeding practices Bathing practices Massage practices Cord care</td>
<td>Feeding practices Hygiene and skincare practices Thermal practices</td>
</tr>
<tr>
<td><strong>Overall conclusion</strong></td>
<td>Both wipes were appropriate to use on infants and provide more normalized skin condition and barrier function versus the cloth and water standard</td>
<td>Daily cleansing with a mild baby wash was clinically well-tolerated for babies as young as 1 day old. Health professionals have the opportunity to recommend cleansing practices beyond water alone</td>
<td>Oil massage is an important traditional domiciliary practice in Bangladesh. Given its potential for beneficial and harmful effects, further research is needed on the value of this practice</td>
<td>Predominance of risky traditional newborn care practices (such as massage with mustard oil) stresses the need for promoting health education programs on improving newborn care practices</td>
<td>Many of the commonly practiced behaviours are detrimental to the health and survival of newborns.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Compliance not reported</td>
<td>Abstract only</td>
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<tr>
<td><strong>Risk of Bias</strong></td>
<td>Unclear</td>
<td>High</td>
<td>Moderate</td>
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<tr>
<td><strong>Author/date/country</strong></td>
<td>Furber et al. (2012)</td>
<td>UK</td>
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<tr>
<td><strong>Topic area and aims</strong></td>
<td>To explore the complexities of diaper area cleansing for women</td>
<td>To gain insight into current practices and beliefs related to newborn bathing and assess the feasibility of conducting an RCT of wash product vs. water alone</td>
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<tr>
<td><strong>Theoretical perspective</strong></td>
<td>Unclear</td>
<td>Interpretive framework (Parahoo, 1997)</td>
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<tr>
<td><strong>Design</strong></td>
<td>Mixed methods study (qualitative component included diaries and structured interviews)</td>
<td>Interview study</td>
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<tr>
<td><strong>Setting and context</strong></td>
<td>Large regional maternity hospital, North West England</td>
<td>Large teaching hospital, North West England</td>
</tr>
<tr>
<td><strong>Sampling strategy and sample size</strong></td>
<td>Women who participated in a randomised controlled trial of cleansing wipes vs. water and cotton wool (n=280)</td>
<td>Purposive sampling (n=56) Midwives (n=20), Health Visitors (n=10), women in antenatal and immediate postnatal period (n=26)</td>
</tr>
<tr>
<td><strong>Other participant characteristics</strong></td>
<td>Mean age 29 years. 56% white women, 20% Asian, 18% Black.</td>
<td>Median age 34 years. White British (n=21), Pakistani (n=1), Black British African (n=1), White other (n=1), Mixed White/Asian (n=1), Chinese (n=1)</td>
</tr>
<tr>
<td><strong>Data collection methods</strong></td>
<td>Diaries (n=224) Structured Interviews (at 4 weeks n=252, at 8 weeks n=237)</td>
<td>In depth interviews, broad topic areas, lasting 20-90 minutes Some longitudinal (n=22) Field notes taken</td>
</tr>
<tr>
<td><strong>Analytic approach</strong></td>
<td>Thematic analysis (Braun &amp; Clarke, 2006)</td>
<td>Thematic analysis (Miles &amp; Huberman, 1994)</td>
</tr>
<tr>
<td><strong>Quality rating</strong></td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

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Appendix 8: Table of Study Characteristics

| Studies published since original review in 2013 (literature search January 2015) |
|----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Aims and objectives** | To investigate the effect of sunflower seed oil on skin barrier development in low birthweight premature infants | To investigate the effects of topical ointment therapy on neonatal sepsis in premature infants | To evaluate if topical therapy with sunflower seed oil can improve skin barrier and protect from infection in preterm infants | To investigate whether daily application of moisturizer to neonates at high risk for atopic eczema prevents the development of atopic eczema/allergic sensitization | To test whether skin barrier enhancement from birth represents a feasible strategy for reducing the incidence of atopic eczema in high-risk neonates | To assess the effects of two different skin care practices on healthy skin barrier function maturation |
| **Design** | RCT | RCT | RCT | RCT | RCT | RCT |
| **Participants** | PRETERM infants <37 weeks gestation, <48 hrs old, 1500-2500g weight | PRETERM infants <34 weeks gestation, <24 hours old | PRETERM infants <34 weeks gestation, <72 hours old | TERM newborns at high risk for atopic dermatitis | TERM (>37 weeks) newborns at high risk for atopic dermatitis | TERM (?) healthy newborns <10 days old |
| **Setting** | Charité Universitätsmedizin Berlin, Germany | Neonatology Clinic of Tepecik Training and Research Hospital, Izmir, Turkey | Children’s Hospital of Fudan University, Shanghai, China | National Center for Child Health and Development, Tokyo, Japan | UK: Nottingham University Hospital, Derby Hospital, United Lincolnshire Hospital, USA: Oregon Health & Science University Hospital/Clinics | Department of Obstetrics and Gynecology, S. Orsola-Malpighi Hospital (University of Bologna) |
| **Sampling strategy and sample size** | Newborn preterm infants born between November 2009 and December 2010 (n=22) | Newborn preterm infants born between September 2010 and September 2012 (n=197) | Newborn preterm infants born between September 2010 and June 2012 (n=428) | Newborn infants born between November 2010 and November 2013 (n=118) | Newborn infants born between May 2010 and May 2011 (n=124) | Newborn infants born between October 2012 and December 2012 (n=94) |
| **Intervention** | Application of sunflower seed oil on the whole body surface every 3-4 hours during the first 10 days of life, followed by subsequent cessation of treatment until study end, versus no treatment | Application of topical ointment (Aquaphor™) to the whole body for 14 days versus no treatment. Both groups had broad-spectrum antibiotic therapy after baseline blood cultures | Application of sunflower seed oil (n=153) or Johnson oil (n=140) for 14 days versus no treatment (n=135) | Daily application of 2e Douhet emulsion from the first week of life until 32 weeks of age versus no treatment. Both groups were also prescribed petroleum jelly | Intervention group: parental choice from an oil, a cream/gel or an ointment applied over the whole body surface from within 3 weeks of life to 6 months of age versus no treatment | Washing with liquid baby cleanser and hydrated with almond oil once a day, versus no treatment |
| **Outcomes** | TEWL Skin hydration Skin pH Sebum Neonatal Skin Condition Score (NSCS) Microbiological colonization | Sepsis Skin condition Rate of diagnosed infections | Incidence of atopic eczema Allergen-specific IgE TEWL Skin hydration Skin pH Skin colonization by Staphylococcus aureus | Feasibility of atopic eczema prevention approach Trial processes/parameters Incidence of atopic eczema at 6 months old | TEWL |
| **Overall conclusion** | Sunflower seed oil application may retard postnatal skin barrier maturation in preterm infants | Applying topical ointment did not affect the risk of neonatal sepsis in preterm infants | Topical oil can improve skin condition of preterm infants without increasing infection. Sunflower seed oil is much better than Johnson oil | Daily application of moisturizer during the first 32 weeks of life reduces the risk of atopic dermatitis in infants | The results demonstrate that emollient therapy from birth represents a feasible, safe, and effective approach for atopic dermatitis prevention | Skincare regimens could influence the process of functional adaptation of the skin |
| **Notes** | Unclear randomization method, blinding, no CONSORT flow diagram | Unclear recruitment rate, blinding, no CONSORT flow diagram | Abstract only | Unclear randomization method 83.9% completion (n=99) | Pilot study, not powered 87% completion (n=108) | Cleanser only used in the intervention group: cannot assess impact of oil alone |
| **Risk of Bias** | High | High | Unclear | Moderate | Moderate | High |
### Criteria for appraising qualitative research studies

<table>
<thead>
<tr>
<th>Stages</th>
<th>Essential Criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and Purpose</td>
<td>Clear statement of, and rationale for, research questions/aims/purposes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study thoroughly contextualised by existing literature</td>
<td></td>
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<tr>
<td>Design</td>
<td>Method/design apparent, and consistent with research intent</td>
<td></td>
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<tr>
<td></td>
<td>Data collection strategy apparent and appropriate</td>
<td></td>
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<tr>
<td>Sampling Strategy</td>
<td>Sample and sampling method appropriate</td>
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</tr>
<tr>
<td>Analysis</td>
<td>Analytic approach appropriate</td>
<td></td>
</tr>
<tr>
<td>Interpretation</td>
<td>Context described and taken account of in interpretation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clear audit trail given</td>
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<td></td>
<td>Data used to support interpretation</td>
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<tr>
<td>Reflexivity</td>
<td>Researcher reflexivity demonstrated</td>
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<tr>
<td>Ethical Dimensions</td>
<td>Demonstration of sensitivity to ethical concerns</td>
<td></td>
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<tr>
<td>Relevance and Transferability</td>
<td>Relevance and transferability evident</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 10

**GRADING SYSTEM**
created by Downe et al (1) based on the work by Lincoln & Guba (2)

<table>
<thead>
<tr>
<th>A</th>
<th>No, or few flaws. The study credibility, transferability, dependability and confirmability is high.</th>
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</thead>
<tbody>
<tr>
<td>B</td>
<td>Some flaws, unlikely to affect the credibility, transferability, dependability and/or confirmability of the study.</td>
</tr>
<tr>
<td>C</td>
<td>Some flaws that may affect the credibility, transferability, dependability and/or confirmability of the study.</td>
</tr>
<tr>
<td>D</td>
<td>Significant flaws that are very likely to affect the credibility, transferability, dependability and/or confirmability of the study.</td>
</tr>
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</table>

Reference


Appendix 11

Publication:

Infant massage: The practice and evidence-base to support it

Abstract

Parents across the globe have been massaging their babies for centuries. The popularity of infant massage in Western countries is a relatively recent phenomenon; the trend has probably developed due to the perceived health benefits. In some Eastern cultures, the practice of infant massage is passed on from one generation to the next. In Western cultures, it is more likely that new parents will attend a local baby massage class with an instructor. Whichever form the practice takes, it is important to know that there is no potential for harm to the baby. This article will consider the perceived benefits of infant massage, how to massage, the role of the health professional and whether we should be concerned about what products, if any, should be used for infant massage.

Keywords: Massage, Oil, Evidence, Skin care, Dermatology

The practice of infant massage is not a new phenomenon. It is a part of nature—at birth, mammals massage their newborns by licking and grooming them to encourage their body systems to normalise (Ishikawa and Shiga, 2012). In humans, midwives ‘massage’ newborns through drying to stimulate a response to take their first breath.

Early records of massage practice and research are diverse. It has been documented as early as 2760BC in China (Mitzel-Wilkinson, 2000). In Asia, infant massage is a long-established mothering tradition, passed down from generation to generation (Porter, 1996). Influenced by Florence Nightingale, massage training was provided by nurses and physicians for many health-related conditions during the 1880s and into the 1900s (Ruffin, 2011).

In a series of experiments with monkeys, Harlow (1958) found tactile stimulation in mother–infant interaction improved confidence and secure emotional behaviour. In the 1930s, research studies suggested that massage therapy could increase blood circulation and reduce muscle atrophy (Field et al, 2007).

More recent research has further suggested that the practice of infant massage provides benefits for both mother and baby. The popularity and demand for infant massage resulted in the establishment of the International Association of Infant Massage (IAIM) in 1986, whose membership spans more than 40 countries (McClure, 2001).

Infant skin

Human skin is the largest organ of the body and protects its internal components (bones, muscles, ligaments, blood vessels and internal organs) from injury (Lewis-Jones, 2012). The skin has three layers: the epidermis; the dermis; and the hypodermis. The epidermis is the first point of contact for the application of topical products. The stratum corneum is the outermost layer of the epidermis (the visible part of the skin). Its main function is to act as a barrier to penetration by external irritants and to protect against excessive water loss. Skin barrier function can be affected by genetic and environmental factors. Examples of the latter include water quality, pollution, detergents and the application of skin care products.

At term birth, the skin is sufficiently mature to withstand extrauterine life; however, infant skin does not become comparable to that of an adult until approximately 12 months of age (Stamatas et al, 2010). During this time, infant skin is more vulnerable than adult skin because it is different in several ways. For example, the stratum corneum of neonates is 30% thinner in neonates and the epidermis is 20% thinner (Stamatas et al, 2010). This puts infants at a greater risk of permeability and dryness than adults. In addition, the neonatal body surface to body weight ratio is greater than in adults, and infant skin has a greater absorption rate than that of adults. The consequence of this difference is an increased vulnerability to the effects of topical treatments (Nikolovski et al, 2008).

Dry skin is common in the first few months of a baby’s life (Saijo and Tagami, 1991). The recommendation to new parents to use topical oils for the prevention or treatment of neonatal dry skin has become traditional practice (Walker et al, 2005; Cooke et al, 2011). While there is a dearth of evidence to support the practice of recommending topical application of natural oils, there is a readiness to believe that what is ‘natural’ is also ‘safe’ (Lavender et al, 2009; Bedwell and Lavender, 2012).

Maternal and neonatal benefits

Maternal benefits

Some research studies have considered infant massage as an intervention to improve the mother–infant relationship and maternal mental health.
Infant massage positively affected the mood state of mothers in one randomised study \(n=39\) (Fujita et al, 2006).

Attendance at an infant massage class was found to provide a means of postnatal peer support, reducing isolation in a mixed methods study \(n=156\) (Clarke et al, 2002). In Clarke’s study, the quantitative data were not significant for all outcomes but the qualitative data supported this conclusion.

Infant massage has been shown to improve mother–infant interaction for mothers with postnatal depression in a randomised study \(n=34\) (Onozawa et al, 2001). However, the authors acknowledged that, due to the small sample size, it could not be determined which aspect of the massage class contributed to the improvement.

Infant massage was shown to be an effective method of improving attachment in a quasi-experimental non-randomised study \(n=117\) (Gürol and Polat, 2012). In this study, the attending doctor made the decision about the allocation of mothers to the intervention or control group; therefore, allocation bias may exist, which would affect the credibility of the findings.

Underdown et al (2013) conducted a realist evaluation to assess which parent–infant dyads would benefit most from an infant massage programme. The study found that only dyads at moderate risk (one to two risk factors above normal) would benefit, rather than those at low or high risk. The authors suggested that these parents should be targeted and that further research in the form of randomised controlled trials (RCTs) was required to assess the intervention with a targeted sample in a robust way.

A selection of studies investigating the maternal benefits of infant massage have been presented as examples but, overall, there is very little research to support the suggested benefits. The majority of research is methodologically weak. Further research is required to establish the genuine benefits for parents who perform infant massage.

Term infant benefits

A Cochrane systematic review of infant massage incorporated 34 studies totalling 3984 healthy term babies aged up to 6 months (Bennett et al, 2013). More than half of the studies \(n=20\) were rated as being at a high risk of bias with regard to their design and conduct. The studies included addressed outcomes of physical health and mental health and development. Physical health outcomes included weight, growth, sleep duration, crying/distress times, blood bilirubin levels and illness episode frequency. Mental health and development outcomes included motor skills, personal and social behaviour and psychomotor development. The findings of the review and associated meta-analyses do not support the use of infant massage in the low-risk population of parent and term infant dyads. The authors acknowledged that the reason for this conclusion may have been the poor methodological quality of 20 of the studies, and the lack of attention to the biological plausibility of the outcomes being measured. The review considered only papers looking at the benefits for the term baby; studies on benefits for mothers and preterm babies were excluded. The review authors concluded that future research should concentrate on higher-risk population samples, such as those in the study by Underdown et al (2013).

Preterm infant benefits

Weight gain is the most consistent outcome associated with preterm infant massage (Scafidi et al, 1990; Mathai et al, 2001; Sankaranarayanan et al, 2005; Field et al, 2010; Kulkarni et al, 2010). One explanation put forward for this weight gain is the separate finding that significantly lower levels of energy and stress behaviour were expended among preterm babies in the intervention groups (Lahat et al, 2007), which meant that they were able to ‘sleep and grow’ (Lampl and Johnson, 2011). Another explanation is that infant skin has a high rate of absorption (Nikolovski et al, 2008), so topical oil may have been absorbed systemically to provide a nutritional function (Fernandez et al, 1987; Solanki et al, 2005). The most important finding from preterm infant massage studies is the significant reduction in mortality and infection (Darmstadt et al, 2005; Darmstadt et al, 2008; Mendes and Procianoy, 2013).
2008). Darmstadt’s research demonstrated a 26% reduction in mortality (Darmstadt et al, 2008), and that preterm babies were 49% less likely to develop a nosocomial infection when massaged with sunflower seed oil compared to no treatment (Darmstadt et al, 2005). Reduction in infection in a preterm population is related to reduction in mortality.

How to massage an infant

There are no standardised guidelines describing a routine method for performing infant massage. Field (2002) suggests massage in 15 minute sessions, three times a day. Each block of 15 minutes consists of 5 minutes of tactile stimulation, followed by 5 minutes of kinaesthetic stimulation, followed by 5 minutes of tactile stimulation. Parents and health professionals can provide the massage equally effectively (Ferber et al, 2002). Massage should not be carried out within an hour of feeding, to minimise the risk of vomiting. The whole body should be included in the massage technique and a moderate pressure is recommended for optimal effect (Field, 2002).

Mathai et al (2001) suggests a slightly different technique where sessions start with two phases of tactile stimulation, before a final phase of kinaesthetic stimulation. The first phase includes placing the baby in a prone position and providing 12 strokes of 5 seconds, each administered from the head through the neck and shoulder to the buttock. The second phase includes placing the baby in a supine position and providing 12 strokes of 5 seconds each administered from the face, through the cheeks, chest, abdomen, upper limb, lower limb, palms then down to the soles of the feet. These two phases are followed by a third phase of kinaesthetic stimulation providing flexion and extension of the major joints.

Using a lubricant during infant massage is recommended to avoid friction (Kulkarni et al, 2010). Many natural oils have been documented as topical applications routinely used in infant massage including mustard oil (Darmstadt and Saha, 2002; Mullany et al, 2005), sunflower oil (Ahmed et al, 2007), coconut oil (Sankaranarayanan et al, 2009), olive oil (Cooke et al, 2011) and sesame oil (Agarwal et al, 2000). However, topical oils may induce an allergic response (Solanki et al, 2005; Kulkarni et al, 2010) in the recipient and/or the provider. There have been documented case studies of allergic contact dermatitis on the hands of workers using olive oil (Malmkvist et al, 1990; Kränke et al, 1997; Isaksson and Bruze, 1999; Wong and King, 2004). No studies have looked at the long-term effects of using oils on baby skin, but the question has arisen as to whether early use of topical oils with babies has a connection with the development of atopic eczema (Danby et al, 2013).

Role of the health professional

There is no national or international guidance on what constitutes best practice with regard to infant massage. There are no recognised standards nor official regulation of infant massage instructors. The IAIM advises not to use any oil topically with a high oleic acid content, such as olive oil (Bond, 2015). The IAIM statement is followed by the abstract of one small randomised study of adult volunteers (n=19) (Danby et al, 2013), which reflects on the association between the use of topical oil and the development of atopic eczema caused by the effect on skin barrier function. The study relates the findings to the potential implications for infant skin care.

Health professionals have a duty to protect the public from harm (Nursing and Midwifery Council, 2015). They should therefore recommend only treatments and practices that are beneficial. The evidence-base for infant massage is methodologically limited, and the recommendation arising from a large systematic review (Bennett et al, 2013) is that further research is required to investigate exactly what the benefits are.

Massage lubricants

Many instructors will advise parents to use a topical oil on their baby’s skin during massage (Cooke et al, 2011; Bond, 2015). Acceptability of massage with oil was considered in a randomised study in Bangladesh (Ahmed et al, 2007). The study found that the majority of participants started infant massage within 1 hour of birth (61%) with mustard oil (88%), which was applied all over the body (89%). Babies who were admitted to hospital were randomised to sunflower oil or Aquaphor ointment application. Parents perceived that these were superior to mustard oil and suggested they would use these products in preference to mustard oil in their massage practice in future. This demonstrates that health professionals may hold a certain level of influence over parental practices. The reasons given by parents for using topical oil included keeping the baby warm (22%), preventing infection (18%), improving the skin condition (6%) and improving the overall health of the baby (8%).

A previous study showed that 96% of caregivers had practised infant oil massage (Darmstadt and Saha, 2002). Although a popular practice, particularly in Eastern countries, there is a dearth of research considering the effect of topical oils.
on infant skin. Despite the lack of evidence, midwives in the UK commonly recommend topical oils for the prevention or treatment of infant dry skin or for infant massage, namely olive oil (80%) and sunflower oil (20%) (Cooke et al, 2011). Several functional mechanistic studies have been carried out in mice and adult volunteers, which suggest that oils with a high oleic acid content may be harmful to skin barrier function and be connected to the development of atopic eczema, while oils with a high linoleic acid content may have a repairing effect on skin barrier function (Darmstadt et al, 2002; Danby et al, 2013).

The OBSeRvE (Oil in Baby SkincaRE) pilot study (Cooke et al, 2013), which is currently in progress, is intended to establish evidence of the effects of topical olive oil and sunflower oil on term infant skin barrier function and to assess the feasibility of conducting a definitive RCT; results are expected soon.

Results will be of interest, particularly in view of the recent small study of preterm babies (n=22) (Kanti et al, 2014), which found that sunflower oil may impede skin barrier development, a finding that is contrary to the current evidence-base. Caution is required so that previous research (Darmstadt et al, 2008), which found that using topical sunflower oil on the skin of preterm babies resulted in a significant reduction in infection and mortality, is not ignored. Kanti’s study did not include mortality or infection as an outcome. Sunflower oil possibly has an antimicrobial effect on preterm skin, which produced the significant results. The effect of topical sunflower oil on the different outcome measures of skin barrier function and mortality/infection have produced diverse findings; this warrants further investigation.

The combination of the lack of clinical trial evidence and the negative mechanistic data from the mouse and adult studies means that recommendation of topical oils should be made with caution. In view of our desire as midwives not to cause harm to babies, a recommendation to avoid the use of topical oils should be considered until evidence is available to support this practice.

Conclusions

Newborn infant massage is becoming more popular. Midwives and other maternity health professionals require a sound evidence-base to provide the best advice to new parents about their newborn baby’s skin care. For infant massage, the majority of the available evidence is methodologically limited and further robust research is required.

There are no clinical guidelines and there is no regulation of practice. This is of concern, particularly in view of research that suggests some topical oils may have an adverse effect on skin barrier function, possibly contributing to the development of atopic eczema.

Further robust research, preferably in the form of RCTs, will provide midwives and other maternity health professionals with a sound knowledge of the benefits of infant massage to both mothers and infants, and the optimal choice of massage lubricant to ensure that recommendations and practices benefit infant skin.

Conflict of interest: this article has been sponsored by Johnson & Johnson Consumer Companies, Inc. Johnson & Johnson did not contribute to its content in any way.

Funding: this article is independent research funded from a doctoral research fellowship award (DRF–2012–05–160) supported by the National Institute for Health Research. The views expressed here are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Bennett C, Underdown A, Barlow J (2013) Massage for promoting mental and physical health in typically developing infants under the age of six months. Cochrane Database Syst Rev 4: CD009938
Newborn infant massage is a global practice. The existing evidence base is methodologically limited; it is therefore difficult to draw conclusions to inform clinical practice. Health professionals need to be cautious about recommending topical oils for infant massage until more is known about their effects on newborn and baby skin. Further research is recommended, preferably in the form of randomised controlled trials, to provide a comprehensive evidence-base to inform clinical guidelines and practice.

Key points

- Newborn infant massage is a global practice.
- The existing evidence base is methodologically limited; it is therefore difficult to draw conclusions to inform clinical practice.
- Health professionals need to be cautious about recommending topical oils for infant massage until more is known about their effects on newborn and baby skin.
- Further research is recommended, preferably in the form of randomised controlled trials, to provide a comprehensive evidence-base to inform clinical guidelines and practice.


practices. *Evid Based Midwifery* 7(4): 112–21


Appendix 12

Summary Participant Information Leaflet given to pregnant women in the antenatal period at approximately 28 weeks gestation
Will anyone know I’m doing this?

Only the people that need to know you are in the study will be told, which includes your midwife and GP, if you are happy with that. All of the information we collect about you or your baby will be handled in confidence.

Where can I find out more?

More detailed information about the study is in the Participant’s Information Sheet, which you will be given after birth, or sent to you before birth if you complete the form overleaf. You might also want to talk to your Midwife or ring the Trial Office (number overleaf) if you have any questions.

Thank you for reading this
The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

If you are interested in further information about the study, please provide the following details to allow us to contact you after birth.

I am happy for Alison Cooke, the lead researcher, to contact me in the hospital following the birth of my baby to give me further information about taking part in the OBSeRvE Trial.

Name

Address

Phone

Due Date of your baby _______________________________________________

Signature

Date of signing_____________________________________

What is the OBSeRvE trial?

This is a summary of a research study called OBSeRvE which we would like to invite you to take part in. It is up to you to decide if you want to take part or not. Before you decide whether to take part, you need to understand why the research is being done and what it would involve for you and your baby.

Why are you inviting me?

You have been invited to join because you will shortly become a mother.

What is the study about?

The use of oils in baby skincare to prevent or treat dry skin is common. We want to find out what effect this has on baby’s skin.

What will happen if I take part?

We will allocate babies to one of the treatment groups and ask mums like yourself to use a different approach to caring for your baby’s skin for 28 days. The groups will be using olive oil, sunflower oil or no oil. The group your baby is allocated to will be chosen by chance using a random sequence organised by computer. We will look at your baby’s skin once in hospital before you go home, and once when the baby is 28 days old. We will also ask you to complete a short questionnaire at each visit.

What tests will we do?

None of the tests will hurt your baby. They involve placing a small probe on your baby’s skin (a little like a small microphone), or looking at your baby’s skin.

Will there be any other tests?

Apart from the questionnaire we would like to ask some of you to take part in a short interview lasting 30-60 minutes. This will be to find out what your thoughts were about having a baby in a research study.

Are there any risks?

We do not anticipate any problems, but whichever group your baby is allocated to, we will monitor your baby’s skin.

What happens when the study ends?

After the end of the treatment period (28 days) you will be free to use whatever skincare products you choose on your baby.

What happens to the results?

We will present the results in a professional journal and at conferences. Individual results will not be available but you will be able to have a copy of the study results if you would like.

The OBSeRvE Study has been approved by Greater Manchester East Research Ethics Committee Reference Number 13/NW/0512.
The OBSeRvE Study: The use of Oil in Baby Skincare pilot study: A pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

Research Team: Alison Cooke, Suresh Victor, Michael Cork, Tina Lavender

Participant Information Sheet for Mothers and Babies
(Version 5, 23/01/14)

You and your baby are being invited to take part in a research study being conducted as part of a Ph.D. degree. Before you decide whether to take part we would like you to understand why we are doing this research and what taking part would involve. Please take time to read this leaflet, and, if you wish to, discuss it with your doctor, midwives, family or friends. Please feel free to ask us if anything is not clear, or if you would like more information. Thank you for taking the time to read this.

Summary of the Study

Many health professionals recommend the use of olive oil or sunflower oil to prevent or treat dry skin in babies. Others advise parents not to use any oil on their baby’s skin. There has been no research to consider which approach has any immediate or long-term effect on the way your baby’s skin functions, and the advice given to parents may therefore be conflicting. At present we do not know if any oil is better or worse for a baby’s skin than no oil.

We are conducting a research study to find out whether olive oil, sunflower oil or no oil is best for a baby’s skin. We will do this by allocating babies taking part in the study randomly to each of three groups to use olive oil, sunflower oil or no oil for 28 days, and then assessing their skin to see if the oil causes any changes. The skin assessments that we will do will not harm your baby. We will carry out the assessments twice; once before you leave the hospital and then again after 28 days. You and your baby’s participation in this study will help us to find out which skincare treatment (olive oil, sunflower oil or no oil) may be better, and may help to guide future advice for newborn skincare.

If this summary has interested you and you are considering taking part with your baby, please read the following information before making any decision.

What are we trying to find out?

Newborn babies are likely to have dry skin at some point. Many health professionals recommend the use of oils to prevent or treat baby dry skin. Others advise parents not to use any oil. There has been no research to consider which approach is best, and the advice given to parents can be conflicting. At present we do not know if any oil is better or worse for a baby’s skin than no oil. We are conducting a research study to find out whether olive oil, sunflower oil or no oil is best for a baby’s skin by comparing these three approaches.
Why have I been invited?
You have been invited because your baby is likely to be, or has been, born after 37 weeks of pregnancy.

Do I have to take part?
No. It is entirely your choice. When you have had your baby we will come and describe the study to you and go through this information sheet with you in person. You will then be given time to think about taking part and ask any questions before making a decision. You are free to withdraw at any time, without giving a reason and without your decision affecting the standard of care you receive, now or in the future.

What will happen to me if I take part?
If you agree to join the study you will be asked to sign a consent form on behalf of your baby, and you will be given a copy of this information sheet and the consent form to keep. Your baby will be included in what is known as a randomised trial. This means that a computer will decide at random whether you should apply olive oil, sunflower oil or no oil on your baby’s skin for 28 days. The results from the three treatment groups will be compared with each other to see if one treatment is better for baby skin than another. We will check your baby’s skin before you leave the hospital and once more after 28 days, at the Maternal and Fetal Health Research Centre on the 5th Floor of St. Mary’s Hospital.

We will ask you to complete two short questionnaires. You may also be asked to take part in a short interview about your experiences of taking part in the study lasting 30-60 minutes, at a time and place of your choice. You will be interviewed by the principle researcher Alison Cooke, who is a Registered Midwife. There are no right or wrong answers we just want to try and understand your experiences.

How do I apply the oil?
If you are asked to apply olive oil or sunflower oil, you will be provided with sufficient oil to last for 28 days. You will use 4 drops of the oil on each of your baby’s left forearm, left thigh and abdomen, twice a day until 10 hours prior to the final assessment (28 days). We ask that you loosely wrap your baby in a blanket for 15 minutes following each application, before dressing. You will be given full instructions and a demonstration by a Research Midwife. We will provide a diagram for you to take home so that it is clear where to put the oil on your baby.

What if I am asked not to apply any oil?
You will be advised not to use any oil on your baby’s skin for 28 days. After that time you can choose to use oil if you wish.

Can I use other baby skincare products?
Whichever group you are allocated to, you will be given full guidance. You are asked not to use any other oils, creams, sponges, flannels, wipes or powders on the treated areas (left arm, left leg and abdomen) during the 28 day period. At the end of the study you are free to cleanse and moisturise your baby using whichever products you prefer. If you are worried about your baby’s skin during the 28 day treatment period you should contact Alison Cooke, the Principle Researcher, named at the end of this document.

Can I change my mind?
Yes. If you wish to stop using the oil provided, or start using oil, please let us know. However, we would still be interested in knowing your baby’s progress, and with your permission, will keep in touch with you. Any information collected up to the time you advise us you wish to stop will be anonymised and included in our findings, unless you advise us not to.
What will the skin checks involve?
We will check your baby’s skin in two different ways: 1) skin surface measurements; 2) questionnaires.

1. Skin surface measurements
We will first look at your baby’s skin. The Principle Researcher, Alison Cooke, will carry out 5 measurements on the left forearm, left thigh and upper abdomen. We will carry out the same measurements on babies in the no oil treatment group. None of the assessments hurt your baby. They will involve touching a probe to the top of your baby’s skin (see pictures on right). The first measurement uses a technique called infrared spectroscopy; this is a tool that can be used to take a type of ‘picture’ of your baby’s skin. This can show up changes in the skin before they are visible to the naked eye. Prior to the measurement, the skin is prepared by the application of a D-Squame disc three times to remove the very top skin cells which are already dead and being shed from the skin. The D-Squame disc is about the size of a £1 coin, less sticky than sellotape and much less sticky than the adhesive on a nappy flap. These discs will be tested to look at the levels of natural moisturising factor in the top layer of skin. This may help us to find markers in the skin that indicate possible future development of skin conditions. The second measurement will assess how well the skin works as a barrier (Trans-Epidermal Water Loss (TEWL) test). The third will assess skin surface hydration (degree of dryness). The fourth will measure the skin surface pH; how acid or alkaline the skin surface is, and the final measurement will establish how well the skin is. You can stay with your baby throughout the tests, which should take no more than 60 minutes to complete.

2. Questionnaires
It is important for us to find out what you think about the group your baby was allocated to, what you think about the trial, the tests and how you felt about the assessments. We will therefore ask you to complete two questionnaires; one before you leave hospital and one when you return for the second assessment when your baby is 28 days old. We will also telephone you once a week during the 28 day period, to see how you are doing and whether you have any concerns. With your consent you may be asked to take part in a short interview to find out more about your views, which can take place in a setting of your choice.

What happens to the information we collect?
Any identifiable data such as name and address will be removed to protect you and your baby’s anonymity. If you agree to take part in an interview, this will be recorded with your consent. The recording will be transcribed, written down word for word, so that Alison Cooke, the principle researcher, and the research team can analyse what people have said. Once the recordings have been transcribed, the recordings will be destroyed.

What if there is a problem?
We do not anticipate any problems. However, regardless of the group your baby is allocated to, we will monitor your baby’s skin regularly and should problems arise we will refer you to an appropriate doctor.

What are the possible benefits of taking part?
There are no direct benefits for you or your baby for taking part in this study. However by taking part in this research you and your baby will help to provide information that will inform the design of a larger trial comparing different skincare routines which may help to
guide future clinical practice. You will be reimbursed for any out of pocket expenses (up to £25.00, with valid receipts). On completion of the clinical assessments, questionnaires and return of any remaining oil at 4 weeks, you will also be given a gift voucher to say thank you for the time that you have given up.

**What if relevant new information becomes available?**
If any new information comes to light about the use of oil on babies’ skin, the Researcher will tell you about it and discuss whether or not you and your baby should continue to take part. It is your decision whether to continue in the study.

**Complaints**
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (Tel: 0161 306 7758). If they are unable to resolve your concern or you wish to make a complaint about the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research.complaints@manchester.ac.uk.

**Harm**
In the event that something does go wrong and you or your baby are harmed during the research you may have grounds for a legal action for compensation against The University of Manchester but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

**Will my taking part in this study be kept confidential?**
We will follow ethical and legal practice and all information collected about you and your baby during the course of this study will be kept strictly confidential. Any information about you or your baby that leaves the hospital will have the name and address deleted, so that you and your baby cannot be recognised by it. This includes data that are transmitted electronically. Each of you will be allocated a unique study number which will be used for recording demographic and trial data. All electronic data will be stored on a password protected and fully encrypted computer and will be identifiable only by a unique study number. Personal contact details will be recorded separately on paper and stored in a locked filing cabinet in a locked research office. Any information included in written reports/presentations will not identify you or your baby by name, but use a false name or unique study number only. Only the members of the research team will have access to you or your baby’s identifiable data.

If you consent to take part in the study with your baby, some parts of your medical record, your baby’s medical record, and the data collected for the study will be looked at by authorised persons from the Sponsor organising the research. Regulatory authorities and authorised representatives from Central Manchester NHS Foundation Trust may also want to check that the study is being carried out correctly. Your name, or your baby's name however, will not be disclosed outside of the hospital. Details about the study and your participation will be kept in your handheld maternity notes, so that clinicians caring for you (GP, Midwife, and Obstetrician) will be aware of your involvement. Your baby’s GP will be informed about your baby’s participation in the study by letter, with your consent. Information kept by the NHS and records maintained by the General Register Office may be used to follow up the health status of you and your baby. All information will remain confidential at all times. Should further studies be planned related to you and your, or your baby’s, involvement in this study, we will contact you to seek your permission.

**What will happen to the results of the research study?**
The study results and findings will be written up as a Thesis for a Doctoral degree. The study results will also be published in a professional journal and presented at professional conferences. Your individual results will not be available. Please contact Alison Cooke for a copy of the results.
Who is organising and funding this research?
This research study is being undertaken as part of an education programme through The School of Nursing, Midwifery & Social Work at The University of Manchester, in partnership with The University of Sheffield, and funded by a Doctoral Research Fellowship from the National Institute for Health Research. The research is closely monitored by a supervisory and advisory team. The hospital and other clinicians do not receive any payment if you take part in this project.

Who has reviewed this study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by Greater Manchester East Research Ethics Committee (reference number 13/NW/0512). It has also been reviewed by The University of Manchester and Central Manchester NHS Foundation Trust.

Contact details for further information:
If you require further information about this study please contact:

Principle Researcher/Midwife: Alison Cooke, School of Nursing, Midwifery and Social Work, The University of Manchester. Email: Alison.Cooke@manchester.ac.uk. Tel: 0161 306 7758

Professor of Midwifery: Dame Tina Lavender, School of Nursing, Midwifery and Social Work, The University of Manchester. Email: Tina.Lavender@manchester.ac.uk. Tel: 0161 306 7744

If you require independent advice about research in general please contact Sarah Leo, Divisional Research manager, St Mary’s Hospital, Central Manchester NHS Foundation Trust. Tel. 0161 276 6393. Email: sarah.leo@cmft.nhs.uk

Thank you for reading this and considering taking part in the study.
Appendix 14: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Case Report Form Part A: Version 2, 29/07/13

FORM 1: TRIAL ENTRY

Part A: Eligibility

Patient Hospital Number: ..........................

Yes

1. Is baby’s gestation greater than or equal to 37 weeks at birth.

2. Singleton pregnancy.

3. Within 48 hours of birth.

4. Maternal age greater than 16 years.

5. No major congenital malformations, limb defects or chromosomal anomaly.

6. No arrangement for adoption/foster care.

7. No impairment of epidermal integrity or active skin disease/disorder.

8. No admission to neonatal unit.


If all boxes are ticked, then baby is eligible to be recruited into OBSeRvE

Send GP Letter soon after consent is obtained.

Date: ____________________

Person: ____________________
The OBSERVe Study: The use of Oil in Baby Skincare Pilot Study: A pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

CONSENT FORM FOR MOTHERS AND BABIES
(Version 5, 23/01/14)

Study Number: ________________

Participant Identification Number for this trial: ________________

Research Team: Alison Cooke, Suresh Victor, Michael Cork, Tina Lavender

Please initial box

1. I confirm that I have read and understand the information sheet dated 23rd January 2014 (version 5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my and my baby’s participation is voluntary and that I am free to withdraw, and withdraw my baby, from the study at any time without giving any reason, without any medical care or legal rights being affected.

3. I understand that relevant sections of my, and my baby’s, medical notes and data collected during the study may be looked at by individuals from The University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to taking part in this research. I give permission for these individuals to have access to our records.

4. I agree to my GP, and my baby’s GP, being informed of our participation in this study.

5. I agree that D-Squame samples may be taken from my baby, and that any samples which remain unused at the end of the study will be destroyed.

6. I agree to taking part in an interview lasting 30-60 minutes.
Appendix 15: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Consent Form for Mothers and Babies: Version 5, 23/01/14

7. I agree to my conversation being audio recorded during interview. □

8. I agree to my anonymised quotations being used in journal papers and conference presentations. □

9. I agree to being contacted again to take part in similar research projects in the future. □

10. I would like to be sent a summary of the research findings. Name: ____________________________ Email: ____________________________

11. I agree to take part in the above study. □

Name of Participant ____________________________ Date ____________________________ Signature ____________________________

Name of Person taking consent ____________________________ Date ____________________________ Signature ____________________________

When completed, 1 for patient; 1 for researcher site file (original); 1 to be kept in medical notes
## BSeRvE: Oil in Baby SkincaRE Study

**Study Title:** OBSeRvE: Oil in Baby SkincaRE study

The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

Thank you for taking part in this study. The questionnaire should only take a few minutes. Please hand the questionnaire to the researcher, when completed.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is your full name?</td>
<td></td>
</tr>
<tr>
<td>What is your postal address?</td>
<td></td>
</tr>
<tr>
<td>What is your telephone number?</td>
<td></td>
</tr>
<tr>
<td>How old are you?</td>
<td></td>
</tr>
<tr>
<td>How many children do you have?</td>
<td></td>
</tr>
<tr>
<td>With which ethnic group do you identify?</td>
<td></td>
</tr>
<tr>
<td>With which ethnic group do you identify your baby as?</td>
<td></td>
</tr>
<tr>
<td>Do you have atopic eczema? If yes, what treatment do you use?</td>
<td></td>
</tr>
<tr>
<td>Do you have any other skin conditions? If yes, please state</td>
<td></td>
</tr>
<tr>
<td>Does anyone in your own family have atopic eczema?</td>
<td></td>
</tr>
<tr>
<td>If yes, please state who, e.g. your partner, your parents, any other children</td>
<td></td>
</tr>
<tr>
<td>Baby’s hospital record number</td>
<td></td>
</tr>
<tr>
<td>How did you hear about this study?</td>
<td></td>
</tr>
</tbody>
</table>

Date .......................... .........................................................

Thank you for completing this questionnaire.
Appendix 16: The OBSrVe Study: The use of Oil in Baby Skincare Pilot Study
Baseline Questionnaire: Version 2, 29/07/13

Ethnicity Groups

1. White British
2. White Other
3. Indian
4. Pakistani
5. White Irish
6. Mixed
7. Black Caribbean
8. Black African
9. Bangladeshi
10. Chinese
11. Asian Other
12. Black Other
13. Other
Part C: Background of Mother

Mother’s Hospital Number:
......................................................

For initial completion:

Date: ____________________ Person: ___________________
(subsequent additions must be initialled and dated)

Information from booking visit

Mother’s Date of birth:  

day  month  year

Ethnicity  .................

What is the best estimate of gestation based on?

Last Menstrual Period (LMP)  

Antenatal scans before 12 weeks  

Antenatal scans after 12 weeks  

Birth

Date of Birth:  

day  month  year

Time:  

Where was the Birth? Current hospital / other hospital .............../ health centre / home

Type of Birth:  Vaginal Birth/ Elective Caesarean section/ Emergency Caesarean section

Onset of Labour:  Spontaneous/ Induced

Past Medical History

Family history of atopic eczema?  

Yes  No

(medically diagnosed / topical steroid treatment)

Which family member?  Baby’s mother / baby’s father / baby’s sibling
Appendix 18: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Case Report Form Part D: Version 1, 21/02/13

Part D: Background of Baby

Patient Hospital Number:  
---------------------------------------

Date of Birth:  
Time of birth:  

Birth weight:  grams  Gender ____ (M/F)

Gestation:  weeks  days

Vernix at birth:  Absent (none)  
Minimal (creases only)  
Extensive (more than creases)

Condition of skin at birth:  Normal  
Dryness score (see below)  
Milia  
Other (please describe below)

Has the baby had a first bath?  

Date of first bath:  
Time:

Were any skin products used during the first bath?  

What products were used?

Dryness and scaling scale (circle one)

<table>
<thead>
<tr>
<th>Score</th>
<th>Grade Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of dryness or scaling</td>
</tr>
<tr>
<td>1</td>
<td>Slight dryness and/or scaling</td>
</tr>
<tr>
<td>2</td>
<td>Mild–moderate dryness to severe dryness and/or scaling</td>
</tr>
<tr>
<td>3</td>
<td>Moderate-severe dryness and/or scaling</td>
</tr>
<tr>
<td>4</td>
<td>Severe dryness and/or scaling</td>
</tr>
</tbody>
</table>
Part B: Consent and Randomisation

Patient Hospital Number:

Yes/No

1. An OBSRVe Trial patient information leaflet has been given and explained to mother

2. An OBSRVe Trial signed informed consent form has been completed and documented in the medical notes

3. Family history of atopic eczema?

If box 1 and box 2 are ticked, then baby is eligible for randomisation.

Box 3 required prior to randomisation phone call.

Commence Form 2: Baseline Observations immediately after randomisation.

Maternal Initials: .......................  
Maternal DOB (MM/YY): ..............

Randomisation Number:.....................

Date and Time of randomisation:.................................................

Date: ____________________  
Person: ___________________

Date: ____________________  
Person: ___________________
FORM 2: Baseline Observations (within 48 hrs of birth)

Form 2 should be commenced immediately after randomisation

Person: _________________ Date: ______________

Date and time of assessment:      Time

Awake (calm) / Awake (crying) / Asleep

**Upper abdomen**
Measurement from umbilicus: ________ cm (Umbilicus to nipple line = ..........cm)

<table>
<thead>
<tr>
<th></th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Left Forearm**
Measurement from wrist: __________ cm (Wrist to ante-cubital fossa = ..........cm)

<table>
<thead>
<tr>
<th></th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Left Thigh
Measurement from knee: ________ cm (Mid-patella to head of femur = ......cm)

<table>
<thead>
<tr>
<th></th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 – 80)</th>
<th>Erythema</th>
<th>Melanin (4 – 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Observation
Dryness and scaling scale (circle one)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of dryness or scaling</td>
</tr>
<tr>
<td>1</td>
<td>Slight dryness and/or scaling</td>
</tr>
<tr>
<td>2</td>
<td>Mild–moderate dryness to severe dryness and/or scaling</td>
</tr>
<tr>
<td>3</td>
<td>Moderate-severe dryness and/or scaling</td>
</tr>
<tr>
<td>4</td>
<td>Severe dryness and/or scaling</td>
</tr>
</tbody>
</table>

Rash grading scale (Circle one)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of rash</td>
</tr>
<tr>
<td>1</td>
<td>Slight rash–slight erythema and/or scaling</td>
</tr>
<tr>
<td>2</td>
<td>Mild rash–moderate to severe erythema and/or scaling, slight papules and oedema</td>
</tr>
<tr>
<td>3</td>
<td>Moderate rash–moderate to severe erythema and/or scaling, moderate ulceration, moderate to severe papules and oedema</td>
</tr>
<tr>
<td>4</td>
<td>Severe rash–severe erythema and/or scaling, severe ulceration, papules, and oedema</td>
</tr>
</tbody>
</table>

Medical / cleansing moisturising products used?

.........................................................................................................................

Advice Given?

.........................................................................................................................

Referral needed? Yes/No

Signature: ........................................
Dear Dr

Re: Patient name: 
Address: 
DOB: 

We are writing to inform you that the above named patient has consented to participate in the OBSERVE Study.

The study is a randomised controlled trial to obtain data regarding the most suitable method for the prevention and treatment of infant dry skin. The study will recruit healthy infants with and without a propensity to eczema.

Babies will be randomised to treatment with either topical olive oil or sunflower oil or no oil for a period of 28 days from birth. Clinical and biophysical assessment of baby skin will be carried out by a research midwife at birth and 28 days. Mothers will also complete a questionnaire at these time periods. We do not anticipate any serious adverse reactions. However, should there be any skin related problems Consultant Dermatologist Michael Cork (Sheffield Children’s Hospital NHS Foundation Trust) will provide initial advice and write to you.

The study has been designed in conjunction with neonatal and dermatological input and has been reviewed by independent experts in dermatology, neonatology and midwifery. The study has been reviewed and approved by The University of Manchester, Central Manchester NHS Foundation Trust and the Greater Manchester East Research Ethics Committee.

If you have any questions, please do not hesitate to contact me on 0161 306 7758 or alison.cooke@manchester.ac.uk

Yours Sincerely

Alison Cooke
Midwife / Principle Investigator
**Weekly Telephone Questionnaire**

**Study Title: OBSeRvE: Oil in Baby SkincaRE Study**

The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomized controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

Introduce self. Ask if it is a convenient time to talk. Advise the participant that the call should take no longer than 5 minutes. Important: Advise participant not to disclose which group they have been allocated to.

<table>
<thead>
<tr>
<th>Date:</th>
<th>Phone Call Number (1, 2 or 3):</th>
<th>Study ID Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you used any of the products listed? <strong>Remind participant not to disclose which group they have been allocated to</strong> (tick all that apply and specify the name of the product, how many times used, and where on the baby’s body it was used)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Talcum powder**
  - Type ..................................................
  - How often? ...........................................
  - Body part ...........................................

- **Soap**
  - Type ..................................................
  - How often? ...........................................
  - Body part ...........................................

- **Oil (not provided by study)**
  - Type ..................................................
  - How often? ...........................................
  - Body part ...........................................

- **Bath wash**
  - Type ..................................................
  - How often? ...........................................
  - Body part ...........................................

- **Baby wipes**
  - Type ..................................................
  - How often? ...........................................
  - Body part ...........................................
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Please specify</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weekly telephone questionnaire: Version 1, 08/06/13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thank participant. Advise we will phone again next week (if applicable).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Has your baby had any signs of a rash on the left forearm, left thigh or abdomen (above tummy button)?</strong></td>
<td>No</td>
<td>Yes, please specify</td>
<td></td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. Have you had any reason to consult a doctor or nurse about your baby?</strong></td>
<td>No</td>
<td>Yes, please specify</td>
<td></td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>4. Has your baby been prescribed any medication?</strong></td>
<td>No</td>
<td>Yes, please specify</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>5. Do you have any concerns about your baby’s skin?</strong></td>
<td>No</td>
<td>Yes, please specify</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Thank participant. Advise we will phone again next week (if applicable).

After call: Any disclosure of group allocation? □ Yes □ No
Details:
.............................................................................................................................................................................

Signed: ..............................................................................................................................
Print Name: ..............................................................................................................................
FORM 3: Follow up assessment (28 days)

Date: __________ Person: __________

Maintenance of intervention for \( \geq 28 \) days.  
Yes [ ] No [ ]

Date and time of last application.  
\[ \text{day} \quad \text{month} \quad \text{year} \]  
Time \[ \text{Time} \]

Date and time of assessment:  
\[ \text{day} \quad \text{month} \quad \text{year} \]  
Time \[ \text{Time} \]

Interval between last application and assessment …………………………………………………

Was there any change to treatment (describe below)?  
Yes [ ] No [ ]

<table>
<thead>
<tr>
<th>Temp</th>
<th>Humidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Awake (calm) / Awake (crying) / Asleep

**Upper abdomen**  
Measurement from umbilicus: _______ cm (Umbilicus to nipple line = _______.cm)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Left Forearm**  
Measurement from wrist: _______ cm (Wrist to ante-cubital fossa = _______c)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Left Thigh
Measurement from knee: ________ cm (Mid-patella to head of femur = ______ cm)

<table>
<thead>
<tr>
<th></th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Observation
Dryness and scaling scale (circle one)

<table>
<thead>
<tr>
<th>Grade Description</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of dryness or scaling</td>
<td>Slight dryness and/or scaling</td>
<td>Mild--moderate dryness to severe dryness and/or scaling</td>
<td>Moderate-severe dryness and/or scaling</td>
<td>Severe dryness and/or scaling</td>
<td></td>
</tr>
</tbody>
</table>

Rash grading scale (Circle one)

<table>
<thead>
<tr>
<th>Grade Description</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of rash</td>
<td>Slight rash--slight erythema and/or scaling</td>
<td>Mild rash--moderate to severe erythema and/or scaling, slight papules and oedema</td>
<td>Moderate rash--moderate to severe erythema and/or scaling, moderate ulceration, moderate to severe papules and oedema</td>
<td>Severe rash--severe erythema and/or scaling, severe ulceration, papules, and oedema</td>
<td></td>
</tr>
</tbody>
</table>

Medical / cleansing moisturising products used during treatment period?

.................................................................

Advice Given?

.................................................................

Referral needed?  Yes/No

Signature: ..........................
**Follow up Questionnaire**
*(To be completed by participant 4 weeks post birth)*

**Study Title: OBSeRvE: Oil in Baby SkincaRE Study**

The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomized controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

Thank you for taking part in this study. We would be most grateful if you would complete this questionnaire as honestly as you can. The questionnaire should only take a few minutes. Please hand the questionnaire to the researcher, when completed.

**Part A (1): About your baby**

<table>
<thead>
<tr>
<th>Date</th>
<th>Assessment Number</th>
<th>Study Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Do you or any of your family members have atopic eczema?</td>
<td>☐ No ☐ Yes, please state who e.g. mother ………………………………………………………… …………………………………………………………</td>
</tr>
<tr>
<td>2.</td>
<td>How are you feeding your baby?</td>
<td>☐ Breastfeeding (exclusive) ☐ Bottle feeding ☐ Mixed (Breast and bottle)</td>
</tr>
<tr>
<td>3.</td>
<td>Have you used any of the products listed? (tick all that apply and specify the name of the product, how many times used, and where on the baby’s body it was used)</td>
<td>☐ Talcum powder Type …………………………………… How often? ……………………….. Body part ………………………………</td>
</tr>
</tbody>
</table>
### Follow up questionnaire (28 days): Version 1, 21/02/13

<table>
<thead>
<tr>
<th>Soap</th>
<th>Type</th>
<th>How often?</th>
<th>Body part</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil (not provided by study)</td>
<td>Type</td>
<td>How often?</td>
<td>Body part</td>
</tr>
<tr>
<td>Bath wash</td>
<td>Type</td>
<td>How often?</td>
<td>Body part</td>
</tr>
<tr>
<td>Creams</td>
<td>Type</td>
<td>How often?</td>
<td>Body part</td>
</tr>
<tr>
<td>Lotions</td>
<td>Type</td>
<td>How often?</td>
<td>Body part</td>
</tr>
</tbody>
</table>

4. **How many times per week do you bath (immerse) your baby?**

   ......... times per week

5. **What have you used to assist you in bathing your baby? (tick all that applies)**

   - Flannel
   - Baby sponge
   - Family sponge
   - Hand only
   - Other, please specify .......

6. **Other than the group you were allocated to (i.e. oil or no oil) have you used anything else to moisturise your baby?**

   - no
   - yes, please specify..............................
   - How often applied? .................
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.</td>
<td>What type of washing powder do you use to wash your baby’s clothes?</td>
<td>Biological, Non-biological</td>
</tr>
<tr>
<td>8.</td>
<td>Has your baby been prescribed any medication?</td>
<td>No, Yes, please specify</td>
</tr>
<tr>
<td>9.</td>
<td>Have you had any reason to consult a doctor or nurse about your baby?</td>
<td>No, Yes, please specify</td>
</tr>
<tr>
<td>10.</td>
<td>Do you have any concerns about your baby’s skin?</td>
<td>No, Yes, please specify</td>
</tr>
</tbody>
</table>
A (2) Please indicate, by a tick, which statement you agree with most. Relate each statement to the regime that your baby was allocated to (i.e. oil or no oil). Please relate to the areas of left thigh, left forearm or upper abdomen (above nappy area) only.

<table>
<thead>
<tr>
<th></th>
<th>Tick</th>
<th>Tick</th>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Does not help my baby's dry skin adequately</td>
<td></td>
<td>Helps my baby's dry skin adequately</td>
</tr>
<tr>
<td>2.</td>
<td>Makes my baby smell nice</td>
<td>Makes no difference to how my baby smells</td>
<td>Makes my baby smell unpleasant</td>
</tr>
<tr>
<td>3.</td>
<td>Does not make me feel closer to my baby</td>
<td>Makes no difference to how close I feel to my baby</td>
<td>Makes me feel closer to my baby</td>
</tr>
<tr>
<td>4.</td>
<td>Is good for my baby's skin</td>
<td>Makes no difference to my baby's skin</td>
<td>Is bad for my baby's skin</td>
</tr>
<tr>
<td>5.</td>
<td>Makes my baby's skin more dry</td>
<td>Makes no difference to how dry my baby's skin is</td>
<td>Makes my baby's skin less dry</td>
</tr>
<tr>
<td>6.</td>
<td>My baby likes it</td>
<td>My baby does not mind</td>
<td>My baby does not like it</td>
</tr>
<tr>
<td>7.</td>
<td>Is not a convenient method of skin care</td>
<td>Makes no difference in terms of convenience</td>
<td>Is a convenient method of skin care</td>
</tr>
<tr>
<td>8.</td>
<td>Timing interfered with my daily activities</td>
<td>Made no difference to daily activities</td>
<td>Spent more quality time with my baby</td>
</tr>
<tr>
<td>9.</td>
<td>Would not like treatment to become routine</td>
<td>No preference to skin care treatment</td>
<td>Would like treatment to be routine</td>
</tr>
</tbody>
</table>
Appendix 24: The OBSerV E Study: The use of Oil in Baby Skincare Pilot Study

Follow up questionnaire (28 days): Version 1, 21/02/13

Part B: About your feelings of taking part in this study

1. If you could turn the clocks back, would you take part in this research?
   - Yes
   - Unsure
   - No
   Please make additional comments if you wish ...........................................
   ..........................................................
   ..........................................................
   ..........................................................

2. How do you feel about the information that you received about the study?
   - Information was good
   - Information was adequate
   - Information was poor, please give details ..........................................
   ..........................................................
   ..........................................................
   ..........................................................

3. Overall, how did you feel about the treatment you were allocated to?
   - Extremely satisfied
   - Fairly satisfied
   - Somewhat dissatisfied
   - Extremely dissatisfied

4. Would you recommend the way you moisturised your baby to a friend?
   - Yes
   - No
   - Unsure

5. What are your views on the measurements taken on your baby?
   ..........................................................
   ..........................................................
   ..........................................................
What do you think are the positive aspects of taking part in this study?

What do you think are the negative aspects of taking part in this study?

Please indicate if you are happy for the researcher, Alison Cooke, to contact you by telephone, to take part in an interview

- Yes, telephone number ..............................
- No

Please indicate if you would like a copy of the research findings

- Yes, postal address or email .............................
- No

Thank you for taking the time to complete this questionnaire.
LONGER TERM FOLLOW UP CONTACT FORM

Patient Hospital Number:
…………………………..

1. Mother’s NHS number

2. Baby’s NHS number

3. Address of grandparents (maternal side)

Date: ____________________

Person: ____________________
Appendix 26: OBServE Modified Skin Assessment Tool

**Clinical Observation**

*Dryness and scaling scale (circle one)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of dryness or scaling</td>
</tr>
<tr>
<td>1</td>
<td>Slight dryness and/or scaling</td>
</tr>
<tr>
<td>2</td>
<td>Mild—moderate dryness to severe dryness and/or scaling</td>
</tr>
<tr>
<td>3</td>
<td>Moderate-severe dryness and/or scaling</td>
</tr>
<tr>
<td>4</td>
<td>Severe dryness and/or scaling</td>
</tr>
</tbody>
</table>

*Rash grading scale (Circle one)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of rash</td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
<td>Mild rash—moderate to severe erythema and/or scaling, slight papules and oedema</td>
</tr>
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<td>Moderate rash—moderate to severe erythema and/or scaling, moderate ulceration, moderate to severe papules and oedema</td>
</tr>
<tr>
<td>4</td>
<td>Severe rash—severe erythema and/or scaling, severe ulceration, papules, and oedema</td>
</tr>
</tbody>
</table>
The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function

Protocol

Version 8, 30th January 2014

Clinical Trials Registration Number: ISRCTN37373893

National Institute for Health Research Clinical Research Network Portfolio Study ID: 14926

Greater Manchester East REC Reference Number: 13/NW/0512

Cooke A, Victor S, Cork MJ, Lavender T
Appendix 27: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Protocol: Version 8, 30/01/14

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<td>11</td>
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<td>12</td>
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<tr>
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<td>13</td>
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<td>3.4 Outcomes</td>
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<td>3.4.1 Procedures for assessment of trial outcomes</td>
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</tr>
<tr>
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<td>3.5.2 Qualitative data analysis</td>
<td>17</td>
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<td>21</td>
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<td>23</td>
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<tr>
<td>4.8 Ethical issues</td>
<td>23</td>
</tr>
<tr>
<td>4.8.1 Confidentiality and anonymity</td>
<td>23</td>
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Dr Malcolm Campbell
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Funding Organisation

Alison Cooke is funded by a National Institute for Health Research Doctoral Research Fellowship. This report is independent research supported by the National Institute for Health Research (Doctoral Research Fellowship DRF-2012-05-160). The views expressed in this report are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Sponsor

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Manchester
M13 9PL
1. Background

1.1 Baby’s Skin

Dry skin is a common occurrence in the first few months after birth (Saijo and Tagami, 1991). Dry skin has been defined as “a cutaneous reaction pattern reflecting abnormal desquamation of diverse etiologies” (Madison, 2003). In normal skin, corneocytes are shed from the skin in small enough quantities that they are not visible to the naked eye; however in dry skin the skin appearance becomes rough and flaky if this normal process is disturbed in any way. In an infant this is a normal process of adaptation to life outside of the uterus. This physical process results from the change in environment from the surroundings of wet amniotic fluid in-utero, to the dry conditions of the atmosphere.

Atopic eczema (synonym atopic dermatitis) is an inflammatory skin condition characterised by dry and scaly skin, redness, itching and blistering (figure 1). Allergic disease affects up to 30% of children aged 2 to 15 in the UK (Gupta et al., 2004). Prevalence of atopic eczema has increased substantially over the past 30 years (Simpson et al., 2009). Atopic eczema begins as a disease of the skin barrier. The skin barrier breaks down allowing penetration of allergens and irritants that interact with the immune system. Affected children are also predisposed to allergic asthma and allergic rhinitis (Gustafsson et al., 2000), known as the ‘atopic march’ (Spergel and Paller, 2003) (figure 2). It is suggested that approximately 60% of sufferers develop atopic eczema in the first year of life (Bieber, 2008). The prevalence of atopic eczema has increased to its current level from approximately 5% of children in the 1940s (Taylor et al., 1984). In that time the genetic structure of skin has not changed; however the way that we care for an infant’s skin from birth has changed, including increased use of soaps, other harsh detergents and oils (Cork et al., 2009, Danby et al., 2013). These environmental changes may contribute to the development of atopic eczema.

Infant skin is physiologically different to adult skin; the stratum corneum is 30% thinner and the epidermis is 20% thinner (Stamatas et al., 2010); this difference in skin structure results in increased permeability and dryness. Infant skin is also more vulnerable to the use of topical treatments as the ratio of infant body surface to body weight is higher than for adults (Nikolovski et al., 2008). The infant skin barrier continues to develop during the
first year of life (Stamatas et al., 2011); infants are therefore more vulnerable not only at birth but throughout their first year.

Infant skin is prone to an increased rate of trans-epidermal water loss (TEWL) and reduced stratum corneum hydration due to differences from adult skin such as less lipids, melanin and natural moisturising factors (Nakagawa et al., 2004, Chiu and Blume-Peytavi, 2004). Infants may also experience a weakening of the skin barrier due to their elevated skin surface pH. High skin surface pH (low acidity) results in increased activity of proteases which break down corneodesmosomes (supportive component of the stratum corneum) and hinders the activity of enzymes which are required for lipid processing (Cork et al., 2009, Hachem et al., 2003).

These differences between infant and adult skin in both structure and function suggest a greater vulnerability to environmental factors, including infant skincare products. The volume of products available to parents for use on their newborn baby has dramatically increased over the past 30 years. This leaves new parents and health professionals in a dilemma as to what is best for infant skin care (Danby and Cork, 2011). The use of topical products may contribute to the development of adverse skin conditions, including atopic eczema (Cork et al., 2009). Although there has been no trial assessing the use of oil on term infants' skin, health professionals continue to recommend its use (Cooke et al., 2011, Lavender et al., 2009).

Parents want to use skin products to make their infant look and smell nice (Lavender et al., 2009, Furber et al., 2012). Midwives and other infant health professionals commonly advise new parents to use olive oil on their infants to prevent or treat dry skin (Cooke et al., 2011). Infant skin conditions can cause parental anxiety (Adalat et al., 2007). Although dry skin in normal in term infants, parents may be anxious and want to treat it. Parents will often adhere to advice given to them by health professionals with regard to care of a newborn infant (Lavender et al., 2009). Skincare advice given to new parents by health professionals is likely to be based on traditional practice, personal experience and anecdotal evidence, due to a dearth of robust evidence. Importantly, the practice of using some topical oils and emollients on infant skin may contribute to a wider public health issue: atopic eczema, while other oils may have a positive effect and prevent its development (Danby and Cork, 2011).

Societal interest in ‘natural’ products is high (Allemann and Baumann, 2009), especially for parents of infants (Cottingham and Winkler, 2007). There is a readiness amongst parents to use oil for infant skincare, and a readiness amongst maternity professionals to recommend it. There is a misconception that because a product is ‘natural’ it must be ‘safe’ (Bedwell and Lavender, 2012, Lavender et al., 2009). Oils have been used in the cosmetic, pharmaceutical and perfumery industries for many years. However, oils are governed by cosmetic guidelines for testing and research (Council of the European Communities, 1976) which are not as rigorous as those for medicines for human use (Department of Health, 2004). This means that oils have been used as medicinal and homeopathic remedies for many years without any collection and analysis of toxicological data. There may be a toxic effect on infant skin that has been treated with topical oils; the infant skin surface area in relation to body weight is high and absorption is relative to the surface area exposed (Rutter, 1987). Topical applications may cause irritation, damage or systemic effects through absorption of the oil in to the body. There is some concern that some topical skin preparations may have carcinogenic properties (Cui et al., 2011,
Sanchez-Prado et al., 2013), particularly if they contain a preservative such as Bronidox or Bronopol found in soap and gel in one study (Sanchez-Prado et al., 2013). It is therefore essential that research is conducted to establish what effect, if any, the use of oils has on infant skin.

An infant’s skin plays an important role in the prevention of infection. It is therefore necessary to preserve its integrity and pH balance. The vulnerability of a newborn infant’s skin when it is first exposed to life outside of the uterus creates the potential for numerous skin problems including napkin rash, cradle cap, infant Candida, baby acne and atopic eczema (synonym atopic dermatitis). These problems have created concerns about newborn infant skin care regimens, not only for parents but also for health professionals. Infection is one of the leading causes of neonatal morbidity and mortality in low resource countries (Darmstadt et al., 2002). The vulnerability of infant skin, together with the use of topical oils which may be harmful, combined with poor hygiene conditions, has the potential for increased hazards of infection. Nosocomial sepsis is more common in preterm infants where the stratum corneum is not fully mature (Conner et al., 2009), and skin does not have the protective benefit of vernix (Yoshio et al., 2003). There have been several studies (Darmstadt et al., 2008, Kiechl-Kohlendorfer et al., 2008, Darmstadt et al., 2005, Darmstadt et al., 2004, Edwards et al., 2004, Darmstadt and Saha, 2002), and a Cochrane systematic review (Conner et al., 2009), which have considered methods of preventing infection in preterm infants, but none considering infection in term infants.

The use of oils and emollients in preterm infants (≤36+6 weeks of gestation at birth) has been studied in various ways. A Cochrane systematic review of these studies is in progress (Seliem et al., 2009). On the contrary, there has been very little research in healthy term newborn infants.

Several term infant skincare randomised controlled trials were conducted recently to consider the use of infant wash and infant wipe products in comparison to use of water alone (Lavender et al., 2012a, Lavender et al., 2011). This was the first time that parents and health professionals were able to access robust evidence to make informed choices about products that could be recommended and used on newborn infants. One area which has not been investigated is the topical use of oils to prevent or treat newborn infant physiological dry skin and atopic eczema.

The application of olive oil, and to a lesser extent sunflower oil, is recommended by health professionals to new mothers for use on their term infant’s skin (Cooke et al., 2011, Lavender et al., 2009), to prevent or treat dryness or as part of massage. The use of emollients is not commonly recommended, however parents have the choice of a diverse range of emollient infant skincare products from numerous manufacturers. In a recent UK national survey (Cooke et al., 2011), 52% of responding maternity and neonatal units recommended the use of oil for baby skincare; 82% of these units recommend olive oil for parents’ use on their infant’s skin and 20% recommend sunflower oil. Health professionals, such as midwives and health visitors, believe these oils to be ‘natural’ and therefore not harmful to infant skin (Lavender et al., 2009).

Current research in this area is limited, making it difficult to assess the effectiveness of this practice. Research has shown that olive oil of certain compositions (high ratio of oleic acid to linoleic acid) may affect skin barrier function in mice (Darmstadt et al., 2002, Jiang and Zhou, 2003) and adults (Danby et al., 2013, Naik et al., 1995). This composition of oil
Appendix 27: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Protocol: Version 8, 30/01/14

disrupts the lipid structure of the stratum corneum, and is a potential risk factor in the development or exacerbation of atopic eczema. Optimal sunflower oil (high ratio linoleic acid to oleic acid) has been shown in the same population to promote skin barrier repair (Danby et al., 2013, Darmstadt et al., 2004, Darmstadt et al., 2008). The vulnerability of a baby’s skin suggests the potential for more skin problems. There has been no research to determine the effect of olive oil or sunflower oil on a term baby’s skin barrier function. It is important to provide evidence to support clinical practice, particularly if that practice may be detrimental to those in our care.

We know that 60% of atopic eczema cases occur in the first year of life, and 45% in the first six months of life (Bieber, 2008). This period of time is when midwives, maternity workers and other infant health professionals have the most influence with parents. Health professionals may find it difficult to give evidence based advice to new parents, as we do not have sufficient evidence to guide practice. It is important to provide this evidence, to give a high quality basis for clinical practice and informed decision making. Some oils are potentially harmful; however others may provide some benefit. Given the rise in prevalence of atopic eczema, it is timely to conduct this research.

We propose a pilot randomised controlled trial (RCT) to look at the effect of the most commonly used oils (olive oil and sunflower oil) on an infant’s skin barrier function.

1.2 Complex Intervention Framework

We will use the development and feasibility phases of the Complex Intervention Framework (Medical Research Council, 2008)(figure 3). This framework has been chosen as there may be a need to modify organisational, mothers' and health professionals' behaviour. Work is required to establish proof of concept (effect of olive oil or sunflower oil) and to test trial procedures. An RCT is the gold standard for research study designs. This proposal is a pilot RCT with a nested qualitative study to be structured around the Complex Intervention Framework (Medical Research Council, 2008), to ensure that we can proceed to a full trial with the knowledge that we can achieve high quality evidence with the potential to change a clinical practice which has been traditional for more than three decades. A pilot study will provide detail with regard to proof of concept, optimal primary outcome measure, recruitment strategy, consent processes, practicalities of assessment, patient compliance and what sample size will be necessary to provide results which are significant; statistically and clinically. The qualitative study will assist us in understanding the practical issues of participation and acceptability; how participants felt about taking part in an RCT and views of treatment allocation.

This pilot trial is timely because of the readiness of parents to use olive oil and sunflower oil on infant skin. It is important to determine which oils are good for skin and which may impair skin barrier function. We have discussed the proposed study with the National Eczema Society, who agree that a randomised controlled trial (RCT) is the only way to achieve evidence that can change behaviour of a practice that has become so ingrained. The investigator has also liaised with the Medicines for Children Research Network (MCRN), a Clinical Trials Unit, and the Neonatal Clinical Studies Group, for support and guidance regarding study design.
1.2.1 Development Phase
In the first part of the development phase we conducted a UK national survey of all maternity and neonatal units to assess what oils are recommended to new parents and used within the UK maternity service (Cooke et al., 2011). This phase also has the benefit of the existing body of work already undertaken by Professor Dame Tina Lavender (Lavender et al., 2011, Lavender et al., 2009, Lavender et al., 2012b). The proposed study builds on the previous experience of the research team in infant skincare. To date, three RCTs have been conducted (pilot wash product versus water trial, definitive wash product versus water trial, and wipes versus water trial). All trials recruited to target, compliance was good (>80%), there were no serious adverse events and the trials were deemed to be acceptable by participants. This proposed pilot study will benefit from the lessons learned from these recently completed trials.

In the second part of this phase a Cochrane review of randomised controlled trials and a systematic review of all other available evidence, including observational and non-randomised experimental studies, are in progress. The review includes contacting all major cosmetic and dermatology pharmaceutical companies to access their unpublished research.

The decision to perform a randomised controlled trial is underpinned by 1) the necessity for robust, gold standard research which has the potential to change practice, and 2) safety. With regard to safety, we are researching a healthy population. The incidence of clinically detectable skin problems is likely to be low.

1.2.2 Feasibility and piloting phase
Having completed the development phase of the MRC framework, the next step in our preparation for a definitive trial will be a feasibility study. In summary: a) the systematic review is likely to find a dearth of evidence, b) consumers have called for further research, c) olive oil may impair skin barrier function; sunflower oil may improve it, and d) there is a need to evaluate current clinical practice. Therefore, we propose a randomised controlled trial of olive oil and sunflower oil versus no treatment. A study assessing the impact of the use of oil in infant skincare is timely, as this has been the subject of much debate in a number of recent conferences, such as Excellence in Paediatrics, 2011 and the International Confederation of Midwives Triennial Congress, 2011. There is a dearth of
research in this area and so care is required to plan an adequately powered trial. This protocol describes the proposed feasibility (pilot) study.

2. Research Methodology

2.1 Hypothesis

The regular application of sunflower oil, when compared to no oil or olive oil, improves the skin barrier function of new born term infants.

2.2 Design

We aim to pilot a single-centre, assessor-blinded, three-arm randomised controlled trial that will assess the feasibility of testing the hypothesis. The pilot will test the application of the protocol, and estimate clinical effect and trial parameters to assist in developing a definitive (phase III) RCT.

2.3 Outcomes

2.3.1 Proposed primary outcomes for trial

- Rate of change of basal transepidermal water loss (TEWL) between day 2 and day 28 after birth
- Skin barrier function as measured by the change in spectral profile of lipid lamellae assessed by infrared spectroscopy between day 2 and day 28 after birth

2.3.2 Proposed secondary outcomes for trial

- Rate of change in skin surface hydration between day 2 and day 28
- Rate of change in skin surface pH between day 2 and day 28
- Change in clinical observations (erythema, dryness and scaling, need for medical products/attention: (Lund and Osborne, 2004))
- Maternal satisfaction: the views of mothers on taking part in the trial; acceptability, protocol compliance, group allocation, convenience, and information provision, measured using a specifically designed questionnaire which has gained content validity by being informed by earlier work (Lavender et al., 2011, Lavender et al., 2009, Lavender et al., 2012b)

2.4 Specific aims of the pilot trial

1. To generate pilot data concerning the hypothesis that the regular application of sunflower oil, when compared with no oil or olive oil, improves the skin barrier function of newborn term infants
   a. To measure the rate of change in spectral profile of lipid lamellae and TEWL
   b. To explore the acceptability of trial participation for parents of newborn infants
2. To assess proof of concept regarding the effect of olive oil and sunflower oil on skin barrier function
   a. To assess extent of effect of intervention on skin barrier function
   b. To observe rate of compliance to treatment regime
   c. To observe rate of loss to follow up
   d. To observe acceptability of the study to consumers
3. To examine the feasibility of using infrared spectroscopy investigations in a clinical trial within a healthy term newborn infant population
   a. To observe acceptability of infrared spectroscopy to parents and infants
   b. To observe any disruption of services in the hospital, the community or in primary care (explored through parents views)
   c. To assess intra-subject variability of infrared spectroscopy measurements at each time point in the conditions under which the trial will be conducted (e.g. for infants with vernix at time of assessment, for infants who had had first bath)

4. To inform the sample size calculation
   a. To estimate the magnitude of infrared spectroscopy measurements in the newborn infant and use this together with clinical judgement to estimate an effect size for a definitive trial
   b. To estimate the inter-individual variability (standard deviation) at each assessment and thus to estimate the pooled sample size for the definitive trial

5. To refine trial design
   a. To inform potential recruitment rates
   b. To determine parent’s views of the information provided
   c. To determine the number of women needed to approach to obtain the required sample
   d. To determine the dropout rate for follow up assessment
   e. To pilot measures of the clinical condition of the skin (erythema, dryness and scaling)
   f. To examine the feasibility of measures of skin surface pH
   g. To examine the feasibility of measures of hydration
   h. To determine the optimal primary outcome measure for the definitive trial

6. To optimise trial management
   a. To inform consent processes and pilot participant information sheets
   b. To pilot data collection sheets
   c. To test data retrieval processes

3. Method

3.1 Sample and Setting

The sample will be drawn from Central Manchester NHS Foundation Trust (CMFT) St Marys Hospital, a large regional teaching unit with approximately 7400 births per annum (2011/2012), of which approximately 6750 infants were born full term.

3.1.1 Eligibility

_Inclusion criteria for screening phase:_ Women carrying singleton pregnancies who are booked to give birth at St Mary’s Hospital, Manchester.

_Exclusion criteria for screening phase:_ Women known to be carrying an infant with a chromosomal abnormality or other syndromic diagnosis; women known to be having their infant placed in foster care or adopted, women with multiple pregnancies, maternal age of less than 16 years.

_Inclusion criteria for trial:_

- newborn term infants (born on or after 37\textsuperscript{+0} weeks gestation) less than 72 hours old
- in good health (determined by investigator)

**Exclusion criteria for trial:**

**Women**
- maternal age of less than 16 years
- unable to communicate consent for their infant to take part in the trial due to learning difficulties

**Infants**
- admission to neonatal unit
- phototherapy
- limb defects
- non-traumatic impairment of epidermal integrity defined as abnormal epidermis or dermis such as collodion baby or congenital ichthyosis
- any medical history that may prevent the participation in the study until study conclusion
- currently participating in another clinical trial
- evidence of active skin disease or disorder at first visit – for the purposes of this study the following normal variations will not be considered skin disorders: erythema neonatorum / erythema toxicum; milia

**Inclusion criteria for qualitative interviews:** Any parent with an infant taking part in the OBSeRvE pilot RCT who has consented to take part in the qualitative study, and is purposively selected for interview.

**3.1.2 Sample Size for pilot trial**

We will recruit 100 infants from St. Mary’s Hospital, Central Manchester NHS Foundation Trust (CMFT), randomising 33 per group, allowing for 10% drop-out to collect outcome data on 30 per group (suggested as a suitable number of participants for a pilot RCT; (Lancaster et al., 2004)).

Based on the research team’s previous experience, we have estimated the need to approach three women to every one woman recruited to the study. As approximately 15-20 women may be available to approach over the time set aside for recruitment per week, we estimate a cautious recruitment rate of 5 women per week; a recruitment period of 20 weeks. However we will continue recruiting until we have achieved the required sample size.

We propose to conduct an interim analysis after 30 babies have been recruited, to assess loss to follow up with regard to the need to return to the hospital for the follow up assessment. If loss to follow up is high, we will offer a follow up home visit for all measurements except for the spectroscopy assessment for which the equipment is not portable. However it is important in this pilot study that we obtain sufficient spectroscopy data in order to determine the optimal primary outcome for the main trial. We will therefore continue to recruit until we have spectroscopy data from 90 participants (30 olive oil group, 30 sunflower oil group, and 30 control group).
Greater Manchester is an ethnically diverse county. In the last financial year (2011/2012), of mothers who gave birth at St Mary’s 27.1% were White British, 18% were of Asian origin, 11.9% were of Afro-Caribbean origin and 1.7% were of oriental origin. The remaining mothers were of mixed backgrounds or had not stated their ethnicity. The parents of all infants born during the recruitment period fulfilling the inclusion criteria will be approached and given the opportunity to take part in the study. This will hopefully ensure ethnic diversity. Patients will not be excluded if English is not their first language as an interpreting service will be available, for translation of study documents, trial assessment appointments and qualitative interviews. The randomisation process should help to ensure that equivalent numbers of male/female participants and varying ethnicities should be provided within both study groups (control and intervention).

3.2 Recruitment

All potentially eligible women will be provided with information about the study during the antenatal period. Information will be administered via community midwives and hospital midwives. This will provide women with time to consider participation in the trial. Willing participants will be asked to complete a short written statement antenatally giving consent to be approached about the trial following birth of their baby. Other eligible women will be identified postnatally by the lead investigator using the Bedman computer system which gives basic details about inpatients. The lead investigator will then approach the clinical midwife with the list of identified women and ask if there is any reason not to approach them. If a woman has indicated in her antenatal records that she does not wish to be approached for research, or if the clinical midwife knows of any reason why the lead investigator should not approach identified woman then no approach will be made. The clinical team will maintain the right to stop the lead investigator approaching women. Once permission has been obtained from the clinical team the lead investigator will approach women with details about the study. All women who consent to take part in the study will be asked to complete a short questionnaire containing closed questions regarding demographic details and family history of atopic eczema.

The definition of ‘family history of atopic eczema’ will be “at least one of father, mother, or sibling who has had a medical diagnosis of atopic eczema/atopic dermatitis and who has had topical steroid treatment”.

Eligible women who completed the questionnaire prior to birth, and those identified postnatally for whom the lead investigator has obtained permission from the clinical team, will be approached within 72 hours of birth on the labour ward or the postnatal ward by the lead investigator, who is a midwife and is GCP trained, to confirm their willingness to participate. All eligible women who are approached will be given a copy of the Participant Information Sheet and given the opportunity to ask questions. Those who wish to participate will be asked for consent for their infant to participate in the trial. Consent bearing women will then be randomised by an independent research midwife, who is GCP trained, to one of the experimental arms or the control arm within 72 hours of birth. Randomisation will be 1:1:1 by a central telephone-based service provided by the MAHSC-CTU. The randomisation sequence will be computer generated. Randomisation will be stratified according to whether or not there is a family history of atopic eczema. The randomisation is in blocks within eczema history strata (yes, no) and the block size
will vary at random between 6 and 15 (i.e. 6, 9, 12 or 15) to guard against predictability
and to ensure allocation concealment. The randomisation service is available Monday to
Friday 0900 – 1700.

Following randomisation women will be given the appropriate advice and materials by
the independent research midwife. General Practitioners (GP’s) will be notified of
participation by letter (appendix 18), following maternal consent.

All participants in the pilot RCT (control and intervention groups) will be asked to consent
for the qualitative component. Purposive sampling will be utilised to select 18 to 20
participants for interview based on responses to the final questionnaire (completed after
the treatment period has ended at 28 days). Purposive sampling will be necessary to
create a diverse group who have varying positive and negative experiences of the
research process. The lead investigator will telephone the identified participants for
interview within 28 days of follow up assessment.

3.3 Intervention

Infants will be randomised to one of three groups: Group A olive oil (intervention group
A), Group B sunflower oil (intervention group B) or Group C no oil (control group). The
study will be assessor blinded, and participants in the intervention groups (A and B) will
be blinded to which oil they are using. The lead investigator will perform the assessments.
Randomisation and instructions for parents regarding allocated group will be performed
by an independent identified research midwife in order to maintain assessor blinding.
Olive oil and sunflower oil will be provided for the intervention groups as appropriate and
first application will be demonstrated by an independent research midwife on the right
thigh of the infant (this will not be an assessed site). Parents will then begin using the oil
as instructed from the day after the initial assessment. Parents will be asked to apply oil
as instructed up until 10 hours prior to the time of follow up assessment to avoid any
interference with the results caused by oil residues and to maintain assessor blinding.
Follow up assessment will be on a date as close as possible to the infant being 28 days
old.

3.3.1 Intervention Groups

Women in the intervention groups (Group A: olive oil; Group B: sunflower oil) will be
asked to apply 4 drops of the oil provided (with a defined oleic acid and linoleic acid
content from a single supplier) twice daily on each of three sites; infant's left forearm,
upper abdomen (above nappy area) and left thigh (figure 4). The treatment period will
commence on the day following randomisation (day 2 or 3 after birth) and end ten hours
prior to the follow up assessment. Parents will be asked to wrap their infant loosely in a
blanket for 15 minutes following application.

Oil will be provided in opaque plastic dropper bottles, which will be weighed before and
after treatment. The weight of oil after the treatment period will help us to confirm
compliance with the protocol. The oil will therefore be collected from the participants
once the treatment period has ended. Diagrammatic leaflets will be provided to ensure
parents apply oil to the correct areas of their infant's skin at each application.

3.3.2 Control Group
Those in the control group (Group C) will not apply any oil to their infant’s skin. Participant blinding is not possible in this trial as it is impossible to identify a control oil that we can be confident is safe to apply and would have no effect on epidermal barrier function (Darmstadt et al., 2005). The importance of not applying any emollient to the assessment areas will also be emphasised.

3.3.3 Questionnaire
All participants in the pilot RCT (intervention and control groups) will be asked to complete two questionnaires. The first questionnaire (completed within 72 hours of birth prior to starting treatment) will collect demographic information. The follow up questionnaire (completed at follow up at 28 days once the treatment period has ended) will contain more questions about taking part in the trial; acceptability, practicality, protocol compliance, group allocation, convenience, and information provision.

3.3.4 Parental choice of use of infant skincare products
Parents will be asked not to use alternative infant skincare products on their infants during the treatment period. This will apply to both the intervention and the control groups. However, we will ask parents whether they have used any alternative products during the treatment period, and these details will be recorded. We do not expect that the use of intermittent alternative skincare products will affect the results, as randomisation should ensure that non-compliance will affect all groups equally.

3.4 Outcomes

3.4.1 Procedures for assessment of trial outcomes
All measurements will be taken and recorded by the lead investigator, who has been trained in the use of all equipment. If any other researcher is needed to record outcome measures at a later date in the study, they will be fully trained to ensure inter-rater reliability. All equipment used to obtain recordings of outcome measures will be maintained and calibrated in accordance with the calibration schedule and cleaning standard operating procedures.
Anatomical markers (upper abdomen (above nappy area), left thigh and left forearm) will be used to ensure that assessments are consistent. This will be achieved by measuring from anatomical markers such as the skin crease of the wrist to midpoint on the volar forearm, above the patella to midpoint on thigh, and above umbilicus to midpoint of nipple line for upper abdomen. We will use a number of biophysical measures and clinical observations to assess the skin. Assessments will be performed on all three groups of participants. All measurements will be made by the lead investigator who will be unaware of treatment allocation (assessor blinding). Consent will be renegotiated at each time point. Consent will also be sought to contact participants for longer term follow up, should the researchers feel that this would be beneficial. The instrumental assessments will be carried out after 20 to 30 minutes of acclimatisation. All measurements will be taken in the hospital environment as the measurement equipment is not portable. At each measurement the environmental conditions of the room will be registered: temperature and relative humidity.

3.4.2 Primary Outcome

**Trans-epidermal water loss (TEWL):** The main primary outcome will be the rate of change of basal transepidermal water loss (TEWL) between day 2 and day 28 after birth. TEWL is defined as the flux of condensed water diffusing through the skin. A closed chamber TEWL instrument will be used to measure the flux of water vapour evaporating from the skin surface (Aquaflux Model AF200). The lead investigator will take the measurements at both time points, and will be formally trained in obtaining such measurements, in accord with published guidelines for TEWL measurements (Rogiers, 2001) as adapted by the closed chamber methodology to be used here [http://www.biox.biz/Support/FAQAnswer08.htm].

**Skin Barrier Function:** The co-primary outcome will be skin barrier function as measured by the change in spectral profile of lipid lamellae assessed by infrared spectroscopy between day 2 and day 28 after birth. Infrared spectroscopy is a biophysical measurement that has been used previously to demonstrate the effects of oleic acid on skin barrier (Naik et al., 1995). Jiang et al. (Jiang et al., 2000) suggested that topical application of oleic acid may disrupt stratum corneum lipid lamellae structures and induce permeability defects. Infrared spectroscopy is the most sensitive and specific method to detect changes in the lipid lamellae induced by the application of oils to the skin. Biophysical measurements are used because they can detect the effects of topical products on the structure and function of the skin before anything is visible clinically on the surface of the skin. If a damaging treatment is used on the skin then the biophysical measurements will detect the damage before it has become severe enough to cause clinical signs of damage. This is important from an ethical perspective. This measure will be a surrogate primary outcome as the data collected will be novel data, which has not been assessed previously in infants, but has the potential to be the best indicator of change in skin barrier function. Analysis of the data will help the research team to determine the optimal primary outcome for the main trial.

At each spectroscopy measurement site on the skin surface a non-invasive measurement will be made. Following this procedure, three consecutive sticky-tape discs will be applied to and removed from the site and the measurement repeated. These sticky-tape discs, called D-Squame discs, are about the size of a £1 coin, less sticky than sellotape, and much less sticky than the adhesive on a nappy flap. The D-Squame discs remove the very
top skin cells, which are already dead and about to be lost naturally from the surface of the skin in a process known as desquamation. The measurement will be taken by placing a small probe on the surface of the skin. The D-Squame discs will be analysed to assess the levels of natural moisturising factor (NMF) and desquamatory proteases in the stratum corneum. NMF is derived from the structural protein filaggrin. Both filaggrin and NMF are important for effective barrier function. Low levels of NMF are found in the skin of people suffering from dry skin conditions. There are also reduced levels of NMF in the stratum corneum in carriers of mutations in the filaggrin gene (FLG), which increase the risk of developing atopic dermatitis, so this analysis may help to provide biomarkers for the FLG genotype. We will not perform genotyping. Desquamatory proteases play an important role in the maintenance of barrier function. Elevated activity of these proteases is associated with atopic dermatitis through accelerated breakdown of the skin barrier. Therefore quantification of this activity in newborn infants could provide further insight into an additional risk factor for the development of atopic dermatitis in infancy.

3.4.3 Secondary outcomes

**Skin surface hydration:** We will measure the change in skin surface hydration between day 2 and day 28 using a Corneometer. This measurement tool uses a small probe which is placed on the surface of the skin.

**Skin surface pH:** We will measure the change in skin surface pH between day 2 and day 28 using a skin pH meter. This measurement tool uses a small probe which is placed on the surface of the skin.

**Clinical observation:** We will measure the change in clinical observations (erythema, dryness and scaling, need for medical products/attention) between day 2 and day 28 using a validated skin assessment tool developed by leading nurse researcher Carolyn Lund (Lund et al., 2001).

**Maternal satisfaction:** We will explore women’s views on having an infant participating in a clinical trial, acceptability, practicality, protocol compliance, group allocation, convenience, and information provision. This will be assessed quantitatively in the first instance using the follow up questionnaire at 28 days (appendix 16). After we have analysed the open text responses qualitatively on the follow up questionnaire, we will purposively select between eighteen and twenty participants to take part in a short semi-structured interview lasting 30-60 minutes. This sample size will be increased, if appropriate, to achieve data saturation. These participants will be purposively selected as we will require some participants from each of the three treatment groups, in addition to a variety of negative and positive views (if available). The research team will decide which participants to select based on the responses to the open text questions in the follow up questionnaire.

3.4.4 Equipment

The tests using infrared spectroscopy, TEWL, skin surface hydration and pH, will involve touching a small probe to the surface of the baby’s skin. The tests are simple, non-invasive procedures and will not cause any pain or discomfort to the baby. The probes used for all of the tests can be compared to holding something like a microphone to the surface of the skin (figure 5), and are similar to those used for ultrasound of a mother’s baby when she is pregnant.
All measurements will be performed by the lead investigator, who will be formally trained in obtaining the measurements, with the assistance of a specialist skin research technician. Measurements will be recorded at baseline (within 48 hours of birth and before maternal transfer into the community) and at 4 weeks post-birth (as close to 28 days as possible). All measurements will be taken in the hospital, in a specially allocated, controlled environment.

3.4.5 Qualitative Data Collection
We will collect open text responses from the follow up questionnaire. We will audio record the in-depth semi structured interviews, with consent, and transcribe the interviews verbatim. Women will be given a pseudonym for any quotations used in publication or at conference presentations, to maintain confidentiality and anonymity. The interview schedule (appendix 17) will be informed by the literature review and the information provided in the questionnaire. The interviews will take place in a setting of the participant’s choice; at home or in a private interview room in the hospital.

3.5 Data Analysis

3.5.1 Quantitative Data Analysis
The randomisation will be stratified according to family history of atopic eczema, to ensure that the groups are homogeneous. Data will be double-entered into SPSS for analysis, with the two data files cross-checked in SPSS for errors. The main analyses will be descriptive, involving the estimation of recruitment rates, attrition rates, non-compliance rates, means and standard deviations of primary and secondary outcomes by group at baseline and 4 weeks, and 95% confidence intervals for differences of means of primary and secondary outcomes between groups at 4 weeks. Primary and secondary outcomes at 4 weeks will also be compared by group adjusted for baseline values using analysis of covariance. Inferential results will be interpreted cautiously: the study will not be powered to detect significant differences, as the main aim is to assess proof of concept, feasibility and inform a full-scale trial. Statistical support has been obtained and will be provided by Dr Malcolm Campbell, Lecturer in Statistics at The University of Manchester, who has been part of the research team in a previous skincare study and has provided support for other pilot and full-scale randomised trials.

3.5.2 Qualitative Data Analysis
Qualitative data will be managed using NVIVO software and will be subjected to framework analysis. Framework analysis is a matrix-based method of data analysis which uses five distinct phases; familiarisation, developing a thematic framework, indexing, charting, mapping and interpretation (Ritchie and Spencer, 1994). It is an on-going inductive and iterative process. The framework is developed early on in the process; at
each stage the framework is redefined and conceptualised. Each phase is transparent which enhances rigour.

**Familiarisation**: The transcripts will be read independently multiple times so that the researchers can become immersed in the data. Any field notes taken by the interviewer will also become part of the data.

**Developing a thematic framework**: Notes and emerging themes will have arisen from the familiarisation process. Recurring ideas will be grouped together in order to develop a conceptual framework.

**Indexing**: In this phase, the emerging conceptual framework is compared to the original transcripts to explore how it ‘fits’ (Ritchie and Spencer, 1994). This process will be carried out using the computer qualitative data analysis software NVivo. The whole transcript can be uploaded into NVivo, meaning that the researcher can compare the transcript with the conceptual framework so that the context of the original data is not lost.

**Charting**: Following indexing, we will summarise the data into thematic charts. This will involve adding short summarising statements in the relevant theme section of the thematic framework to create a chart. All of the relevant data can then be seen together, aiding understanding interpretation of the data as a whole (Ritchie and Spencer, 1994).

**Mapping and interpretation**: This phase synthesises the data. At this stage, the summaries in the charting phase are examined against the original data, the themes are reconsidered and more may emerge, and the framework may be developed further. This is a cyclical process as each part of this phase may result in a change to the next part and so on until a final theoretical framework is agreed.

4. **Safety issues**

4.1 **Adverse Event Definitions and Reporting**

An adverse event (AE) is defined as any untoward medical occurrence in a participant recruited to the trial, which does not necessarily have a causal relationship with the treatment (International Conference on Harmonisation, 1996). For this trial, the following episodes are expected neonatal adverse events which will be recorded, but not reported for further investigation:

- Jaundice
- Weight loss
- Feeding difficulties

An adverse reaction (AR) is defined as any untoward and unintended response in a participant recruited to the trial which is related to the oil.

A serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR) is defined as any adverse event, adverse reaction or unexpected adverse reaction, respectively, that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, consists of a congenital anomaly or birth defect, or is otherwise considered medically significant by Professor of Dermatology Michael Cork, Professor of Midwifery Dame Tina Lavender or Senior Lecturer in Neonatology Dr Suresh
Victor (International Conference on Harmonisation, 1996). We do not expect any serious adverse reactions.

The following episodes are expected infant serious adverse events which will be recorded, but not reported for further investigation:

- Admission to hospital for phototherapy treatment (jaundice)
- Admission to hospital for weight loss
- Admission to hospital for feeding difficulties
- Admission to hospital for viral illness
- Admission to hospital for illness resulting from bacterial infection
- Admission to hospital for elective surgery

Adverse events will be recorded on the study documentation (appendices 9 and 10) and collated for each participant on adverse event record forms.

Adverse events will be reviewed at the end of the pilot study by the Trial Steering Committee and the Sponsor.

A SAE will be reported to the Sponsor and the Research Ethics Committee where, in the opinion of co-investigators Michael Cork, Suresh Victor or Dame Tina Lavender, the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Serious adverse events will be assessed by the Sponsor according to their Standard Operating Procedure for Pharmacovigilance. Reporting to the MHRA does not apply in this case. We anticipate that any suspected unexpected serious adverse reactions will be reviewed by the Sponsor within 7 working days and the review passed to the Chair of the Trial Steering Committee for further action. The Chair of the Trial Steering Committee will form an opinion and recommend a course of action, for the Trial, to the Investigators.

4.2 Cutaneous adverse event on-call service

The chances of an adverse event occurring following the application of topical oil for 28 days are small. However we have in place an on-call dermatologist arrangement that is at least as good as any trial of a pharmaceutical product for treating the skin.

Professor Michael Cork is a consultant dermatologist who runs a large paediatric dermatology clinic at Sheffield Children’s Hospital. He will be available on-call 24 hours a day during the trial, to give advice to the research team or other healthcare professionals. If Professor Cork is not available then Dr. Manar Moustafa, who is a senior staff-grade in dermatology at Sheffield Children’s Hospital will also be available to provide advice. This on-call service is the same service that is provided for patients and volunteers for clinical studies in Sheffield.

If an inter-current skin condition occurs in an infant during this trial, the most likely scenario is that it would be unrelated to the trial. Following a phone call from the investigator, photographs can be sent via email or Skype can be used if needed. Professor Cork will ask questions to determine if it is likely that the skin condition is related to
participation in the trial. If it is considered that it were / could be related to participation in the trial, Professor Cork will make an immediate decision regarding further participation in the trial. He will then offer advice regarding any treatment that may be required. Professor Cork is able to receive emailed photographs of skin from anywhere via his laptop computer. This facility is not usually needed, as a description of the skin appearance is usually sufficient to make a clinical assessment.

Professor Cork’s decision will be brought to the attention of the Trial Steering Committee who will determine whether treatment allocation should continue in these infants.
Appendix 27: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
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Figure 6: Study Overview
4.3 Withdrawal from treatment / Intention to treat analysis

Any data collected up to the point of the following events will be included in the analysis under the intention to treat principle:

a) Phototherapy for Jaundice: If participants are readmitted to the hospital for jaundice to receive phototherapy treatment, they will be required to stop using oil, and will therefore no longer comply with the intervention.
b) Parent / legal guardian withdraws consent to continue treatment.
c) Changes in the condition of the skin that are not acceptable to the parent / legal guardian.
d) Intercurrent illness preventing further treatment.
e) Development of serious disease.
f) Any change in the infant’s condition that justifies the discontinuation of treatment in the clinician’s opinion.

If a parent / legal guardian wishes to withdraw an infant from trial treatment, the investigator will attempt to document the reason and explain the value of remaining on trial follow up and, if willing, to still have data collected as per the trial schedule. Generally, follow up will continue unless the participant explicitly also withdraws consent for follow up. Following withdrawal from trial treatment, participants will be treated according to parental preference.

If the parent / legal guardian who voluntarily withdraws from the trial has previously consented to follow up in the trial, data up to the time of withdrawal will be included in the trial if anonymised. If the parent / legal guardian explicitly state their wish not to contribute further data to the study, the investigator should document this (appendix 11).

In other situations the investigators will document the reasons for withdrawal (appendix 12).

**Infants will be requested to return for follow up, regardless of whether treatment is discontinued, as per intention to treat analysis. This will be regardless of reason for discontinuation.**

4.4 Stopping Rules

We do not anticipate any reason for stopping the trial as this is a treatment commonly recommended, and the treatment period is short. However, this will be reviewed with regard to adverse events, as necessary. Any adverse events will be considered initially by Professor Michael Cork. If there are any concerns with the type of adverse events arising, an emergency Trial Steering Committee meeting will be called (possibly through electronic means at discretion of Chair). The Trial Steering Committee consists of independent clinical specialists (neonatal, midwifery, dermatology, clinical trials) and users (see Trial Management Section below). In these circumstances, the Committee will decide whether to continue, monitor or stop the trial.
4.5 Methods to reduce bias

The study will be assessor-blinded, and the two intervention groups will be participant-blinded to which oil they are using. Parents will be advised not to use oil on their infant in the ten hours prior to time of appointment on the day of assessment in order to maintain assessor blinding. Participants will be randomised, aiming to provide homogeneity across the study groups. Analysis will be confirmed by two members of the research team, with input from a Statistician. There will be user involvement throughout and input from the Trial Steering Committee.

4.6 Trial Management

The trial will be sponsored by The University of Manchester with dermatology and skin barrier technical support from The University of Sheffield. A trial steering committee has been formed, with an independent Chair, and representation from a Clinical Trials Unit and parent group.

The trial will be managed day to day by the lead investigator, Alison Cooke, as part of a Doctor of Philosophy (Ph.D.) degree, supervised by Professor of Midwifery Dame Tina Lavender and co-supervised by Professor of Dermatology Michael Cork and Neonatologist Dr Suresh Victor. Randomisation will be performed independently via the Nottingham Clinical Trials Unit (CTU). An identified research midwife will contact the CTU to obtain the randomisation confirmation and will inform participants of their treatment group to maintain assessor blinding. Data collection and data analysis will be performed by Alison Cooke, under the supervision of the Trial Management Group.

Roles:
Alison Cooke: Principal Investigator. Role includes recruitment, consent, data collection, data analysis, and dissemination.
Professor Dame Tina Lavender: Primary supervisor. Role includes supervision, assessment of adverse events, data analysis, and dissemination.
Professor Michael Cork: Co-supervisor. Role includes supervision, assessment of adverse events, data analysis, and dissemination.
Dr Suresh Victor: Co-supervisor. Role includes supervision, assessment of adverse events, data analysis, and dissemination.
Skin Research Technician (John Chittock). Role includes use of spectroscopy equipment, training Alison Cooke in use of spectroscopy equipment.
Research Midwife (TBC). Role includes contacting CTU, informing participants of randomised treatment group, demonstrating administration of oil for protocol compliance, provision of oil to intervention participants.

The Trial Steering Committee will include:
Independent Members:
Chair: Dr Mark Turner, Senior Lecturer Neonatology, Liverpool Women's Hospital
Dr Kevin Hugill, Senior Lecturer Neonatal Nursing, University of Central Lancashire
Dr Vinod Elangasinghe, Senior Dermatologist, Chesterfield Royal Hospital
Gill Singleton, Senior Midwife, Tameside District General Hospital
Margaret Cox, Chief Executive Officer, National Eczema Society
Professor Lelia Duley, Nottingham Clinical Trials Unit
Lisa Rowe, Parent Representative:
Trial Management Group:
Professor Dame Tina Lavender, Professor of Midwifery, The University of Manchester
Professor Mike Cork, Professor of Dermatology, The University of Sheffield
Dr Suresh Victor, Senior Lecturer in Neonatology, The University of Manchester
Dr Malcolm Campbell, Statistician, The University of Manchester
Alison Cooke, Midwife, Doctoral Research Training Fellow

We will actively seek to encourage user involvement. We have the benefit of user involvement from within a wider programme of research for infant skincare through the Professor of Midwifery Dame Tina Lavender. These users have already been consulted and will continue to contribute throughout the study process. Users will particularly be involved with regard to Patient Information Leaflets, diagrammatic instructional leaflets and the recruitment and consent processes. The MCRN has a parents group already actively involved in research processes. This group will be consulted. The research team have also received advice on, and support for, the proposed study from the National Eczema Society.

4.7 Regulatory Issues

This study uses oils that are already recommended to new parents by health professionals for the treatment or prevention of infant dry skin and for infant massage. This is not a trial of an investigational medicinal product. Nevertheless all parties to the trial will conduct the trial to the same standards as a clinical trial of an investigational medicinal product. Ethical approval will be obtained prior to recruitment. The study will be conducted in accord with the Declaration of Helsinki, the terms of a favourable ethical opinion, the Standard Operating Procedures of the Sponsor and the NHS Research Governance Framework.

4.8 Ethical Issues

We aim to recruit 100 healthy term infants to the pilot trial. It is essential to perform assessments of healthy term infants' skin. Previous research has studied mice or adults. Often the use of adult data to inform the treatment of children is inappropriate due to physiological differences between adults and children (Edwards and McNamee, 2005, Medical Research Council, 2004). Children are not small adults (Medical Research Council, 2004). Developing effective treatments for children will often necessitate testing on children (Yeung, 2007).

The clinical advice currently given to parents is to use olive oil or sunflower oil for the prevention or treatment of infant dry skin or for massage. It is not confirmed by any evidence whether this practice is good for, or harmful to, infants. Furthermore, the advice given to parents by health professionals is conflicting with regard to which oil, if any, to use. Therefore this investigation is required in order to confirm that clinical practice is evidence based and consistent. This is a minimal harm study. We are not applying any oil to infant skin that is not already currently recommended.

There is a burden on parents to bring their infant to the local hospital for the second assessment. This is unavoidable as the infrared spectroscopy equipment is non-portable. Travel expenses will be paid to participants, together with a voucher to remunerate and
thank participants for their time. The remuneration offered will be adjusted according to whether the participants have attended the hospital for follow up assessment (higher remuneration) or had a home visit (lower remuneration).

4.8.1 Confidentiality and Anonymity
The participants will be advised that data will be held securely, and that all personal information will be kept strictly confidential. All participants will be given a study number and identifying personal details will be kept separately from this in a locked cabinet within a locked room at the research centre. Pseudonyms will be used for the purposes of transcription and verbatim quotation within any publication. Recorded tapes will be destroyed after transcription in the presence of the complete research team.

4.9 Progression Rules
The pilot will lead to development of a full trial if certain conditions are met:
1. There is convincing proof of concept as agreed by the Trial Steering Committee.
2. If compliance to treatment regime is greater than 80%.
3. If loss to follow up to at least one of the primary outcomes is less than 10%.
4. If the sample size calculation suggests that a full trial would be feasible and likely to achieve an important result within 3 to 5 years.
5. If the study appears to be acceptable to the majority of consumers.

4.10 Dissemination
The results of the study will be published in a professional peer reviewed journal, and presented at local, national and international conferences. All participants will be offered a copy of the results.

5. Conclusion
This work aims to inform the feasibility of running a full RCT. A full trial has the potential to influence clinical practice for midwives, infant health professionals and dermatologists, within 5 years of completing the pilot. Results from a full trial will equip health professionals with research based evidence to inform new mothers about infant skincare. The programme of work may also provide a potential benefit to infants with regard to maintenance of healthy skin and avoidance of childhood skin diseases including atopic eczema.

5.1 Benefits to the NHS
The potential benefits of this study include novel information about infant skin integrity and an improved understanding of the applicability of measurement techniques in this area. The investigator will be able to publish this data irrespective of the results of the main trial. This is translational research which makes scientific research applicable to the population. A full trial will have national and international relevance for infant skincare management. Direct NHS costs for managing allergic disease including atopic eczema are estimated to be in excess of £1 billion per year (Gupta et al., 2004). The indirect costs to the NHS are unknown; atopic eczema accounts for 15-86% of parental sleep disruption, associated with resulting anxiety and depression (Meltzer and Moore, 2008). A full trial
Appendix 27: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
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may contribute to the development of prevention regimens for atopic eczema and other allergic diseases. This would be of benefit to patients, their carers, and the NHS.

5.2 Study Timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>RCT</th>
<th>Nested Qualitative Study</th>
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<tbody>
<tr>
<td><strong>Month 1-5</strong></td>
<td>Develop working protocol</td>
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<tr>
<td>January 2013 to</td>
<td>Trial Steering Committee meeting</td>
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<tr>
<td>May 2013</td>
<td>Apply for ethical approval</td>
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<tr>
<td><strong>Month 6-8</strong></td>
<td>Liaise with ethics committee regarding any changes needed for study</td>
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<tr>
<td>June to August 2013</td>
<td>Inform all hospital staff about the study</td>
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<tr>
<td><strong>Month 9-14</strong></td>
<td>Recruit participants</td>
<td>Recruit participants</td>
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<tr>
<td>September 2013 to</td>
<td>Conduct assessments</td>
<td>Collect qualitative data from questionnaires and interviews</td>
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<tr>
<td>November 2013</td>
<td>Collect data from assessments and questionnaires</td>
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<td></td>
<td>Input data to SPSS</td>
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<tr>
<td><strong>Month 12-14</strong></td>
<td>Preliminary analysis of recruitment and analysis of follow up uptake</td>
<td>Recruit participants</td>
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<tr>
<td>December 2013 to</td>
<td>for infrared spectroscopy</td>
<td>Collect qualitative data from questionnaires and interviews</td>
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<tr>
<td>February 2014</td>
<td>Reassess sample size if necessary to obtain required number of</td>
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<td></td>
<td>spectroscopy measurements</td>
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<td></td>
<td>Trial Steering Committee meeting</td>
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<td></td>
<td>Continue to recruit participants and collect data from assessments</td>
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<td></td>
<td>and questionnaires</td>
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<td></td>
<td>Continue to input date to SPSS</td>
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<tr>
<td><strong>Month 15-20</strong></td>
<td>Continue to recruit participants if necessary</td>
<td>Continue to recruit participants if necessary</td>
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<tr>
<td>March 2014 to</td>
<td>Continue to input data to SPSS</td>
<td>Transcribe and code data from interviews</td>
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<td>August 2014</td>
<td>Cross check data in SPSS</td>
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<td>Data Analysis</td>
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<tr>
<td><strong>Month 21-27</strong></td>
<td>Writing up results</td>
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<tr>
<td>September 2014 to</td>
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<td>March 2015</td>
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<tr>
<td><strong>Month 28 onwards</strong></td>
<td>Report findings</td>
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<td>Dissemination</td>
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Reference List


Appendix 27: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
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## Appendices

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Appendix 28: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Qualitative Interview Schedule: Version 1, 13/03/13

Study Title: OBSeRvE: Oil in Baby SkincaRE study
The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

INTERVIEW SCHEDULE

BEFORE THE INTERVIEW
- Explain that matters discussed will not affect level of care
- Explain tape recording and transcription
- Explain unique study number (confidentiality)
- Explain use of pseudonyms (anonymity)
- Explain can stop at any time
- Explain that the interview is intended to take no longer than one hour
- Explain can refuse to answer a question
- Give opportunity to ask questions
- Check consent

CHECK TAPE WORKING

In line with the qualitative approach of the study, the interview will be semi-structured and response led. The following areas will be explored however, with these key questions guiding the interview:

ACCEPTABILITY
- How did you feel about your baby taking part in this type of study?
- Was there anything particular you liked/didn’t like about being in the study?
- What did you think about the equipment that was used in the study to take skin measurements from your baby?
- What did you think about the length of time your baby was in the study?
- Are there any ways you think we could improve the study?

PRACTICALITY / CONVENIENCE
- How did being in the study fit in with your daily activities?
- How did you feel about the time spent having the tests done?
- How did you find the length of time it took you to fulfil the requirements of the study?
- How easy did you find following the treatment routine? How did you feel about the time spent using oil (if applicable)?
Appendix 28: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Qualitative Interview Schedule: Version 1, 13/03/13

BSeRvE: Oil in Baby SkincaRE Study

PROTOCOL COMPLIANCE

- How easy was it for you to follow all the instructions required for your part of the research?
- How easy was it for you to follow the instructions for the length of time for which your baby was in the study?

GROUP ALLOCATION

- What did you think of the treatment you were allocated to?
- Did you think about the other treatments? Would you have preferred to use a different treatment? Why?

INFORMATION PROVISION

- What did you think about the study participant information sheet you were provided with?
- How easy to understand did you find it?
- Did it cover everything you wanted to know about the study?
- Was there anything you felt should have been included that wasn't?
- What did you think about the diagrams?

Prompts to encourage depth:

- In what way?
- What was it like?
- Can you explain that to me?
- Why do you think that?
- What does it mean to you?

FOLLOWING THE INTERVIEW

- The researcher will complete a reflexive diary
- The researcher will advise the participant that a summary of the findings will be sent to her for verification
- The researcher will thank the participant for her time
Appendix 29: MHRA confirmation of non-CTIMP study

From: Clinical Trial Helpline <ctdhelpline@mhra.gsi.gov.uk>
Sent: 04 June 2013 17:42
To: Alison Cooke
Subject: RE: Scope - protocol review: The use of Oil in Baby Skincare (OBSERVE) Pilot Study

Notification that a Clinical Trial Authorisation (CTA) is not required

Dear Ms A Cooke,

Thank you for your email dated 23rd May 2013.

I can confirm that your proposal is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC and no submission to the Clinical Trials Unit at the MHRA is required.

Kind regards

Clinical Trial Helpline
MHRA

From: Alison Cooke [mailto:Alison.Cooke@manchester.ac.uk]
Sent: 23 May 2013 15:37
To: Clinical Trial Helpline
Subject: Scope - protocol review: The use of Oil in Baby Skincare (OBSERVE) Pilot Study

I attach a copy of the Protocol for the above proposed study. Please could you confirm the status of the study? We believe that this is a non-CTIMP but have been asked to confirm this with you by our University Ethics Team.

Kind regards

Alison Cooke

Best wishes

Alison Cooke

Midwife / Ph.D. Student (NIHR Doctoral Research Fellow)
School of Nursing, Midwifery and Social Work
The University of Manchester

Jean McFarlane Building Room 4.313
Oxford Road
Manchester
M13 9PL

T. 0161 306 7758
E. Alison.Cooke@manchester.ac.uk

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For more information on the Department of Health's email policy, click

http://www.dh.gov.uk/DHTermsAndConditions/fs/en?CONTENT_ID=4110945&chk=x1C3Zw
Appendix 30

Correspondence providing favourable ethical opinion from Greater Manchester East Research Ethics Committee
19 July 2013

Mrs Alison Cooke, Midwife / Ph.D. Student
The University of Manchester
Oxford Road
Manchester
M13 9PL

Dear Mrs Cooke

Study title: The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby's skin barrier function

REC reference: 13/NW/0512
IRAS project ID: 120090

The Research Ethics Committee reviewed the above application at the meeting held on 16 July 2013. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Assistant Co-ordinator Sian Goodwin, nrescommittee.northwest-gmeast@nhs.net.

Discussion

You were commended on a very well presented and thorough application. It was noted that the issue of coercion has been addressed and avoided well. The plan to translate the documentation and results where necessary was praised.

The use of user groups was highlighted and the committee were of the view that this had been beneficial given the high standard of the documentation. The committee sought clarification on the recruitment process. It was clarified that parents will have been given a summary of what is involved in the study between 1 and 5 weeks prior to it starting, they will also get the full information sheet at least an hour before consent is taken. It was suggested by the committee that the information sheet and consent form should be titled in a way that highlights that the consent is being given for the parent and the baby. You agreed this would be possible.
The committee noted that other skin products shouldn't be used during the study and questioned whether this was on the affected area or the entire body. It was confirmed that it is only the affected area that other skin products shouldn't be used on. This will be explained to the parents at the time of consent. Parents will be asked frequently if they have used any other products and if they have this will be taken into consideration a confounding variable.

The committee raised the point that the parents may be able to decipher which product they have been given. You accepted that this a possibility but stressed that they will be presenting the products in opaque bottles labelled X or Y in an attempt to avoid unblinding the trial.

The committee questioned how the safety of the products will be monitored. It was stressed that there is no evidence that any of the components are likely to increase incidence of jaundice or any other skin disorders. If there were any unusual findings they would be reported to the steering committee.

A concern was raised around whether the results of this trial could be generalised given the level of contents disparities between oils currently on the market. It was confirmed that the research team have acknowledged this and in the long term they would need to lobby for the labelling of oils.

**Ethical opinion**

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

- Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at [http://www.rdforum.nhs.uk](http://www.rdforum.nhs.uk).

**Ethical review of research sites**

**NHS Sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.
For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

**Additional conditions**

1. In the information sheet where it asks 'Can I change my mind?' Please answer yes followed by the relevant information.

2. Please re-title the participant information sheet and consent form to make it clear that the mother is consenting on behalf of her and her baby.

3. The information sheet needs to say that the baby’s GP will be informed about participation in the study with the mother’s consent.

4. Amend the consent form to include that tissue samples will be taken from the baby and will be destroyed at the end of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

*It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).*

**Approved documents**

The documents reviewed and approved at the meeting were:

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<td>Investigator CV</td>
<td>Cooke</td>
<td>04 June 2013</td>
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<td>Letter from Sponsor</td>
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<td>Other: Funding confirmation letter</td>
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<td>Other: Summary CV for Supervisor</td>
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<td>Cork</td>
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<td>Victor</td>
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<tr>
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<td>Participant Information Sheet: OBSeRvE PIS</td>
<td>3</td>
<td>15 June 2013</td>
</tr>
</tbody>
</table>
Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/NW/0512 Please quote this number on all correspondence
We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee’s best wishes for the success of this project.

Yours sincerely

PP:
Mr Francis Chan
Chair

Email: nrescommittee.northwest-gmeast@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: Mrs Lynne Macrae, University of Manchester

Dr Lynne Webster, Central Manchester NHS Foundation Trust
## NRES Committee North West - Greater Manchester East

### Attendance at Committee meeting on 16 July 2013

#### Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Mr David Asher</td>
<td>Retired Community Locum Pharmacist</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mr R Trevor Benn</td>
<td>Retired Statistician</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Mr James Burns</td>
<td>Retired</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Mr Francis Chan</td>
<td>Consultant Orthopaedic Surgeon</td>
<td>Yes</td>
<td>Chair</td>
</tr>
<tr>
<td>Dr Jacqueline Crowther</td>
<td>Research Assistant</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Dr Mary Dolan</td>
<td>Nurse Lecturer</td>
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<tr>
<td>Dr Michael Hollingsworth</td>
<td>Retired Senior Lecturer in Pharmacology</td>
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<tr>
<td>Mr Christopher Houston</td>
<td>Lay Member</td>
<td>Yes</td>
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</tr>
<tr>
<td>Mr Simon Jones</td>
<td>Specialist Podiatrist - Paediatrics</td>
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<td>Dr Priyadarshan Joshi</td>
<td>Consultant Psychiatrist</td>
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<td>Dr Philip Lewis</td>
<td>Consultant Cardiologist</td>
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<td>Professor Janet Marsden</td>
<td>Professor of Ophthalmology and Emergency Care</td>
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<td></td>
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<tr>
<td>Mrs Clementinah Rooke</td>
<td>Postgraduate Researcher Bank Staff Nurse (RMN)</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Mrs Mary Speake</td>
<td>Clinical Research Practice Educator</td>
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#### Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
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<tbody>
<tr>
<td>Nicola Burgess</td>
<td>Assistant Committee Co-ordinator</td>
</tr>
<tr>
<td>Sian Goodwin</td>
<td>Acting Assistant Co-ordinator</td>
</tr>
<tr>
<td>Ian Hodge</td>
<td>Student Nurse (Observer)</td>
</tr>
<tr>
<td>Benjamin Speake</td>
<td>Student (Observer)</td>
</tr>
</tbody>
</table>
31 July 2013

Mrs A Cooke
Midwife / Ph.D. Student (NIHR Doctoral Research Fellowship)
The University of Manchester
Room 4.313
Jean McFarlane Building
The University of Manchester
Oxford Road
Manchester
M13 9PL

Dear Mrs Cooke

Study title: The use of Oil in Baby SkincaRE (OBSerVe) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function

REC reference: 13/NW/0512
IRAS project ID: 120090

Thank you for your email of 29 July 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 22 July 2013.

Documents received
The documents received were as follows:

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A Research Ethics Committee established by the Health Research Authority
### Approved documents
The final list of approved documentation for the study is therefore as follows:

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<tr>
<td>Letter from Sponsor</td>
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<td>14 June 2013</td>
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<tr>
<td>Other: Funding confirmation letter</td>
<td></td>
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<td>Summary/Synopsis</td>
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You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.
Yours sincerely

Signed on behalf of
Elaine Hutchings
Committee Co-ordinator

E-mail: nrescommittee.northwest-gmeast@nhs.net

Copy to: Ms Lynne MacRae, University of Manchester

Dr Lynne Webster, Central Manchester NHS Foundation Trust
28 August 2013

Mrs A Cooke  
Midwife / Ph.D. Student (NIHR Doctoral Research Fellowship)  
University of Manchester  
Room 4.313 - Jean McFarlane Building  
The University of Manchester  
Oxford Road  
Manchester  
M13 9PL

Dear Mrs Cooke

Study title: The use of Oil in Baby SkincaRE (OBSerVe) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function

REC reference: 13/NW/0512
IRAS project ID: 120090

Thank you for your email of 28 August 2013. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 22 July 2013

Documents received
The documents received were as follows:

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Approved documents
The final list of approved documentation for the study is therefore as follows:

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<tr>
<td>Summary/Synopsis</td>
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<td>18 January 2013</td>
</tr>
</tbody>
</table>

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor’s responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

13/NW/0512 Please quote this number on all correspondence

Yours sincerely

Signed on behalf of
Elaine Hutchings
Committee Co-ordinator

E-mail: nrescommittee.northwest-gmcentral@nhs.net

Copy to:    Ms L MacRae - University of Manchester

                                   Dr L Webster - Central Manchester NHS Foundation Trust
Appendix 31

Correspondence providing favourable ethical opinion for Substantive Amendment no.1 from Greater Manchester East Research Ethics Committee
19 December 2013

Mrs A Cooke
Midwife / Ph.D. Student (NIHR Doctoral Research Fellowship)
University of Manchester
Room 4.313
Jean McFarlane Building
The University of Manchester
Oxford Road
Manchester
M13 9PL

Dear Mrs Cooke

Study title: The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function

REC reference: 13/NW/0512
Amendment number: Substantial amendment 1
Amendment date: 30 November 2013
IRAS project ID: 120090
To add one further analysis measurement with regard to the D-Squame discs

The above amendment was reviewed by the Sub-Committee in correspondence and finalised on 18 December 2013.

Ethical opinion

The Sub-Committee found no ethical issues with this amendment

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

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Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

13/NW/0512: Please quote this number on all correspondence

Yours sincerely

Signed on behalf of
Mr Francis Chan
Chair
E-mail: nrescommittee.northwest-gmeast@nhs.net

Enclosure: List of names and professions of members who took part in the review

Copy to: Dr L Webster - Central Manchester NHS Foundation Trust

Ms L Macrae - University of Manchester
NRES Committee North West - Greater Manchester East

Attendance at Sub-Committee of the REC meeting on 18 December 2013, held by correspondence

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<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
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<tbody>
<tr>
<td>Mr Francis Chan</td>
<td>Consultant Orthopaedic Surgeon</td>
<td>Expert</td>
</tr>
<tr>
<td>Dr Michael Hollingsworth</td>
<td>Retired Senior Lecturer in Pharmacology</td>
<td>Lay</td>
</tr>
<tr>
<td>Professor Janet Marsden</td>
<td>Professor of Ophthalmology and Emergency Care</td>
<td>Expert</td>
</tr>
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</table>

Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miss Siân Goodwin</td>
<td>Acting REC Assistant</td>
</tr>
</tbody>
</table>
Appendix 32

Correspondence providing favourable ethical opinion for Substantive Amendment no.2 from Greater Manchester East Research Ethics Committee
14 February 2014

Mrs A Cooke
Midwife / Ph.D. Student (NIHR Doctoral Research Fellowship)
University of Manchester
Jean McFarlane Building – room 4.322b
The University of Manchester
Oxford Road
Manchester
M13 9PL

Dear Mrs Cooke

Study title: The use of Oil in Baby SkincaRE (OBSERve) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function

REC reference: 13/NW/0512
Amendment number: Substantial Amendment 2
Amendment date: 05 February 2014
IRAS project ID: 120090

The above amendment was reviewed by the Sub-Committee in correspondence and finalised on 13 February 2014. This amendment covered various areas including change of inclusion criteria; screening changes; change to the number of interviews taking place; and minor additions to the protocol.

Ethical opinion

The Sub-Committee found no ethical issues with the elements included in this Substantial Amendment. The Sub-Committee commented that it is an improvement to the research that participants are approached directly by the researcher rather than through a member of the clinical care team.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.
Approved documents

The documents reviewed and approved at the meeting were:

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<th>Document</th>
<th>Version</th>
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<td>23 January 2014</td>
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Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

13/NW/0512: Please quote this number on all correspondence

Yours sincerely

Signed on behalf of

Mr Francis Chan
Chair

E-mail: nrescommittee.northwest-gmeast@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr L Webster - Central Manchester NHS Foundation Trust

Ms L MacRae – The University of Manchester
NRES Committee North West - Greater Manchester East

Attendance at Sub-Committee of the REC meeting held by correspondence and finalised on 13 February 2014

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Francis Chan (Chair)</td>
<td>Consultant Orthopaedic Surgeon</td>
<td>Expert</td>
</tr>
<tr>
<td>Dr Michael Hollingsworth</td>
<td>Retired Senior Lecturer in Pharmacology</td>
<td>Lay</td>
</tr>
<tr>
<td>Professor Janet Marsden</td>
<td>Professor of Ophthalmology and Emergency Care</td>
<td>Expert</td>
</tr>
</tbody>
</table>

Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sian Goodwin</td>
<td>REC Assistant</td>
</tr>
</tbody>
</table>
Appendix 33

Correspondence providing favourable ethical opinion from Central Manchester NHS Foundation Trust Research and Development department
Dear Miss Cooke

PIN: R03317 (Please quote this number in all future correspondence)
CSP Reference: 120090
REC Reference: 13/NW/0512
Research Study: The use of Oil in Baby SkincaRE (OBSeRVe) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function

Thank you for submitting the above study for NHS R&D permission. University of Manchester is the Sponsor for this study which is on the NIHR portfolio.

I am pleased to confirm that the Research Office has now received all necessary documentation, and the appropriate governance checks have been undertaken. This letter is issued subject to the research team complying with the attached conditions, Trust SOPs, the DH Research Governance Framework, and any other applicable regulatory requirements. This approval is in relation to the documentation listed.

CMFT are required to report whether the research was initiated within 70 days or provide valid reasons for not doing so. The target date for this study is listed below:

- NIHR 70 Day from Valid Submission to 1st Patient Recruited: 16 September 2013

Further information regarding the NIHR target can be found on the intranet.
R&D Approval Letter

Please update CRIMSON with the date when the first patient was recruited. If you or one of your team requires training on CRIMSON please contact Michael.Horrocks@cmft.nhs.uk

I would like to take this opportunity to wish you well with your research.

Yours sincerely

Lorraine Broadfoot
Research Operations Manager
Date: 2/8/2013

Encs. NHS SSI form

cc. Sarah Leo Divisional Research Manager
Dame Tina Lavender School of Nursing

Documents Acknowledged/Approved

<table>
<thead>
<tr>
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<th>Version</th>
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<td>29 July 2013</td>
</tr>
<tr>
<td>Interview Schedules/Topic Guides</td>
<td>1</td>
<td>13 March 2013</td>
</tr>
<tr>
<td>Investigator CV</td>
<td>Cooke</td>
<td>04 June 2013</td>
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<tr>
<td>Letter from Sponsor</td>
<td></td>
<td>14 June 2013</td>
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<td>Other: Summary CV for Supervisor</td>
<td>Lavender</td>
<td>22 May 2013</td>
</tr>
<tr>
<td>Other: Second Supervisor CV</td>
<td>Cork</td>
<td>19 June 2013</td>
</tr>
<tr>
<td>Other: Third Supervisor CV</td>
<td>Victor</td>
<td>24 May 2013</td>
</tr>
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<td>Other: Poster</td>
<td>5</td>
<td>29 July 2013</td>
</tr>
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<td>Other: Case Report Form 1</td>
<td>2</td>
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<td>Other: Case Report Form 2</td>
<td>2</td>
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</tr>
<tr>
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<td>Other: Case Report Form</td>
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<tr>
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<td>29 July 2013</td>
</tr>
<tr>
<td>Participant Information Sheet: OBSerVe PIS</td>
<td>3</td>
<td>15 June 2013</td>
</tr>
<tr>
<td>Participant Information Sheet</td>
<td>4</td>
<td>29 July 2013</td>
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<tr>
<td>Participant Information Sheet: Summary</td>
<td>2</td>
<td>29 July 2013</td>
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<td>Protocol</td>
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<td>1</td>
<td>21 February 2013</td>
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<td>Questionnaire: Non Validated: Weekly telephone</td>
<td>1</td>
<td>08 June 2013</td>
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<td>Questionnaire: Baseline</td>
<td>2</td>
<td>29 July 2013</td>
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<td>REC application</td>
<td>120090/4668/09/1/439</td>
<td>20 June 2013</td>
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<td>Referees or other scientific critique report</td>
<td>SL1</td>
<td>10 April 2013</td>
</tr>
<tr>
<td>Referees or other scientific critique report</td>
<td>SL2</td>
<td>22 April 2013</td>
</tr>
<tr>
<td>Summary/Synopsis</td>
<td>1</td>
<td>18 January 2013</td>
</tr>
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</table>
Conditions of Approval:-

- All researchers involved in the study need to have received training appropriate to their role covering aspects of Research Governance or Good Clinical Practice (GCP). Trust policy states GCP training needs to be renewed every 3 years.

- The Research Office must be informed of: (please forward copies of amended documents by email)
  - The actual start date of the project
  - Any changes to the protocol throughout the course of the project
  - Any amendments sent to the MHRA or Research Ethics Committee
  - Any changes to the management of the project
  - Any extensions to the project, and associated additional funding, if applicable.

- The Research Office must be notified immediately of all Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) via email adverse.events@cmft.nhs.uk or Research Office fax: 276 5766 and/or by copy of official notification to the regulatory authorities (NRES, MHRA as applicable).

- All research taking place on CMFT Trust premises is subject to the Trust monitoring programme, either as part of the annual 10% audit requirement or "triggered" monitoring. The Chief and/or Principal Investigator is required to make him/her self available for any monitoring visit, on a mutually agreed date.

- All Principal Investigators are required to complete and submit an annual self-assessment at the request of the Research Office.

- All Principal Investigators are required to provide recruitment (accrual) data to the Research Office monthly.

- The Research Office must be given a minimum three months' notice, in writing, if the Principal Investigator leaves the employment of CMFT Trust.

- The Research Office must receive immediate notification if the Principal Investigator is unable to continue to fulfil his/her duties as PI for other reason e.g. long-term sickness

- Any evidence of fraud &/or misconduct must be immediately brought to the attention of the Research Office either via the Incident Reporting system, or by direct communication.

Failure to comply with any of the above may result in withdrawal of approval for the project and the immediate cessation of the research. Persistent failure to comply may result in disciplinary action.
Appendix 34

Correspondence providing favourable ethical opinion for Substantive Amendment no.1 from Central Manchester NHS Foundation Trust Research and Development
Dear Alison,

Re: R03317 / CSP 120090: The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function

REC Reference: 13/NW/0512
Principal Investigator: Alison Cooke
Amendment Number: Substantial Amendment 1
Amendment Date: 30 November 2013

Thank you for your correspondence informing the department of an amendment to the above project; we acknowledge receipt of the following and approve the amendment.

<table>
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<tr>
<th>Document</th>
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<th>Dated</th>
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<tbody>
<tr>
<td>NRES Amendment Approval Letter</td>
<td>Substantial Amendment 1</td>
<td>19 December 2013</td>
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<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>Substantial Amendment 1</td>
<td>30 November 2013</td>
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<tr>
<td>Protocol</td>
<td>7</td>
<td>29 November 2013</td>
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</table>

We have amended the Trust’s database to reflect these changes as required.

I would like to take this opportunity to thank you for keeping the Trust informed and wish you continued success with your project.

Yours sincerely,

Lorraine Broadfoot
Research Operations Manager

Date: 3/2/2014

cc GMCLRN, Matthew Jones (on behalf of Sarah Leo)
Appendix 35
Correspondence providing favourable ethical opinion for Substantive Amendment no.2 from Central Manchester NHS Foundation Trust Research and Development
Mrs A Cooke
Midwife/Ph.D. Student (NIHR Doctoral Research Fellowship)
University of Manchester
Jean McFarlane Building – Room 4.322b
The University of Manchester
Oxford Road
Manchester
M13 9PL

Dear Alison,

Re: R03317 / CSP 120090: The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function
REC Reference: 13/NW/0512
Principal Investigator: Alison Cooke
Amendment Number: Substantial Amendment 2
Amendment Date: 05 February 2014

Thank you for your correspondence informing the department of an amendment to the above project; we acknowledge receipt of the following and approve the amendment.

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<th>Dated</th>
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<tbody>
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<td>Substantial Amendment 2</td>
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<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>Substantial Amendment 2</td>
<td>05 February 2014</td>
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<tr>
<td>Participant Information Sheet</td>
<td>5</td>
<td>23 January 2014</td>
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<td>Protocol</td>
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</tr>
<tr>
<td>Participant Consent Form</td>
<td>5</td>
<td>23 January 2014</td>
</tr>
</tbody>
</table>

We have amended the Trust’s database to reflect these changes as required.

I would like to take this opportunity to thank you for keeping the Trust informed and wish you continued success with your project.

Yours sincerely

Lorraine Broadfoot
Research Operations Manager

Date: 20/2/2014

cc GMCLRN; Caroline Leech
Appendix 36: Confirmation of favourable ethical opinion endorsement from the University of Manchester

From: Eliza Pimlott
Sent: 07 August 2013 11:28
To: Alison Cooke
Subject: RE: OBSeRvE Study: The use of Oil in baby Skincare Study

Dear Alison,

I write to confirm that we have received all the necessary documentation and can confirm that the University has endorsed the favourable NRES ethical opinion. There is therefore no ethical impediment to the research project proceeding. Our reference for the study is 13143.

Best wishes,

Eliza

Eliza Pimlott
Secretary to Dr T Stibbs
Room 2.004 John Owens Building
University of Manchester
Oxford Road
Manchester, M13 9PL

Please consider the environment before printing this email

From: Alison Cooke
Sent: 01 August 2013 10:33
To: Timothy Stibbs; Eliza Pimlott
Subject: OBSeRvE Study: The use of Oil in baby Skincare Study

Dear Tim and Eliza

As requested by Lynne Macrae, I attach herewith the documents required to ensure Insurance Cover is in place for my study. These documents include the following:

1. IRAS REC Form
2. REC letter confirming conditions met
3. Protocol v5 290713 including the following revised appendices and appendices mentioned separately in REC approval letter:
   a. Appendix 2: Flowchart (listed as summary/synopsis in REC approval letter)
   b. Appendix 3: Case Report Form 1 v2 290713
   c. Appendix 7: Case Report Form 2 v2 290713
   d. Appendix 8: Case Report Form 3 v2 290713
   e. Appendix 11: Case Report Form 6 v2 290713
   f. Appendix 15: Questionnaire: Baseline v2 290713
   g. Appendix 16: Questionnaire: Follow up v1 210213
   h. Appendix 17: Interview Schedule v1 130313
   i. Appendix 18: GP Letter v2 290713
   j. Appendix 20: Poster v5 290713
   k. Appendix 23: Questionnaire: Weekly telephone v1 080613
4. Summary Participant Information Sheet v2 290713
5. Participant information Sheet v4 290713
6. Consent Form v4 290713
7. Investigator CV (Cooke)
8. Investigator CV (Lavender)
Appendix 36: Confirmation of favourable ethical opinion endorsement from the University of Manchester

9. Investigator CV (Victor)
10. Investigator CV (Cork)
11. Referees report SL1 100413
12. Referees report SL2 220413
13. Letter from sponsor
14. Funding confirmation letter
15. Insurance Indemnity letter
16. Completed insurance assessment form

Please let me know if you require any further information.

Kind regards
Alison Cooke

Best wishes
Alison Cooke

Midwife / Ph.D. Student (NIHR Doctoral Research Fellow)
School of Nursing, Midwifery and Social Work
The University of Manchester

Jean McFarlane Building Room 4.313
Oxford Road
Manchester
M13 9PL

T. 0161 306 7758
E. Alison.Cooke@manchester.ac.uk
Appendix 37: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Adverse Event Form: Version 1, 26/02/13

Adverse Event Form

Site Number: ___________________________________________                  | Visit Date: ___ ___ / ___ ___ / ___ ___ ___ ___
Participant ID: ___________________________________________                  | d   d          m          m          m          y          y          y          y

Has the participant had any adverse events (AE) during this study?  ☐ Yes  ☐ No  (if yes, please list all adverse events below.)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Study Intervention Relationship</th>
<th>Action Taken Regarding Study Intervention</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Mild</td>
<td>1 = Definitely related</td>
<td>1 = None</td>
<td>1 = Resolved, no sequel</td>
<td>1 = Yes</td>
<td>1 = Yes</td>
</tr>
<tr>
<td>2 = Moderate</td>
<td>2 = Possibly related</td>
<td>2 = Discontinued permanently</td>
<td>2 = AE still present, no treatment</td>
<td>2 = No</td>
<td>2 = No</td>
</tr>
<tr>
<td>3 = Severe</td>
<td>3 = Not related</td>
<td>3 = Discontinued temporarily</td>
<td>3 = AE still present, being treated</td>
<td></td>
<td>(if yes, complete SAE form)</td>
</tr>
<tr>
<td></td>
<td>4 = Reduced dose</td>
<td>4 = Residual effects present, not treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 = Increased dose</td>
<td>5 = Residual effects present, treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 = Delayed dose</td>
<td>6 = Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 = Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Severity</th>
<th>Relationship to Study Treatment</th>
<th>Action Taken</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious Adverse Event</th>
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</tr>
</tbody>
</table>

Appendix 37: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Adverse Event Form: Version 1, 26/02/13
### FORM 5: Serious Adverse Events

<table>
<thead>
<tr>
<th>Patient Hospital Number:</th>
<th>Randomisation Study Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>_______________________</td>
<td>__________________________</td>
</tr>
</tbody>
</table>

Date: ___________ Person completing form: _____________

**Expected Serious Adverse Event?**  Yes / No **(complete relevant section)**

**Expected:**
- Admission to hospital due to: Yes/No

- Phototherapy treatment: [ ] Date of 1st treatment [ ]
  - day [ ] month [ ] year

- Weight loss: [ ] Date of 1st diagnosis [ ]
  - day [ ] month [ ] year

- Feeding difficulties: [ ] Date of 1st diagnosis [ ]
  - day [ ] month [ ] year

- Viral illness: [ ] Date of 1st diagnosis [ ]
  - day [ ] month [ ] year

- Bacterial infection: [ ] Date of 1st diagnosis [ ]
  - day [ ] month [ ] year

- Elective Surgery: [ ] Date of surgery [ ]
  - day [ ] month [ ] year

**Other Serious Adverse Events:**

1. SAE onset date: ___ ___ / ___ ___ / ___ ___ ___
2. SAE stop date: ___ ___ / ___ ___ / ___ ___ ___
3. Location of serious adverse event: ___________________________________________
4. Was this an unexpected adverse event? [ ] Yes [ ] No
5. Brief description of participant with no personal identifiers:
   - Sex: [ ] F [ ] M Age: _____
   (Note: If this CRF is used as a source document, it must be signed and dated by study personnel.)
6. Brief description of the nature of the serious adverse event (attach description if more space is needed):

____________________________________________________________________________

7. Category of the serious adverse event:

☐ Date of death ___/___/____  ☐ Congenital anomaly/birth defect
☐ Life threatening  ☐ Required intervention to prevent permanent impairment
☐ Hospitalization – initial or prolonged  ☐ Other: ______________________________
☐ Disability/incapacity

8. Intervention type:

☐ Topical oil (specify): ______________________________
☐ None (control group)

9. Relationship of event to intervention:

☐ Unrelated (clearly not related to the intervention)
☐ Possible (may be related to intervention)
☐ Definite (clearly related to intervention)

10. Was study intervention discontinued due to event?  ☐ Yes  ☐ No

11. What medications or other steps were taken to treat the serious adverse event?

____________________________________________________________________________

12. List any relevant tests, laboratory data, and history, including preexisting medical conditions:

____________________________________________________________________________

13. Type of report:

☐ Initial
☐ Followup
☐ Final

Signature of Principal Investigator: ____________________  Date: ________________

(Note: If this CRF is used as a source document, it must be signed and dated by study personnel.)
Appendix 39: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Trial Steering Committee Terms of Reference: Version 2, 12/04/13

BSeRvE: Oil in Baby SkincaRE Study

The use of Oil in Baby SkincaRE (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

TRIAL STEERING COMMITTEE (TSC) TERMS OF REFERENCE

The roles of the TSC

The roles of the TSC are to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health’s Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. It should be noted that the day-to-day management of the trial is the responsibility of the Trial Management Group (TMG).

The main features of the TSC are as follows:

• To provide advice, through its Chair, to the Trial Management Group, the Trial Sponsor, the Trial Funder, and the Host Institution on all appropriate aspects of the trial
• To concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
• The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society
• To ensure appropriate ethical and other approvals are obtained in line with the project plan
• To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
• To provide advice to the investigators on all aspects of the trial

Standard Constitution TSC

The following list identifies the minimum constitution requirements, a set of outline terms of reference, and the primary reporting line for the TSC:

• The TSC will have an independent chair
• The TSC is to have a majority of independent members
• Only appointed members will be entitled to vote and the chair will have a casting vote
• The minimum quorum for a meeting to conduct business is 5 appointed members, of whom the majority are independent members (emergency provision will be at the discretion of the Chair with regard to electronic voting)
Appendix 39: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Trial Steering Committee Terms of Reference: Version 2, 12/04/13

BSeRvE: Oil in Baby SkincaRE Study

• Votes will be carried by simple majority and require that more than half of the voters are independent members
• The chair and members to declare any potential conflicts and/or interests
• Attendance at TSC meetings by non-members is at the discretion of the chair
• The primary TSC reporting line to the Sponsor and Funders is via the chair

Composition of the TSC

• An independent chair
• Independent clinicians with relevant expertise
• At least one individual who is able to contribute a patient and/or wider public perspective
• Although there may be periods when more frequent meetings are necessary, the TSC should meet at least annually
• Minutes of meetings should be sent to all members, the sponsor, and the trial master file

The responsibility for calling and organising TSC meetings lies with the Chief Investigator, in association with the Chair.

The Role of the Chair of TSC

The Chair’s responsibilities include:

• Chairing a meeting to finalise the protocol and to set up a schedule of meetings to align with the project plan
• Establishing clear reporting lines – to the Funder, Sponsor, etc.
• Being familiar with relevant guidance documents
• Providing an independent, experienced opinion if conflicts arise between the needs of the research team, the funder, the sponsor, the participating organisations and/or any other agencies
• Leading the TSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems
• Ensuring that changes to the protocol are debated and endorsed by the TSC; letters of endorsement should be made available to the project team when requesting approval from the funder and sponsor for matters such as changes to protocol
• Being available to provide independent advice as required, not just when TSC meetings are scheduled
• Commenting on any extension requests and, where appropriate, providing a letter of recommendation to accompany such a request
• Commenting in detail (when appropriate) regarding the continuation or termination of the project
Independence

The definition of independent is as follows:

• Not part of the same institution as any of the applicants or members of the project team
• Not part of the same institution that is acting as a recruitment or investigative centre
• Not related to any of the applicants or members of the project team
• For the chair only – not an applicant on a rival proposal

Research Governance Framework information is available at this link: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4122427.pdf
OBSeRvE: The use of Oil in Baby Skincare Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function.

FORM 6: Withdrawal of Treatment/Consent

Patient Study Number: ........................................

Date: ___________  Person: ___________

Date of discontinuation or trial withdrawal

day  month  year

Why was the intervention discontinued or the consent withdrawn?

Parental wish □ Other □ Indicate the reason below

Jaundice (phototherapy treatment)  Yes □ No □

Illness (please specify) ________________________  Yes □ No □

Development of serious disease  Yes □ No □

Death before randomisation  Yes □ No □

Discharge to non-recruiting centre before randomisation  Yes □ No □

Other reasons for withdrawal:

Have the parents agreed that all the already collected data can be used?  Yes □ No □

Have the parents agreed that we can collect clinical data at follow up (28 days)?  Yes □ No □

Date this form was completed

day  month  year

Please let the parents know if treatment or consent has been withdrawn for reasons other than parental wishes

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Appendix 41: TRIAL STEERING COMMITTEE MEMBERSHIP

**Independent members**

Dr Mark Turner (Chair), *The University of Liverpool*

Dr Kevin Hugill, *UCLAN*

Dr Vinod Elangasinghe, *Chesterfield Royal Hospital NHS Foundation Trust*

Professor Lelia Duley, *Nottingham Clinical Trials Unit*

Gill Singleton, *Tameside Hospital NHS Foundation Trust*

Margaret Cox, *National Eczema Society*

Lisa Rowe, *Parent Representative*

**Trial Management Group**

Alison Cooke, *The University of Manchester*

Professor Dame Tina Lavender, *The University of Manchester*

Professor Michael J Cork, *The University of Sheffield*

Dr Suresh Victor, *The University of Manchester*

Dr Malcolm Campbell (Statistician), *The University of Manchester*
# Protocol Deviations Log

**Site:** 

**Participant ID:** 

**Visit Date:** 

---

Did this participant have any protocol deviations?  

- [ ] Yes  
- [ ] No

<table>
<thead>
<tr>
<th>Description of Protocol Deviation</th>
<th>Deviation Category*</th>
<th>Deviation Code**</th>
<th>Date Deviation Occurred (dd/mmm/yyyy)</th>
<th>Date IRB Notified (if applicable)</th>
<th>Principal Investigator's Signature</th>
<th>Date Signed (dd/mmm/yyyy)</th>
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</table>

(Note: If this CRF is used as a source document, it must be signed and dated by study personnel.)

Appendix 42: The OBSeRvE Study: The use of Oil in Baby SkincaRE pilot study

Protocol Deviations Log: version 1, 21/02/13

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*DEVIA TION CATEGORIES*

A. Safety
B. Informed consent
C. Eligibility
D. Protocol implementation
E. Other, specify in log

**DEVIA TION CODES:** Numbers listed by the sample protocol deviations

Safety (Category A)
1. Not reporting an SAE within 24 hours
2. Laboratory tests not done
3. AE/SAE is not reported to IRB
4. Other, specify in log

Informed consent (Category B)
5. Failure to obtain informed consent
6. Consent form used was not current IRB-approved version
7. Consent form does not include updates or information required by IRB
8. Consent form missing
9. Consent form not signed and dated by participant
10. Consent form does not contain all required signatures
11. Other, specify in log

Eligibility (Category C)
12. Participant did not meet eligibility criterion
13. Randomization of an ineligible participant
14. Participant randomized prior to completing baseline assessment, etc.
15. Randomization and/or treatment of participant prior to IRB approval of protocol
16. Other, specify in log

Protocol implementation (Category D)
17. Failure to keep IRB approval up to date
18. Participant receives wrong treatment
19. Participant seen outside visit window
20. Use of unallowable concomitant treatments
21. Prescribed dosing outside protocol guidelines
22. Missed assessment
23. Missed visit
24. Other, specify in log

(Note: If this CRF is used as a source document, it must be signed and dated by study personnel.)

Appendix 42: The OBSeRvE Study: The use of Oil in Baby SkincaRE pilot study
Protocol Deviations Log: version 1, 21/02/13
<table>
<thead>
<tr>
<th>Name</th>
<th>Sources</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCEPTABILITY</td>
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</tr>
<tr>
<td>1. Timing</td>
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<tr>
<td>a. Timing of recruitment</td>
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<td>Effect of birth</td>
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<td>12</td>
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<tr>
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<td>29</td>
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<tr>
<td>Parity</td>
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<tr>
<td>b. Duration of assessment</td>
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<td>0</td>
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<tr>
<td>Change of scenery</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Had something to do</td>
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<td>1</td>
</tr>
<tr>
<td>Mum had a break on the ward</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Reasonable</td>
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<td>13</td>
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<td>c. Duration of study</td>
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<td>Any duration acceptable</td>
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<td>Christmas time difficult</td>
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<td>2</td>
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<tr>
<td>Longer may affect compliance</td>
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<td>Longer may affect retention</td>
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<td>3</td>
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<tr>
<td>Relief when over</td>
<td>4</td>
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<tr>
<td>Reluctant to participate if longer</td>
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<td>13</td>
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<tr>
<td>Satisfactory</td>
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<td>Second assessment</td>
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<td>Should be longer</td>
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<td>4</td>
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<td>Wasn't long</td>
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<tr>
<td>d. Establishing a routine</td>
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<td>Family involvement</td>
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<td>Getting to know baby</td>
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<td>Massage</td>
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<td>No routine</td>
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<td>Partner involvement</td>
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<td>Quality time and bonding</td>
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<tr>
<td>Same routine now</td>
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<td>8</td>
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<td>Study helped to establish a routine</td>
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<td>2. Rationale for participation</td>
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<td>a. Altruism</td>
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<td>Don't progress without research</td>
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<td>30</td>
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<td>Interested in results</td>
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<td>65</td>
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<tr>
<td>To benefit others</td>
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<td>67</td>
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<tr>
<td>b. Minimal burden</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Easy</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Not distressing baby</td>
<td>2</td>
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<tr>
<td>Not hurting baby</td>
<td>5</td>
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<td>Not too onerous</td>
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<td>Vouchers</td>
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<td>c. Family history of atopic eczema</td>
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<td>History of dry skin</td>
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<td>History of eczema</td>
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<td>3. Pre-conceptions</td>
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<tr>
<td>a. Skincare regimes</td>
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<td>0</td>
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<tr>
<td>Didn't want to use oil</td>
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<td>2</td>
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<tr>
<td>Dry skin comes and goes on own</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Now recommends oil</td>
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<td>2</td>
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<tr>
<td>Skin was ok without using anything</td>
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<td>8</td>
</tr>
<tr>
<td>Would have used products</td>
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<td>9</td>
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<td>Would not have used products</td>
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### b. Ideas and beliefs

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<td>Skin condition due to diet</td>
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<td>Topical oils</td>
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### ASSESSMENT AND TREATMENT

#### 1. Group allocation

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<td>a. Effect on the baby</td>
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<td>Best not to know</td>
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<td>Looking for a reaction</td>
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<td>No harm</td>
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<td>What is it</td>
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<td>b. Perceptions of allocation</td>
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<td>Doing something</td>
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<td>Easy option</td>
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<td>Happy being randomised</td>
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#### 2. Compliance

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<td>Delay in cares</td>
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<td>Easy</td>
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<td>Messy</td>
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<td>Need commitment</td>
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<td>Support from family</td>
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<td>Test area minimal</td>
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<td>b. Products</td>
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<td>Bathing awkward</td>
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<td>Control soap</td>
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<td>Protocol violations</td>
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### 3. Equipment

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<tbody>
<tr>
<td>a. Effect on baby</td>
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<tr>
<td>No distress</td>
<td>8</td>
</tr>
<tr>
<td>No harm</td>
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<td>Non-invasive</td>
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<td>b. Parent perceptions</td>
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<td>Bottles</td>
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<td>Day out</td>
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<td>D-Squame</td>
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<tr>
<td>Scary</td>
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<td>Science</td>
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### COMMUNICATION

#### 1. Verbal

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<td>Direct contact</td>
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<td>Important</td>
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<td>More personal</td>
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<tr>
<td>Recommend study to others</td>
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<tr>
<td>Repetition</td>
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#### 2. Visual

<table>
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<tr>
<td>Diagram important as reminder</td>
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<td>Lamination good</td>
<td>3</td>
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<tr>
<td>Left and right</td>
<td>9</td>
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<tr>
<td>Needed more visual or pictorial in PIS</td>
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#### 3. Written

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<th>Element</th>
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<tr>
<td>Covered everything</td>
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<tr>
<td>Didn't read</td>
<td>0</td>
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<tr>
<td>Didn't remember seeing summary PIS</td>
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<tr>
<td>Skim read</td>
<td>2</td>
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<tr>
<td>Understandable and clear</td>
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#### 4. Influence of others

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<tr>
<th>Element</th>
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<td>Category</td>
<td>Count 1</td>
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<td>-------------------------------</td>
<td>---------</td>
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<tr>
<td>a. Staff and hospital</td>
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<tr>
<td>Confidence in midwife</td>
<td>8</td>
</tr>
<tr>
<td>Confidence in non-maleficence</td>
<td>2</td>
</tr>
<tr>
<td>Conflicting advice</td>
<td>5</td>
</tr>
<tr>
<td>Pleasant environment</td>
<td>3</td>
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<tr>
<td>Professional</td>
<td>9</td>
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<tr>
<td>b. Partner</td>
<td>0</td>
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<tr>
<td>Gave mum a break</td>
<td>1</td>
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<tr>
<td>Just had a baby, mind wasn’t</td>
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<tr>
<td>Reliance on partner</td>
<td>5</td>
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<tr>
<td>Took ownership</td>
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</tr>
<tr>
<td>c. Family</td>
<td>0</td>
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<td>Conflicting advice</td>
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<td>Grandparents have their own</td>
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<tr>
<td>Protocol compliance more</td>
<td>3</td>
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<tr>
<td>Reliance on family member</td>
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</table>
### Appendix 44: Framework Chart: Altruism

<table>
<thead>
<tr>
<th></th>
<th>A : Don't progress without research</th>
<th>B : Interested in results</th>
<th>C : To benefit others</th>
</tr>
</thead>
</table>
|1 : Aisha | **Questionnaire:** "This way we can find out what the best treatment is for newborns delicate skin"  
"...it’s like, even for my children, for other children, it’s a skin study, so they will, you know, get something out of it. And because having kids with skin problems, you’re like constantly…, my son, he’s got eczema. They’re trying one cream. Then it’s another. One helps for maybe a few weeks and then, it don’t help anymore. Then you go …to your GP for another one and it’s just what helps at that moment of time. So, it’s always a struggle; you’re always going thr…through something; you can’t use normal products. So it’s like, you know, if that can help, just stay focussed …"

"...I’m just really...I’m just waiting for the results really [laughs]. I’ve just done my bit. I’ve tried, t…you know, to follow all the instructions. I’m just waiting for the results, to be really honest, to see what, you know, what comes out, what’s better for the babies."

"...if the study can help future children, even if they’re not mine or … then yeah, why not, because I’ve seen so many kids with eczema, skin conditions, everything, so, if you’re, like, discovering, like, how does it happen, then why not?"

"...for a kid to go through that, it’s just horrible. And you don’t know what to use, and you don’t know what it’s causing. So, that was, for me, the main thing to, you know, to do it."

|2 : Elaine | "For me it was interesting to find out what it would be at the en…you know, what the outcome would be because so many people say so many different things and I love using creams and oils and ointments and stuff on the skin. So it was… For me that’s why I I agreed to it really ‘cause I I was interested to find out what the outcome would be."

"I’d be quite interested to find out the, the findings and especially with him being the only one … that’s come out with this rash."

"... my daughter’s got eczema, um, you know, and and could it have been caused by something I’ve used or because, you know, I’ve slopped all sorts on her skin when she was the same age as as he is now, so, and for me, if I had another child, I wouldn’t even use anything on the skin now knowing… Doing what I’ve done now I wouldn’t even use anything."
<table>
<thead>
<tr>
<th>3 : Ilia</th>
<th>Questionnaire: &quot;More children seem to either develop eczema at an early age or [there] are more with it. I think this study will shed some light on what may cause more children to have eczema.&quot;</th>
<th>&quot;No, I just want to be informed [laugh]. I just want to be kept informed, I'm quite interested in what...you know, in what your findings are.&quot;</th>
<th>&quot;... it needs to be done, someone needs to do something about this, to find out why kids these days get more eczema.&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 : Indiana</td>
<td>&quot;... I was part of it and I liked it because it was doing some research into skin.&quot;</td>
<td>&quot;... the fact that maybe we would have actually got a better cream out there or something like that, just to...even just ease the symptoms of eczema and stuff like that, because it is such a pain, when you’re a baby, especially. Er, I know what it’s like for my son; he does get so angsty with it and so annoyed with themselves that they’re so itchy, so, it’s just, just the thought of actually getting a cream out there that’d be good for eczemas, yeah. Without it having to be a steroid cream as well [laughs].&quot;</td>
<td></td>
</tr>
<tr>
<td>5 : Jane</td>
<td>&quot;... with it being new you don’t know what’s right, what’s wrong. You get told a hundred different things off a hundred different people. So, start off with one thing, carry on. Learn what’s best.&quot; &quot;Yeah, you have, sort of, some sort of...information that’s relative to all babies, and that’s your thing then as well. You do your thing and it works and also helped being in the research thing because, like, yeah I don’t have to listen, I’m doing this. I’m doing this for my son.&quot;</td>
<td>&quot;There was nothing that was harmful to my son so there, I didn’t see any harm and it is for the future babies, which I may have future babies in the future so it’s all useful stuff really.&quot;</td>
<td></td>
</tr>
<tr>
<td>6 : Jill</td>
<td>&quot;... I like to be involved in any kind of research that’ll help, eh, find things that are better in any way to help people so, yeah, I just... You know, I felt like I was doing something positive towards, hopefully, you know... If any babies are having anything more, problems, you know, of skin issues or anything like that. Yeah, hopefully it’ll... You know, it’s been good to just to be part of it in that sense really.&quot;</td>
<td>Questionnaire: &quot;It will hopefully help find if there is a simple 'home remedy' for dry skin rather than expensive cream or oils that are less natural&quot;</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>
| 7 : Lydia | Questionnaire: "Supporting academic research that will make a difference in paediatric care. Understanding more about what treatments/sensations my baby likes. Recognising that natural/traditional remedies can work."  
"The research has to be done; it’s going to help babies in the future, so, I think it’s absolutely acceptable as long as it’s done in an ethical manner." | "I remember just asking you when the research was going to be, er, published, because I was interested in seeing it."  
"The research has to be done; it’s going to help babies in the future, so, I think it’s absolutely acceptable as long as it’s done in an ethical manner."  
"I liked the fact that it’s research that will help other mums, other dads and other babies of the future." |
| 8 : Margaret | " It’s very interesting. Eh...I don’t know for...for future...for, hmm, doing some...I don’t know cream, oil for baby it’s good because every skin in baby is different and it’s alright for me." |  |
| 9 : Maureen | "... we liked the fact of helping out with research."  
"...I just like to help with any research or anything, ..." | Questionnaire: "That it is interesting to be a part of, interesting that baby will have helped the end findings."  
"... we’re really interested in finding out the results of it, you know, just to see...erm...so, yes, and, you know, I suppose at first we wondered what sort of effects it would have on his skin ..." |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10 : Meg</td>
<td></td>
<td>Questionnaire: &quot;I will be able to look after my baby according to the results&quot;</td>
</tr>
<tr>
<td>11 : Nicole</td>
<td>&quot;I liked the fact that obviously I was helping to further research and things like that and that’s mainly the reason why I agreed to do it, ...&quot;</td>
<td>Questionnaire: &quot;Interesting to see if it made any difference&quot;</td>
</tr>
<tr>
<td>12 : Olivia</td>
<td>&quot;It was nice...nice to know that we were, erm...especially skin things because, because I get quite a few skin problems I think it’s always good to be part of research and help people’s knowledge.&quot;</td>
<td>&quot;... , you help people do what they can to help because obviously it affects the future and things like that.&quot;</td>
</tr>
<tr>
<td>13 : Rachel</td>
<td>Questionnaire: &quot;Will help towards research of knowing (parental knowledge) which oils are best to use on babies' skin. Help towards medical conditions such as eczema/dry skin conditions. Babies will benefit who suffer.&quot;</td>
<td>&quot;... I thought it was an interesting study, and as a new mum I thought it'd be interesting to find out about...more about the baby’s skin, things like that.&quot;</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>14 : Salma</td>
<td>I was curious anyway whether, you know, the oil makes a difference or not, because, erm, my daughter, first daughter’s, erm, skin, was very, very, dry as well when she was born, ... the midwife did tell me to put olive oil on her and I did see improvement. So, I was interested in this study, because I wanted to know was...is it, did it really work or is it just because her...she’s growing and her skin is changing? So, yes, so it would be interesting to know the results.&quot;</td>
<td></td>
</tr>
<tr>
<td>15 : Samantha</td>
<td>Questionnaire: &quot;Positive aspects are that we have been able to help in finding best product for baby’s skin as there is far too many skin products on the market and it's hard to find the best product for specific baby&quot;</td>
<td></td>
</tr>
<tr>
<td>16 : Sarah</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 17 : Ted and Barbara | Barbara: "I thought it was helpful, you know, for the research study, to actually do it. ... So, it could help you find out what’s best for the baby’s skin. ... That’s why I actually chose [this] Hospital ... Because, obviously, I know you do a lot of research, ..."
   Barbara: "... it’s for the research to find out what’s best for them anyway. We might have found out the oil was better than nothing. You just don’t know, do you?"
| Questionnaire: "The information that will come from the study will be useful to people in the future to know what’s best for their baby's skin" |
| 18 : Tom and Marie | Marie: "I’m always happy to get involved with research. I did a few research trials whilst I was pregnant. And I think...if nobody does it then you never find anything out. "
   Tom "... we did it because you don't progress unless you do research, it's as simple as that, you know. " | Marie: "I was quite happy for it to happen; I was quite interested in what the results would be." |
| 19 : Tori | "I think when, so if you can do something like that, there's a chance that it might be useful. I, I would have found it useful to have that information, ..."  
"... just that we did both think it was a really useful thing. Because it's like one of them things, you know like when you see on TV, like there's been a study of such and such, and you've, you actually know that you've been in one. And it's something that you're interested in, which was skin for me, ..." | Questionnaire: "I understand what it's like to have sore skin and think any study trying to find out helpful ways to treat is worthwhile" | "... it's kind of like having a bit of extra information, I suppose. Erm, so yeah, and for others." |
| 20 : Zaynad | "I liked the fact that it was for a good cause that, you know, that a lot of children do suffer from dry skin, and, you know, if you could find something that can help them then why not, so that was the best part for me."  
"... it was pretty important, my niece suffers from eczema and she has suffered from this since she was like, since she was born and she still suffers, she’s 12 years old now and it doesn't affect her life as such but obviously it’s something that, you know, it’s worrying for the parents and, you know, she’s itching and you have to stop her from itching and things like that." | "So it was important, it’s important that, you know, it’s, overall it helps a lot of people who suffer a lot more than just the arm or just under the knees you know."  
Questionnaire: "It will help the future babies with a good skin regime and maybe in long run save the skin from over drying" |
## Appendix 45: OBSeRvE Study Audit

**Faculty of Medical and Human Sciences**  
**University of Manchester**  
**Audit report**

<table>
<thead>
<tr>
<th><strong>Project Title</strong></th>
<th>The use of Oil in Baby Skincare (OBSeRvE) Trial: a pilot, assessor-blinded, randomised controlled trial, to assess the impact of olive oil and sunflower oil on a term baby’s skin barrier function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of Audit</strong></td>
<td>3rd July 2014</td>
</tr>
<tr>
<td><strong>Chief Investigator</strong></td>
<td>Professor Tina Lavender</td>
</tr>
<tr>
<td><strong>School/Institute</strong></td>
<td>School of Nursing, Midwifery and Social Work</td>
</tr>
<tr>
<td><strong>Project Lead/Student</strong></td>
<td>Alison Cooke</td>
</tr>
<tr>
<td><strong>Auditors</strong></td>
<td>Afzal Ali</td>
</tr>
</tbody>
</table>
Background

The audit was carried out of the OBSeRvE study in accordance with the University of Manchester. This allows us to obtain reasonable assurance on the adequacy and effectiveness of the governance, risk management, and control processes. The audit includes reviewing on a test basis project data and source documentation is complete and well organised.

Objectives

The overall objective of the audit was to assess and provide assurance the project documents and data relating to the project is managed adequacy and effectively and recorded appropriately.

The audit also aimed to assist the project team in continuously improving the processes in place. The following elements of the internal controls were covered: Trial Master File; consent forms; personal data; and monitoring of internal reviews.

Audit type

Routine Sponsor Audit

Results

- All the appropriate ethics and R&D approvals are in place for the study.
- The Trial Master File (TMF) contains the main documents for the study as well as evidence of internal and external communications.
- The audit revealed a number of issues with the study:
  - Management and Quality of study documents
    - Completion of some consent forms not as per ethics approval e.g. Overwriting, black fields
    - No document management system to indicate current versions
    - Older versions of the documents have not be crossed and dated to indicate they have been superseded

Conclusions

There were a number of findings as a result of the audit but none that would be considered a serious breach i.e. do not represent a risk to patient safety or the integrity of the scientific data.

Audit Follow-Up

A follow-up visit will be set-up to review progress based on the specific recommendations below. The date will be confirmed with the research team.
# Audit Action Plan

## Project title

**OBSeRvE**

## Action plan lead

<table>
<thead>
<tr>
<th>Name: Alison Cooke</th>
<th>Title: NIHR Doctoral Research Fellow</th>
<th>Contact: <a href="mailto:Alison.cooke@manchester.ac.uk">Alison.cooke@manchester.ac.uk</a></th>
</tr>
</thead>
</table>

## Observations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Action by date</th>
<th>Person responsible</th>
<th>Comments/action plan</th>
</tr>
</thead>
</table>

### APPROVALS

- Ethical approvals in place for the study, and filed in the study file
- R&D approvals in place for the study
- NIHR progress report sent
- Ethics report due to be sent on 01st Aug 14

<table>
<thead>
<tr>
<th>Person responsible</th>
<th>Comments/action plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC Sent 10.09.14</td>
<td></td>
</tr>
<tr>
<td>AC Progress report sent 08.09.14</td>
<td></td>
</tr>
</tbody>
</table>

### STUDY FILE

- Current version of the information sheet and consent documents are present in the file.
- All previous versions of the documents are present in the study file.
- Case report form has varying version numbers

<table>
<thead>
<tr>
<th>Person responsible</th>
<th>Comments/action plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC Complete 10.09.14</td>
<td></td>
</tr>
<tr>
<td>AC Complete 10.09.14</td>
<td></td>
</tr>
<tr>
<td>AC Complete 10.09.14</td>
<td></td>
</tr>
</tbody>
</table>

The team should consider using a document management system that will allow oversight of approvals of all documents and at all sites.

To avoid any confusion with the current version please could you strike through, initial and sign the obsolete versions of the documents.

A management system should be looked at to indicate which version of the form is active.
<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
<th>Responsible Party</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV AND STAFF TRAINING</strong></td>
<td>CV missing – CV/GCP not present for M Campbell on the delegation log</td>
<td></td>
<td>AC CV added 08.09.14 (no GCP as no contact with participants)</td>
</tr>
<tr>
<td></td>
<td>Please add CV/GCP certificate to file for M Campbell</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT INFORMATION, RECRUITMENT AND CONSENT</strong></td>
<td>Ethical approval in place</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R&amp;D approval in place.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A sample of consent forms were reviewed all were signed and dated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHARMACOVIGILANCE</strong></td>
<td>No SUSARs recorded</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No SAEs recorded</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AEs filed in AE folder</td>
<td>AC</td>
<td>Completed 10.09.14</td>
</tr>
<tr>
<td></td>
<td>Please add in study file to reference where this is kept</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RECORD LEGIBILITY AND DATA PROTECTION</strong></td>
<td>Overwriting identified on sample case report form</td>
<td></td>
<td>JC/AC Completed 23.07.14</td>
</tr>
<tr>
<td></td>
<td>Any error/overwriting should be amended as per GCP i.e. line through the erroneous entry, initials and date</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consent forms comments were placed on post-it notes</td>
<td></td>
<td>AC Completed 10.09.14</td>
</tr>
<tr>
<td></td>
<td>Any comment regarding participant non-eligibility to take part and withdrawals should be placed on the screening and recruitment log</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Email 092 from one of the parents give participant name and date of birth, as this contains Personal identifiable data this should be not be held in the study file</td>
<td></td>
<td>AC Removed 10.09.14</td>
</tr>
<tr>
<td></td>
<td>Any personal data should be removed from the study file, if possible you can place a redacted copy of the email where the personal details are blacked out and a note to</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
say where the full email is stored (this can possibly be electronically or in the consent folder)

<table>
<thead>
<tr>
<th>AMENDMENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendments R&amp;D and ethics approvals in place</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONTRACTS AND SPONSORSHIP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of sponsorship letter, insurance arrangements and sponsor conditions on file</td>
<td></td>
</tr>
<tr>
<td>Panman and Financial confirmation is present</td>
<td></td>
</tr>
<tr>
<td>Letter of insurance from sponsor present</td>
<td></td>
</tr>
<tr>
<td>Team meeting minutes present</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHARMACY</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>LABORATORY</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>OTHERS</th>
<th></th>
</tr>
</thead>
</table>

| Equipment maintenance log and sop present |               |
**Follow Up Visit**

This is to acknowledge all audit responses have been actioned for completion and/or action plan in place to change processes.

<table>
<thead>
<tr>
<th>Date of follow up visit:</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CHief Investigator:</th>
<th>Signature:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Auditor:</th>
<th>Signature:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Form 2: Baseline Observations (within 72 hrs of birth)

**Patient Study Number:**

**Form 2 should be commenced immediately after randomisation**

<table>
<thead>
<tr>
<th>Person: ________________</th>
<th>Date: ________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date and time of assessment:</td>
<td>Time</td>
</tr>
<tr>
<td>day</td>
<td>month</td>
</tr>
</tbody>
</table>

**Temp**

**Humidity**

**Awake (calm) / Awake (crying) / Asleep**

### Left Forearm

Measurement from wrist: _________ cm (Wrist to ante-cubital fossa = _______ cm)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Upper abdomen

Measurement from umbilicus: ________ cm (Umbilicus to nipple line = ________ cm)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td></td>
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</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 46: The OBSeRvE Study: The use of Oil in Baby Skincare Pilot Study
Proposed Revised Baseline Observations Form: Version 4, 01/07/15

BSeRVe: Oil in Baby SkincaRE Study

Left Thigh
Measurement from knee: _________ cm (Mid-patella to head of femur = …..cm)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 – 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 – 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Observation
Dryness and scaling scale (circle one)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of dryness or scaling</td>
</tr>
<tr>
<td>1</td>
<td>Slight dryness and/or scaling</td>
</tr>
<tr>
<td>2</td>
<td>Mild–moderate dryness to severe dryness and/or scaling</td>
</tr>
<tr>
<td>3</td>
<td>Moderate-severe dryness and/or scaling</td>
</tr>
<tr>
<td>4</td>
<td>Severe dryness and/or scaling</td>
</tr>
</tbody>
</table>

Rash grading scale (Circle one)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of rash</td>
</tr>
<tr>
<td>1</td>
<td>Slight rash--slight erythema and/or scaling</td>
</tr>
<tr>
<td>2</td>
<td>Mild rash--moderate to severe erythema and/or scaling, slight papules and oedema</td>
</tr>
<tr>
<td>3</td>
<td>Moderate rash--moderate to severe erythema and/or scaling, moderate ulceration, moderate to severe papules and oedema</td>
</tr>
<tr>
<td>4</td>
<td>Severe rash--severe erythema and/or scaling, severe ulceration, papules, and oedema</td>
</tr>
</tbody>
</table>

Medical / cleansing moisturising products used?

.................................................................

Advice Given?

.................................................................

Referral needed?  Yes/No

Signature: ..............................................
**FORM 3: Follow-up assessment (28 days)**

Date: __________  Person: __________

Maintenance of intervention for \( \geq 28 \) days.  
Yes [ ]  No [ ]

Date and time of last application.  
Date: [ ] [ ] [ ]  Time: [ ] [ ]

Date and time of assessment:  
Date: [ ] [ ] [ ]  Time: [ ] [ ]

Interval between last application and assessment ……………………………………………………………

Was there any change to treatment (describe below)?  
Yes [ ]  No [ ]

<table>
<thead>
<tr>
<th>Temp</th>
<th>Humidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Left Forearm**

Measurement from wrist: _________ cm (Wrist to ante-cubital fossa = ……cm)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Upper abdomen**

Measurement from umbilicus: _________ cm (Umbilicus to nipple line = ……cm)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin</th>
<th>pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Left Thigh

Measurement from knee: _________ cm (Mid-patella to head of femur = …..cm)

<table>
<thead>
<tr>
<th></th>
<th>TEWL (pre TS)</th>
<th>Hydration (40 - 80)</th>
<th>Erythema</th>
<th>Melanin pH (4 - 7)</th>
<th>TEWL (post TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurement 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Observation

Dryness and scaling scale (circle one)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of dryness or scaling</td>
</tr>
<tr>
<td>1</td>
<td>Slight dryness and/or scaling</td>
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<td>3</td>
<td>Moderate-severe dryness and/or scaling</td>
</tr>
<tr>
<td>4</td>
<td>Severe dryness and/or scaling</td>
</tr>
</tbody>
</table>

Rash grading scale (Circle one)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>Mild rash–moderate to severe erythema and/or scaling, slight papules and oedema</td>
</tr>
<tr>
<td>3</td>
<td>Moderate rash–moderate to severe erythema and/or scaling, moderate ulceration, moderate to severe papules and oedema</td>
</tr>
<tr>
<td>4</td>
<td>Severe rash–severe erythema and/or scaling, severe ulceration, papules, and oedema</td>
</tr>
</tbody>
</table>

Medical / cleansing moisturising products used during treatment period?

..................................................................................................................................................

Advice Given?

..................................................................................................................................................

Referral needed? Yes/No

Signature: ...........................................
Appendix 48

Brochure for Attenuated Total Reflectance Fourier Transform Infra-Red spectroscopy handheld device
Agilent 4300 Handheld FTIR Spectrometer

AT-SITE. IMMEDIATE RESULTS. TRUE NON-DESTRUCTIVE ANALYSIS.

The Measure of Confidence

Agilent Technologies
BRING THE POWER OF FTIR SPECTROSCOPY OUT OF THE LAB... AND TO THE SAMPLE

From improving composite bonding... to performance-testing of coatings... to verifying polymer identity and authenticity... to measuring metal surface contamination... success depends upon generating actionable, on-the-spot results.

Perform accurate, non-destructive material testing with the Agilent 4300 Handheld FTIR

The versatile, ergonomic 4300 Handheld FTIR is ideally suited to at-site, mid-IR measurement of objects constructed from high-value materials. Its optimized design lets you quickly scan large surfaces or areas, and knowledgeably assess factors such as identity, quality, authenticity, and wear. In addition, the 4300 Handheld FTIR enables you to analyze objects directly — without removing a sample — so you can reduce your dependence on overworked or off-site labs.

In short, the 4300 Handheld FTIR represents a new generation of FTIR innovation for material analysis brought to you by Agilent — the leader in developing handheld and portable FTIR analyzers.
Non-destructive testing, right on the spot

The 4300 Handheld FTIR enables you to take measurements wherever they are needed – regardless of the physical size or location of the object. It delivers immediate, real-time results to help you make informed decisions about factors such as quality control, surface contamination, and which samples require further testing.

You can non-destructively identify, verify, classify, authenticate, and detect counterfeits in a broad range of materials. We call this Positive Material Identification.

With handheld FTIR, you can perform in-service measurements to test materials during their lifetime and determine the affect of use and environment on wear characteristics.

In addition, the 4300 Handheld FTIR improves productivity by allowing you to quickly scan a large surface area and locate the most important measurement points.

Remarkable comfort and superior data

Weighing under 5 lbs (2.2 Kg), the ergonomic 4300 FTIR is ideal for mobile measurements. But do not let its size fool you. The 4300 is also engineered with optimized electronics and an ultra-short internal optical path, so you can count on exceptional results for your most demanding applications.

Even better, the 4300 Handheld FTIR enables anyone to achieve reliable results with custom, easy-switch sample interfaces, zero-alignment optics, and intuitive software.
**ENHANCED MATERIAL ANALYSIS FROM THE PEOPLE WHO DEVELOPED THE ORIGINAL HANDHELD FTIR**

**More reproducible results:** At 5 pounds (2.2 Kg), the 4300 is comfortable to hold and use. It also has a perfect weight distribution with its batteries located in the base to balance the optical head. Optimized ergonomics means better quality results, especially for analyses that require longer measurement times, numerous measurement points, or are on objects that are physically constrained.

**Superior performance:** A proven interferometer design, ultra-short internal optical path, optically matched sample interfaces, and low-noise electronics yield better spectral data.

**The right detector for your application:** For routine analysis, our DGTS detector delivers broad spectral coverage. Our thermoelectrically cooled MCT detector is best for applications that require high performance and speed — and for acquiring numerous spectra over large surface areas.

**Rapid scanning:** The Agilent 4300 Handheld FTIR equipped with MCT detector is ideal for rapidly and conveniently mapping the surface of materials. The enhanced speed of measurement obtained with the MCT detector, combined with the rapid response software and the 4300’s optimized ergonomics, make the analysis of numerous locations on a surface fast and easy.

**Real-time measurements:** Agilent MicroLab Mobile Measurement software was created and enhanced for our portable and handheld spectrometers. Its real-time spectral display complements the rapid scanning capability of the 4300 MCT system.
Longer periods of continuous operation: The lithium ion batteries that power the 4300 can easily be swapped while the system is running.

Control at your fingertips: An integrated touch screen operates all system and data acquisition functions and tilts for easy viewing in ambient light.

Flexibility for every method: Interchangeable, snap-on interfaces require no alignment, and are custom engineered to match optics and electronics. These interfaces are RFID equipped to ensure they are correctly matched to the specific method required for an analysis. You can also choose between two detectors: a DGTS detector for routine analysis, and a thermoelectrically cooled MCT detector for applications that require high performance and speed.

Fast execution of methods and commands with a simple trigger click.

Reliable field measurements, when and where you need them. Visit agilent.com/chem/4300HandheldFTIR
MEET THE NEXT GENERATION OF FTIR MOBILITY

Reliable field measurements *when* and *where* you need them.
Visit agilent.com/chem/4300HandheldFTIR

Touch-screen user interface runs the MicroLab Mobile software.

Flexibility for every method. Interchangeable, snap-on interfaces require no alignment, are custom engineered to match system optics, and are equipped with RFID sensors to ensure the correct match between sample interface and analytical method.

Easy trigger initiates method commands.

4-hour Li ion batteries: "hot" swappable for extended system use.
Advanced optomechanical and low-noise electronics with no alignment needed

Lightweight: just 4.8 lbs (2.2 Kg)

Balanced for easier, and better, measurements

Wrist strap improves comfort and security.

Optically matched sample interfaces afford the highest-quality data for the broadest range of samples

**DIAMOND ATR**
Just right for solids, liquids, pastes, and gels, this interface consists of a diamond ATR sensor, which is impervious to corrosion and scratching. After samples come into contact with the diamond window, the top 2-3 surface microns are analyzed.

**DIFFUSE REFLECTANCE**
Diffuse reflectance is best for samples that reflect little light, such as artwork, soils, rocks and minerals, composites, rough plastics, fabrics, and metal corrosion.

**EXTERNAL REFLECTANCE**
External reflectance, with its 45° angle of incidence, is suitable for smooth, opaque samples that reflect infrared light. It also enables the analysis of thin films and coatings on reflective metal surfaces, such as aluminum and steel.

**GRAZING ANGLE**
Ideal for sub-micron films, the grazing angle interface also works well for measuring trace contamination on reflective metal surfaces. Its 82° angle of incidence improves sample interaction with the infrared energy by increasing sample path length.

**GERMANIUM ATR**
With germanium ATR, only the top 0.5 to 2 micrometers of an object are measured, making this interface a good match for strongly absorbing solids and liquids (such as carbon-filled elastomers and rubbers).
The Agilent 4300 Handheld FTIR non-destructively handles field measurements across diverse industries

**Composites**

The 4300 Handheld FTIR is proven to deliver outstanding results in applications such as:

- Detecting damage caused by excess exposure to heat
- Mapping thermal damage on surfaces
- Guiding sanding, scarfing, and patching repairs
- Measuring oxidative damage from UV light and other environmental factors
- Confirming the effectiveness of plasma treatment in preparing composite surfaces for bonding
- Detecting hydrocarbon and silicone oil contamination
- Assessing moisture levels
- Determining the extent of pre-preg curing
- Identifying and verifying composition

**Polymers**

With its versatile sampling capability, the 4300 FTIR enables you to:

- Identify, verify, and authenticate polymer components
- Measure the degree of cross-linking and cure
- Determine the composition of copolymers
- Analyze rubber and other elastomers – even those containing carbon particles
- Quantify phthalate plasticizer in polymeric materials used in consumer products
- Verify composition and authenticity of seals, gaskets, and O-rings
- Establish the identity and composition of carbon-filled polymers recycled from electronics

Composite thermal damage is represented in the MicroLab Mobile software. Behind the simple-to-use results screen, powerful calibrations embedded in the software provide a method specific to the analysis parameters. The result is color coded in red to show that the sample exceeds the critical threshold, indicating thermal damage.

In the MicroLab method chosen for the pictured O-ring analysis, a threshold was set such that samples within the target group are shown in green while those outside the target group are shown in red. Furthermore, the conditional reporting feature can be used to display a customized alert message such as, “Confirmed FKM Type 1” for samples within the target group and the message “NOT FKM TYPE 1” for samples outside the target group.
Coatings

From paints… to polymers… to adhesives… the 4300 Handheld FTIR lets you confidently:

• Confirm that underlying metal surfaces are clean and contaminant free
• Track the cleaning of contaminants from inorganic and organic surfaces
• Ensure that the correct coating has been applied to the finished product
• Test whether primers and coatings are properly cured
• Measure thickness and uniformity on metal surfaces
• Evaluate monolayer coatings for coverage and uniformity
• Monitor paint aging and weathering
• Identify lacquers, paints, and pigments used in art conservation and restoration
• Determine presence of residual solvent following coating cure

Coating Identification: Protective coatings are a key component to highly polished metal substrates used in lighting and other industrial applications. The 4300 Handheld FTIR can easily identify coatings, in support of quality control or incoming inspection objectives. Measurement of three commonly used protective coatings on polished surfaces (A) demonstrates that these materials are clearly distinguished by their mid IR spectrum. A library search (B) identifies one of the compounds as a silicone protective coating.

Reliable field measurements, when and where you need them. Visit agilent.com/chem/4300HandheldFTIR
Powerful analytical capability, combined with an intuitive user interface, allows users of all levels to obtain great data in the field.

- Pictoral interface simplifies sample measurement
- RFID-enabled to optimize system acquisition parameters, and confirm that your sample interface and selected method are a match
- Real-time analysis mode and rapid scan rate make it easy to analyze the surface of an object, determine areas for more in-depth measurements, and develop a “molecular map” of the object’s surface
- Single-click trigger lets you execute methods quickly — including previously developed calibrations
- Full library search capability allows rapid identification, verification, and authentication
- Color-coded, visual alerts warn you when samples or objects are not within specification
- Automated diagnostics maximize your uptime
- Integrates easily with MicroLab PC software for easy data, methods, and libraries transference
- GLP/GMP compliant
Visual, intuitive user interface and software enable rapid system implementation

The highly acclaimed Agilent MicroLab Mobile software enables users of varied experience to get great results from the 4300 with a minimal training. The software guides the user through the measurement, and the RFID-equipped sample interfaces ensure that the method and measurement parameters are correctly matched. These innovations mean the 4300 will rapidly become an important part of your company’s workflow.

**STEP 1**

From the home screen you can quickly launch analysis, choose a method, and create a new reference method.

**STEP 2**

MicroLab Mobile Software will instruct when to position the spectrometer’s sample interface on the object to be analyzed.

**STEP 3**

During sampling, the progress bar shows the advancement of the data collection.

**STEP 4**

When the progress bar reaches 100%, the prompt will change to Transferring Data. You can then remove the instrument from the sample.

**STEP 5**

Results screen: The results screen will display the calculated component values relative to their critical limits. Components within the acceptable range are shown in green.

Reliable field measurements, when and where you need them. Visit agilent.com/chem/4300HandheldFTIR
More than 60 years of identifying and confirming both target and unknown molecules

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>First commercial recording UV-Vis, the Cary 11 UV-Vis</td>
</tr>
<tr>
<td>1954</td>
<td>Release of the Cary 14 UV-Vis-NIR</td>
</tr>
<tr>
<td>1969</td>
<td>First rapid-scanning Fourier transform infrared spectrometer, the FTS-14</td>
</tr>
<tr>
<td>1979</td>
<td>First use of a mercury cadmium telluride (MCT) detector in a FTIR</td>
</tr>
<tr>
<td>1982</td>
<td>First FTIR microscope, the UMA 100</td>
</tr>
<tr>
<td>1989</td>
<td>Release of the acclaimed Cary 1 and 3 UV-Vis</td>
</tr>
<tr>
<td>1999</td>
<td>First 256 x 256 MCT focal plane array for analytical spectroscopy</td>
</tr>
<tr>
<td>2000</td>
<td>First ATR chemical imaging system</td>
</tr>
<tr>
<td>2007</td>
<td>Smallest, most rugged commercially available interferometer introduced</td>
</tr>
<tr>
<td>2007</td>
<td>TumbLR sample accessory introduced — a revolution in FTIR liquid sampling</td>
</tr>
<tr>
<td>2008</td>
<td>First handheld FTIR, the ExoScan</td>
</tr>
<tr>
<td>2011</td>
<td>The Cary 630 FTIR raises the bar for routine analysis of solids, liquids, and gases</td>
</tr>
</tbody>
</table>

2014: Next-generation, 4300 Handheld FTIR introduced

Whether you specialize in materials science, industrial R&D, quality control, academic research, life sciences, or pharmaceuticals, Agilent molecular spectroscopy instruments can help you discover, characterize, and test your most diverse and challenging materials.

Agilent Service Guarantee

If your Agilent instrument requires service while covered by an Agilent service agreement, we guarantee repair or we will replace your instrument for free. No other manufacturer or service provider offers this level of commitment to keeping your lab running at maximum productivity.

Agilent Value Promise

We guarantee you at least 10 years of instrument use from your date of purchase, or we will credit you with the residual value of the system toward an upgraded model.

For more information

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In other countries, please call your local Agilent Representative or Agilent Authorized Distributor – visit agilent.com/chem/contactus

This information is subject to change without notice.
Appendix 49: Self-reported treatment and product adherence by study week

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Olive Oil N (%)</th>
<th>Sunflower Oil N (%)</th>
<th>No Oil N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Adherence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>25 (80.6)</td>
<td>24 (82.8)</td>
<td>33 (100.0)</td>
</tr>
<tr>
<td>Week 2</td>
<td>23 (79.3)</td>
<td>24 (88.9)</td>
<td>29 (100.0)</td>
</tr>
<tr>
<td>Week 3</td>
<td>25 (92.6)</td>
<td>30 (93.8)</td>
<td>36 (100.0)</td>
</tr>
<tr>
<td>Week 4*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Product Adherence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>22 (73.3)</td>
<td>23 (79.3)</td>
<td>32 (97.0)</td>
</tr>
<tr>
<td>Week 2</td>
<td>24 (82.8)</td>
<td>22 (81.5)</td>
<td>31 (96.9)</td>
</tr>
<tr>
<td>Week 3</td>
<td>24 (88.9)</td>
<td>27 (87.1)</td>
<td>37 (100.0)</td>
</tr>
<tr>
<td>Week 4</td>
<td>16 (57.1)</td>
<td>21 (70.0)</td>
<td>26 (74.3)</td>
</tr>
</tbody>
</table>

*participants were not asked about treatment compliance at 4 week assessment