A qualitative investigation of the impact of Mucopolysaccharidosis sub-types I and II on the quality of life of children and their parents

A thesis submitted to the University of Manchester for the degree of Master of Philosophy (MPhil) in the Faculty of Biology, Medicine and Health

2017

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<td>Mucopolysaccharidoses</td>
<td>MPS</td>
</tr>
<tr>
<td>Mucopolysaccharidosis Hurlers</td>
<td>MPS I-H</td>
</tr>
<tr>
<td>Attenuated Mucopolysaccharidosis II</td>
<td>attn. MPS II</td>
</tr>
<tr>
<td>Hematopoietic Stem Cell Therapy</td>
<td>HSCT</td>
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<tr>
<td>Enzyme Replacement therapy</td>
<td>ERT</td>
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<tr>
<td>Health Related Quality of Life</td>
<td>HRQoL</td>
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<tr>
<td>Quality of life</td>
<td>QoL</td>
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<tr>
<td>Glycosaminoglycan’s</td>
<td>GAG’s</td>
</tr>
<tr>
<td>Ear Nose Throat</td>
<td>ENT</td>
</tr>
<tr>
<td>Pediatric Quality of Life Inventory</td>
<td>PedsQL™</td>
</tr>
<tr>
<td>Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale</td>
<td>HS-FOCUS</td>
</tr>
<tr>
<td>Intelligence Quotient</td>
<td>IQ</td>
</tr>
<tr>
<td>Child Health Questionnaire</td>
<td>CHQ</td>
</tr>
<tr>
<td>Child Health Assessment Questionnaire</td>
<td>CHAQ</td>
</tr>
<tr>
<td>Adolescent health utility measure</td>
<td>AHUM</td>
</tr>
<tr>
<td>Pure Tone Audiogram</td>
<td>PTA</td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
<td>SNHL</td>
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<tr>
<td>Conductive hearing loss</td>
<td>CHL</td>
</tr>
<tr>
<td>Air conduction</td>
<td>AC</td>
</tr>
<tr>
<td>Bone conduction</td>
<td>BC</td>
</tr>
<tr>
<td>Air-bone gap</td>
<td>ABG</td>
</tr>
<tr>
<td>Otitis media with effusion</td>
<td>OME</td>
</tr>
<tr>
<td>Term</td>
<td>Abbreviation</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Hunter Outcome Survey</td>
<td>HOS</td>
</tr>
<tr>
<td>Decibels</td>
<td>dB</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>URTi</td>
</tr>
<tr>
<td>Obstructive Sleep Apnoea</td>
<td>OSA</td>
</tr>
<tr>
<td>Apnoea-Hypopnea Index</td>
<td>AHI</td>
</tr>
<tr>
<td>Juvenile Rheumatoid Arthritis</td>
<td>JRA</td>
</tr>
<tr>
<td>Attention Deficit Disorder</td>
<td>ADHD</td>
</tr>
<tr>
<td>Patient reported outcome measures</td>
<td>PROM</td>
</tr>
<tr>
<td>Continuous positive airway pressures ventilation</td>
<td>CPAP</td>
</tr>
<tr>
<td>Bi-level positive airway pressure therapy</td>
<td>BIPAP</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>CNS</td>
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<tr>
<td>National institute of clinical Excellence</td>
<td>NICE</td>
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</table>
Abstract

A qualitative investigation of the impact of Mucopolysaccharidosis sub-types I and II on the quality of life of children and their parents

Archana Soni-Jaiswal
The University of Manchester, Master of Philosophy (MPhil)
March 2017

Background; Mucopolysaccharidosis (MPS) is a rare, inherited, metabolic storage disorder. There are seven known subtypes, with each one displaying genotypic and phenotypic heterogeneity, producing a spectrum of clinical disease, and ranging from attenuated to severe. Historically children had a short life span with death in adolescence. Disease modifying treatments such as hematopoietic stem cell transplants for MPS I-H and enzyme replacement therapy for attenuated MPS I and MPS II, have transformed this into a chronic illness with survival into early adulthood. However, these children continue to carry a marked burden of disease, with significant morbidity. The impact of disease on the quality of life of the affected children remains poorly understood, with no previous work looking at patients’ perception of their own health, an important domain when considering the impact of treatment. These children also suffer with head and neck problems, including obstructive sleep apnoea and deafness.

Aim; Through this study, we aimed to explore the impact of the disease on the lives of the children, using the principles of grounded theory research.

Method; Children and their parents were invited to participate in semi-structured interviews. The transcribed interviews were coded and emergent themes explored until saturation occurred.

Results; The families of eleven children with MPS I and seven with MPS II were interviewed. Data analysis showed that in MPS I, the presence of airway disease had a profound impact on the emotional well being of parents whilst musculoskeletal disease had the biggest impact on the quality of life of the children themselves, causing chronic pain, restricted mobility, loss of independence and a loss in confidence. In MPS II, parents worried about their child’s ability to fit-in with their peers and achieve social and financial independence. The biggest challenge described by the children with MPS II themselves was from their deafness and language delay.

Conclusion; This is the first study to identify aspects of living with MPS that patient’s and their parents find most challenging. The themes to emerge from this work may form the domains of a new disease specific qualitative outcome measure. This exploratory work will also serve to improve the understanding that health care professionals have of the impact of disease on the lives of these children and their families.
Declaration

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Acknowledgements

Many people deserve thanks for their help and support during this MPhil. I would like to thank Professor Peter Callery, for his patience, guidance, advice and support over the last three years. Also, I would like to thank Professor Iain Bruce for suggesting this project to me, believing in me and guiding me, both in this research, but also in my career in Rhinology.

I would like to thank the team at the Willink Metabolic and Genetics unit for their invaluable support and help, without whom data collection for this project would not be complete.

Finally, I would like to thank all of the patients and their families for giving up their precious time to participate in this research.

Dedication

I would like to dedicate this thesis to my husband, Sujoy, and our daughter, Anaya. Without their patience and support, this research would not have been possible.
1.0 Introduction

Mucopolysaccharidosis (MPS) is a rare inherited metabolic storage disorder. Historically the management of these children was with palliative intent with death occurring in adolescence. Advances in medical care, primarily the use of hematopoietic stem cell transplants (HSCT) and the licensing of enzyme replacement therapy (ERT), alongside better multi-disciplinary management, has transformed MPS into a ‘chronic disease’ with survival into adulthood, although cure is still not possible.

This introduction aims to define Mucopolysaccharidosis sub-types I, II and VI, and their treatment. It aims to explore their health related quality of life (HRQoL), with specific focus on their head and neck disease. It also aims to study how their HRQoL has evolved with newer treatments; to ascertain if any measurement tools are currently available which measure HRQoL in these sub-groups of MPS.

The overall aim of this research project has been discussed in section 1.4. As my personal background is as a clinician in head and neck surgery, I wished, through this project, to explore the overall impact of MPS but also specifically of head and neck disease on the quality of life of these patients and their families. In 2013 (when this study was started), very little was published on the subject being explored. I asked for advice from Professor Ed. Wraith and Dr. Simon Jones, both specialist physicians in the field of
metabolic medicine, with many years of personal experience between them in managing children with MPS. They suggested recruiting patients with MPS I, II and VI for my research study. They felt that these sub-groups of MPS have similar somatic disease manifestations, including head and neck disease and their results could be pooled together for data analysis. Hence, it is with this advice that these three sub-groups were chosen and explored further. However, during the course of the research, it became apparent that although these patients have similar somatic manifestations of disease, the impact of them on quality of life differs for each sub-group and pooling together the data would be a dis-service to the three groups of patients. Although the interviews were conducted simultaneously, data analysis was separate for each sub-group. As we were no longer pooling together data, larger patient numbers for each sub-group group were needed. Further research efforts focused on MPS I and II and these results are presented here in this thesis. The MPS VI arm of this project is currently on going and will be published in the future.

1.1 Mucopolysaccharidoses; Background

Seven different types of MPS have been identified, each one caused by a deficiency in the activity of a single lysosomal enzyme, involved in the degradation of macromolecules known as glycosaminoglycan’s (GAGs) within cellular lysosomes (Neufield and Muenzer 2001). Eleven different enzyme deficiencies have been identified so far (Clarke 2008). With the exception of MPS II, all of the others share an autosomal recessive
inheritance, occurring equally in both sexes. MPS II has an X-linked inheritance, occurring predominantly in male patients (Muenzer 2011). The overall incidence of MPS as a group is 1:25,000 live births (Clarke 2008).

The accumulation of GAG’s within tissues results in progressive cellular damage and organ failure, resulting in multi-system disease (Neufield and Muenzer 2001). Elevated GAG levels are found in urine, blood and cerebrospinal fluid with decreased levels of lysosomal enzyme on assay (Muenzer 2011). The disease may affect the central nervous system, skeletal system and visceral system. Allelic heterogeneity results in different levels of residual enzyme activity. This in turn produces large phenotypic variation. Disease severity and rate of progression lie on a continuous spectrum ranging from mild or attenuated disease with slow progress to severe disease that is rapidly progressive. Both attenuated and severe forms have significant disease morbidity associated with them (Clarke 2008). The disease is always progressive and life-limiting, with an adverse impact on the patients physical and mental health and HRQoL (Wiklund, Raluy-Callado et al. 2013).

MPS I, II and VI have similar somatic disease manifestations, including head and neck disease. MPS VI are spared the neurocognitive disease that may develop in the severe forms of MPS I and II. Enzyme replacement therapy is currently available for all three types.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>GAG substrate</th>
<th>Enzyme deficiency</th>
<th>Gene locus</th>
<th>Genetic inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I</td>
<td>Dermatan Sulphate, Heparan Sulphate</td>
<td>α-1-iduronidase</td>
<td>4p16.3</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>MPS II</td>
<td>Dermatan Sulphate, Heparan Sulphate</td>
<td>Iduronate-2-sulfatase</td>
<td>Xq28</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>MPS III</td>
<td>Heparan Sulphate</td>
<td>A: heparin N-sulfatase B: α-acetylglicosaminidase C: acetyl-CoA D: N-acetylglucosamine 6-sulfatase</td>
<td>A: 17q25.3 B: 17q21 C: 8p11.1 D: 12q14</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>MPS IV</td>
<td>A, B</td>
<td>A: Galactose 6-sulfatase B: β-galactosidase</td>
<td>A: 16q24.3 B: 3p21.33</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>MPS VI</td>
<td>Dermatan Sulphate, Chondroitin Sulphate</td>
<td>Arylsulphatase B</td>
<td>5q11-q13</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>MPS VII</td>
<td>Dermatan Sulphate, Heparan Sulphate, Chondroitin Sulphate</td>
<td>β-Glucuronidase</td>
<td>7q21.11</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>MPS IX</td>
<td>Hyaluronan</td>
<td>Hyaluronidase</td>
<td>3p21.3-p21.2</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

*Table 1: Classification of Lysosomal storage disorders*
1.2 Management of MPS

Hematopoietic stem cell therapy (HSCT) and Enzyme replacement therapy (ERT) have improved the disease severity and life expectancy of patients with MPS I, II and VI, with an overall improvement in their disease burden. Prior to their introduction, treatment of MPS was palliative. A multi-disciplinary approach to management is required with input from both medical and allied health professionals. Treatment choice is determined by defining the risk-benefit profile of available options based on age at diagnosis, cognitive impairment and predicted phenotype (Wraith, Scarpa et al. 2007, Muenzer, Wraith et al. 2009).

1.2.1 Enzyme replacement therapy (ERT)

MPS I, II and VI are all caused by distinct single enzyme deficiencies in the GAG degradation pathway. Purified enzyme produced by recombinant DNA technology is now commercially available for all three sub-types (Valayannopoulos and Wijburg 2011). Laronidase (recombinant α-L-iduronidase; aldurazyme, Genzyme corporation, Cambridge MA) for MPS I, Idursulfase (recombinant I2S; Elaprase, Shire Pharmaceuticals, UK) for MPS II, Galsufase (recombinant N-acetylgalactosamine-4-sulfatase; Naglazyme, Biomarin pharmaceutical, CA) for MPS VI. The purified recombinant enzyme is given as a weekly infusion and placebo controlled double-blind studies have shown that over a twelve month period patients will experienced a reduction in urinary GAG excretion, a reduction in organomegaly, improved cardiac, respiratory and musculoskeletal output as
witnessed by the six minute walk test and a reduction in the apnoea-hypopnea index (AHI) on overnight sleep studies (Harmatz, Giugliani et al. 2008, Muenzer, Beck et al. 2011). Most improvement is seen within the first 12-18 months on treatment following which improvements plateau out (Wraith, Clarke et al. 2004, Muenzer, Guscavas-Calikoglu et al. 2007, Clarke, Wraith et al. 2009). Most centers are now initiating ERT soon after the diagnosis is established (Muenzer, Beck et al. 2011). With MPS I, five year follow-up data has been reported and shows that the systemic improvements persist long term. Patients who begin ERT prior to puberty will grow substantially in comparison with those that start it after puberty. In MPS II, children younger than 10 years will see a 14.6cm increase in height compared to those treated with placebo (Schulze-Frenking, Jones et al. 2011). Ocular disease may remain stable or worsen (Sifuentes, Doroshow et al. 2007, Muenzer, Wraith et al. 2009).

The infused enzymes are unable to cross the blood-brain barrier. In children with severe cognitive disease, an argument can be made that the ERT may reduce the systemic disease burden, with an overall improvement in quality of life (QOL). However, this is offset by the burden of the weekly enzyme infusions, both on the child and their family. Also, the ERT does not seem to reverse established cardiac valvular disease or existent skeletal abnormalities (Wraith, Clarke et al. 2004, Clarke, Wraith et al. 2009), hence once again highlighting the need to initiate treatment early, prior to the development of established irreversible disease.
ERT must initially be administered weekly in hospital, due to the small risk of anaphylactic reaction associated with the intravenous protein product. These may be mild such as headache, hypertension, urticaria, flushing, pyrexia and rash or a more severe life-threatening anaphylaxis. Patients become increasingly tolerant of these and the mild transfusion reactions improve with time (Wraith, Clarke et al. 2004, Muenzer, Wraith et al. 2006, Harmatz, Giugliani et al. 2008, Muenzer, Beck et al. 2011, Muenzer, Bodamer et al. 2012). Forty to a hundred percent patients will develop Immunoglobulin G antibodies against the protein product. The antibodies do not appear to reduce the efficacy of the ERT on short-term follow-up although no long-term studies currently exist (Harmatz, Whitley et al. 2004, Muenzer, Beck et al. 2011, Brands, Oussoren et al. 2013).

1.2.2 Hematopoietic stem cell therapy (HSCT)

Stem cell therapy is a treatment in which stem cells obtained from bone marrow, peripheral blood stem cell and more recently umbilical cord blood (Boelens, Wynn et al. 2007) are harvested from a matched donor and transplanted into an affected recipient. The HSCT relies on progressive replacement throughout the body of endogenous hematopoietic lineage cells with the exogenous cells transplanted from the donor (Scarpa, Almassy et al. 2011). These exogenous cells provide a source of leucocytes which in turn produce the deficient enzyme. Affected systemic cells take up the enzyme and use it to degrade the build-up of GAG’s within them and re-establish a production-degradation homeostasis (Hobbs, Hugh-Jones et al. 1981).
Stem cell transplant has been used in the treatment of young children with Hurler’s (severe disease on the spectrum), also known as MPS I-H, since the first allogeneic engraftment in 1980 by the Westminster transplant team on a one-year-old boy (Boelens, Wynn et al. 2007). HSCT is the only treatment modality to preserve intellectual development, unlike ERT that cannot cross the blood brain barrier. The original patient transplanted by the Westminster transplant team had normal levels of enzyme at the age of twenty with an intellectual ability in the low normal range (Krivit, Peters et al. 1999). Alongside this ability to cross the blood-brain barrier, HSCT provides superior metabolic correction than ERT alone, with normal serum antibody levels in 95% and normalised urinary GAG excretion in 100% of transplanted patients. Also it does not initiate antibody formation, a problem encountered with ERT (Aldenhoven, Jones et al. 2015).

HSCT now forms the standard of care for children with MPS I-H. When transplanted using the modified international HCT guidelines (Boelens, Wynn et al. 2007, Bartelink, Lalmohamed et al. 2016), these patients have low levels of treatment toxicity and high-engrafted survival rates, 95.2% overall survival and 90.3% event free survival, over an 8 year follow-up period (Aldenhoven, Jones et al. 2015). Life expectancy is significantly increased, with survival up to 23 years of age (Aldenhoven, Wynn et al. 2015)
However, despite treatment with HSCT, these children continue with substantial residual disease burden. Children with a baseline DQ/IQ lower than 70 have a 70% risk of developing severe cognitive impairment despite being transplanted before the age of 12 months. The transplant itself may lead to short stature. Established skeletal abnormalities and valvular heart disease, as with ERT, do not improve, and despite HSCT may continue to progress over time.

From a head and neck viewpoint, upper airway obstruction, obstructive sleep apnea (OSA) and recurrent upper respiratory tract infections (URTi) resolve within a few months of successful transplant. Levels of hearing loss improve from 88% to 62.8%, directly related to levels of IDUA enzyme levels obtained post-transplant (Malone, Whitley et al. 1988, Krivit, Peters et al. 1999, Muenzer, Wraith et al. 2009, Aldenhoven, Wynn et al. 2015).

For improved functional outcomes, children must be transplanted as early as possible, prior to the development of irreversible tissue damage. Other predictors of improved prognosis post-transplant are a normal leukocyte IDUA enzyme post-HSCT, non-carrier donor transplantation using cord blood, full-donor chimerism, and higher levels of DQ/IQ pre-transplant (Aldenhoven, Wynn et al. 2015).

With transplant survival rates now in excess of ninety percent, we may see HSCT extended on a case-by-case basis to children with attenuated MPS.
type I who display a more severe genotype and phenotype (de Ru, Boelens et al. 2011). We have adopted this practice in our unit.

Evidence for stem cell transplantation in children with MPS II is based on published case series with small numbers owing to the rarity of the disease. Although the HSCT normalizes leucocyte levels of the enzyme, serum levels remain low (Scarpa, Almassy et al. 2011). It improves systemic disease, including cardiac disease which is a major source of mortality in MPS II but does not seem to confer the same neurological improvement as that seen consistently in MPS I. These published case series report outcomes for transplantations on children with pre-existent neurocognitive impairment. Long-term studies on patients transplanted without neurocognitive disease are not available (Vellodi, Young et al. 1999, Guffon, Bertrand et al. 2009). Also, in severe MPS II disease behavioral changes are thought to arise from large genetic deletions, extending into adjacent genes, which would be difficult to improve with HSCT and increased enzyme expression. It has also been hypothesized that enzyme expression in the central nervous system (CNS) after HSCT in MPS II is sub-optimal (Vellodi, Young et al. 1999). Improvement in airway obstruction, OSA and hearing loss have been reported but no quantitative data exists in support of this (Scarpa, Almassy et al. 2011). Furthermore, high rates of post-transplant mortality (70% in the observational study by Vellodi, Young et al, 1999), are seen, offsetting the benefit of HSCT in MPS II (Vellodi, Young et al. 1999).
MPS VI patients do not have the same neurocognitive disease burden and marked skeletal pathology as MPS I and II. The benefits of HSCT in these patients are outweighed by the severe morbidity and high mortality of the transplant. Treatment with HSCT has been superseded by ERT (Giugliani, Harmatz et al. 2007). However, Forty-five patients with MPS VI globally are registered with the Centre for international blood and marrow transplant research with a 1-year survival of sixty-seven percent. No long-term data is available (Valayannopoulos, Nicely et al. 2010).

1.2.3 Other therapies under research

To overcome the inability of systemic ERT to cross the blood-brain barrier and improve neurocognitive manifestations of MPS, intrathecal drug delivery, directly into the cerebrospinal space has been proposed. Animal models have shown promising results (Dickson 2009). Human clinical trials are currently on going. The first one is a multi-center American trial assessing the efficacy of intrathecal alpha-L-iduronidase in patients with MPS type I in decreasing neurodevelopmental deterioration. The enzyme is delivered into the spinal fluid of patients with MPS I-H at intervals, both before and after their HSCT. This open label phase 1 clinical trial has completed patient recruitment and is expected to finish in June 2017 (Orchard 2017). A second study is one assessing intrathecal Idursulfase-IT in MPS II Hunters with mild cognitive impairment. This is a randomized, open label, multicenter trial, studying the effects of Intrathecal Idursulfase-IT, administered weekly for 52 weeks, in children over the age of three with, to assess impact on neurocognitive function (Shire. 2017). Shire
pharmaceuticals UK are also running a long-term safety study (Shire. 2017). These studies have also completed patient recruitment and should finish in October 2017.

Neonatal gene therapy in mice with MPS I has shown very promising results with complete correction of clinical disease. The newborn mice are injected with retroviral vector that programs hepatocytes within the liver to secrete the deficient enzyme expressing M6P into the circulation, allowing uptake at M6P receptors systemically. Hearing impairment, confirmed on ABR testing, showed complete resolution with high dose therapy and partial resolution with low-dose therapy (Liu, Xu et al. 2005). A phase 1, Multi-center, open–label clinical trial assessing the safety of SB-318, an intravenously delivered Zinc Finger Nuclease is on-going in patients with MPS I. The Zinc Finger Nuclease inserts a correct copy of the IDUA gene in the Albumin locus in hepatocytes with the goal of lifelong therapeutic production of the IDUA enzyme. This trial is currently recruiting adult patients and is due to complete in January 2020 (Sangamo 2020).

In vivo trials of substrate reduction therapy with Genistein, a soy isoflavone, are also under investigation. It inhibits activity at the EGF receptor, in turn decreasing the expression of genes encoding one or more enzymes involved in GAG synthesis. Unlike ERT it does cross the blood-brain barrier. Early studies in the mouse model have shown positive results (Friso, Tomanin et al. 2010).
Ataluren (Translarna™) is a small molecule compound that targets nonsense mutations, as seen in 60-80% of patients with MPS I, with the ability to restore the missing enzyme, α-1-iduronidase. It has recently been approved in Europe for the treatment of nonsense mutation Duchene muscular dystrophy (Ryan 2014). At present an open label clinical trial is underway, recruiting children in Manchester, U.K and Hamburg, Germany, assessing the efficacy of Ataluren in children with MPS I (PTC 2015).

1.3 Mucopolysaccharidoses; Health Related Quality of Life

1.3.1 Definition of HRQoL

Health-related Quality of life is the impact an illness has on the complete ‘physical’, ‘mental’ and ‘social’ well being of a patient. The World Health Organization put these three domains forward in 1995, further describing QOL as, ‘the individuals perception of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’ (WHQOL Group 1995).

The assessment of quality of life can be objective via the measurement of clinical parameters, functional based on performance of tasks and subjective based on the patient’s perception of their own health state (Gill and Feinstein 1994). It is the patient’s perspective that underpins the idea of ‘health related quality of life’ (HRQoL) and will be considered here further.
If we offer a patient a new treatment, it is important to consider how that treatment makes the patient feel and if it fulfills their expectations. This information is vital in assessing the success of that particular treatment, both in clinical medicine and in research; justifying the cost of the treatment in a health care system such as the National Health Service, where treatment is funded by the state. In December 2015, the National Institute of Clinical Excellence (NICE) issued clinical guidance for the use of Elosulfase ERT in MPS IVa (not a sub-group being studies in this thesis). As part of this guidance they released a document, the managed access agreement, which sets out essential auditable measures that need to be collected to evaluate the effectiveness and safety of the treatment. Patients must sign this contractual agreement to receive the treatment. For the first time, QoL measures form part of this agreement and patients must complete the EQ5D-5L utility score, MPS HAQ assessing caregiver burden, the Beck depression score and the Adolescent pediatric pain tool or brief pain inventory score depending on age. The mandatory collection of quality of life data by NICE emphasizes the increasing importance of QoL data and its future role in funding of treatment (NICE 2015).

When improving or developing better treatment strategies it is also important for clinicians and researchers to understand children’s perception of their illness and the dysfunction in physical and mental health they may directly attribute to it. It is important to recognise that patients with the same objective health can have very different subjective experiences of it (Eiser and Morse 2001).
HRQoL can be measured using patient-reported outcome measures (PROM). These are questionnaires with multiple domains or items, each containing stems pertinent to the aspect of HRQoL being assessed. These may be generic, used to compare different chronic illnesses or the illness in question against a normative population. Alternately, they may be disease specific, with improved sensitivity and inclusion of domains pertinent to the illness in question. However, disease specific measures may lack the psychometric sophistication of the generic measures. When choosing a QOL measure, one must ensure that it is reliable, sensitive for change in the population being studied, valid for the group being researched and reproducible (Eiser and Morse 2001, Eiser 2004).

Many available pediatric measures are parent-proxy questionnaires, completed by parents on behalf of their child. However, there is only a moderate correlation between parent and child responses to QOL assessments. Parents and children base their judgment of pediatric HRQoL on different information and have differing perspective. Children report less adverse impact on their own QOL from the disease and fewer problems than their parents. But, parent proxy ratings, although not a true reflection of the child’s perspective of their QOL, when used in conjunction with the child’s ratings, provides a more comprehensive understanding of the impact of disease. They are also invaluable when young children or older children with cognitive impairment cannot complete the measures themselves (Eiser and Jenney 2007, Eiser and Varni 2013).
1.3.2 Evidence for the impact of MPS on the HRQoL of patients and parents

ERT and HSCT have improved the objective and functional outcomes in children with MPS, transforming it into a chronic illness. However, despite the marked improvements these patients still have significant morbidity, which they now carry into adulthood. Much of the published MPS literature takes the form of case series, MDT consensus guidelines (Muenzer, Wraith et al. 2009, Scarpa, Almassy et al. 2011) and clinical trials reporting the efficacy of ERT (Wraith, Clarke et al. 2004, Harmatz, Giugliani et al. 2006, Muenzer, Wraith et al. 2006, Muenzer, Guscavas-Calikoglu et al. 2007). Perhaps due to the evolving nature of the disease, research into the HRQoL in MPS is gaining recognition and a handful of studies have been published in the last few years. This body of work is considered in greater detail in the next section.

1.3.2.a MPS II

Expert panel opinion is that all patients with MPS II experience progressive somatic involvement, whilst only those with the severe phenotype experience learning difficulties with neuro-degeneration and severe cognitive impairment (Muenzer 2011). However, in our experience, only a minority of children with the attenuated form has normal intelligence, with most of them suffering static, non-progressive, learning difficulties. We feel it is the progress of the cognitive disease and learning difficulties that
differentiates the two forms. Licensing of enzyme replacement therapy (ERT), alongside better multi-disciplinary management, has transformed attenuated MPS II into a ‘chronic disease’, with improved functional outcomes, although cure is still not possible.

Using the Pediatric Quality of Life Inventory (PedsQL™), a generic HRQoL instrument that measures physical, mental (emotional) and social dimensions, alongside school functioning on a 23-item scale, Needham et al, show that parents of both attenuated and severe forms and children with the attenuated form of MPS II, report significantly lower HRQoL scores than healthy children. Parents also score their children with poorer scores than children with cancer, although children with the attenuated form score themselves the same as children with cancer. Those with the severe form have significantly lower scores than those with the attenuated disease overall, but also more specifically in the domains physical and school functioning. Both groups have similar scores for emotional and social functioning. The study interestingly shows that ERT does not improve the PedsQL score of children (mean follow-up 33months) (Needham, Packman et al. 2014). This could be because there was no real improvement in their QOL with the ERT or alternately because the PedsQL is not sensitive to changes in QOL caused by ERT.

This work does not provide insight into the specific aspects of the illness that produce a reduction in scores for each of the domains measured. It does not highlight which aspects of the illness patients find most
problematic. It is not disease focused and so may not be sensitive to the specific effects of MPS on HRQoL.

MPS is a heterogeneous group of diseases. No generic outcome measures have specifically been validated for any of the MPS sub-groups and hence may fail to capture the true impact of HRQoL in these children and adolescents, alongside the impact of treatment and evolution of symptoms over time. A fuller picture would be obtained by combining the use of generic questionnaires with validated, psychometrically robust, disease specific questionnaires.

The only described disease-specific outcome measure in the literature is the Hunter Syndrome-Functional Outcomes For Clinical Understanding Scale (HS-FOCUS). It has both parent and child versions, and is designed to measure the functional impact of disease on MPS II. It has six domains, with each individual item (68 for the parent-version and 54 for patient-version) scored on a 4-point ordinal scale. The domains are Walking/Standing, Reach/Grip, Sleeping, Schooling/Work, Activities and Breathing (Wiklund, Raluy-Callado et al. 2013). It does not include any specific domains to assess the impact of these functional restrictions on HRQoL.

The questionnaire along with a detailed description of how it was developed remains unpublished at the time of writing. The questions were developed via a literature review and input from specialists that treat MPS. Parents,
patients and focus groups also contributed to the questions. It is not clear if qualitative interviews were conducted to identify items for inclusion. Qualitative interviews are important in identifying domains relevant to the patients and parents themselves, forming the initial basis for a robust outcome measure (Fayers and Machin 2007).

The HSFOCUS has been validated and shortened (by removal of the breathing domain) for use in MPS II with an internal consistency of >0.70, acceptable test-retest reliability, moderate content and construct validity, good criterion validity and responsiveness for all domains barring Sleep and Schooling/Work. The authors do not comment on floor to ceiling effect, reproducibility and interpretability. This form is not yet in general use but would serve to allow monitoring of disease progression over time and evaluate the benefits of administered treatment (Wiklund, Raluy-Callado et al. 2013, Wiklund, Raluy-Callado et al. 2014). The ‘HSFOCUS’ questionnaire has been used to determine the impact of mild MPS II on adolescents not treated with ERT by Ruley-Collado et al, where parents and children over the age of twelve years, completed a series of questionnaires. Their study showed that the disease, despite being termed mild, had a considerable impact on physical health, with poor scores in the Walking/Standing and Grip/Reach domains, confirmed by the HS-FOCUS questionnaire and three generic measures, the Childhood health assessment Questionnaire (CHAQ) (developed and validated for juvenile arthritis) (Giannini, Ruperto et al. 1997), the Child Health Questionnaire (CHQ) (validated in healthy children) (Landgraf, Abetz et al. 1999) and the Health
Utilities Index (validated in healthy children) (Horsman, Furlong et al. 2003). Key findings were inability to perform daily activities secondary to chronic pain and loss of dexterity, severe disability secondary to deafness, problems with self-esteem and family cohesion and altered perception of self-image. Parent-scores and patient-scores correlated well, although as with other studies, the parent scores were marginally higher. However, these were all measures of function rather than the patients/parents subjective experience of the disease and its impact on HRQoL (Raluy-Callado, Chen et al. 2013).

A survey of seventy-three caregivers and twenty-one patients with MPS II, using the Vineland II questionnaire, reported findings consistent with Ruley-Collado (Needham, Packman et al. 2013). The researchers assessed communication (expressive, receptive and written), daily living (personal care, domestic care and community), socialization (interpersonal relationships, play and leisure time and coping skills), physical activity/motor skills and maladaptive behavior (internalizing and externalizing behaviours) (Sparrow, Cicchetti et al. 2005). The authors reported that children with MPS II had significantly lower functioning than healthy controls in communication, daily living skills, socialization and motor skills in comparison with normative data. These scores worsened with increasing age. In those with mild disease these were within the ‘gross motor’ and ‘coping’ domains, whilst in children with severe MPS II, it was across all domains, with worsening adaptive behavior scores. Those with more severe disease had poorer adaptive functioning scores in comparison
with the mild group. There was no significant correlation between length of
time on ERT and adaptive function scores. The main study drawback was
although the Vineland II is validated for assessment of adaptive behavior of
healthy individuals based on caregiver reports, it has not been validated for
the MPS population and as it is not disease specific, limiting its sensitivity
in measuring the impact of disease and treatment in this population
(Needham, Packman et al. 2013).

The literature on the psychosocial impact of MPS on patients and on their
parents is very sparse. The only published study identified in this review
was by Kuratsubo who prospectively assessed the intellectual ability,
personality trait and mental health of 10 patients with attenuated MPS II in
Japan, not treated with either ERT or HSCT. Their results showed that
patients suffering with an attenuated phenotype have an intelligence
quotient (IQ) slightly lower than the general population. They comment
that the test results may have been skewed due to physical and hearing
disability but do not comment on other social factors such as interruption of
schooling. They also found that despite the multiple medical problems,
these young adults had well-balanced personalities without negative
psychological impact. Although many of these patients had the mental
capacity to work, they could not manage this due to physical or
psychological disability. Their anxiety levels and those of their family were
higher than levels seen within the normal population. These were due to
worry about physical disabilities, guilt about their parents, concerns about
making friends, worry about their physical appearance and the unknown
future ahead of them, stress about marriage, economic burden and getting a job. They did not assess depression (kuratsubo, Suzuki et al. 2009).

The Adolescent health utility measure (AHUM) is a multi-attribute measure that focuses on the key impact of chronic illness amongst older children and adolescents. The AHUM has 6 domains, self-care, pain, mobility, strenuous activity, self-image and health perception, measured on a Likert scale. It was used in the Idursulfase ERT trial for the treatment of MPS II and showed a significant improvement over 53 weeks in all domains, with the most benefit seen in the dimensions of self-care and bodily pain (Beusterien, Yeung et al. 2012). However, it does not measure HRQoL, which is of interest in this study, but is designed for use in cost-benefit analysis of an intervention. A preference value is assigned to each health state experienced by the patient and then used in Quality adjusted life year analysis (cost-effectiveness analysis).

1.3.2.b MPS I

The body of published work assessing the impact of HRQoL on children with MPS I is sparse in comparison with MPS II. Researchers appear to have concentrated their research efforts on collaborative trials, initially assessing the effectiveness or ERT and HSCT, and more recently improving outcomes with HSCT in MPS I.

In 2015, the first paper to assess the impact of MPS I on quality of life was published. The Vineland Adaptive Behavior scale and CHQ were
administered to post-transplant children with MPS I-H. The results show that adaptive functioning in children with MPS I-H, post-HSCT, is associated with genotype, with poorer adaptive ability and cognitive ability seen in those children with more severe genetic mutations. Children with MPS I-H are two standard deviations below healthy controls for impact of physical disease on QOL, despite HSCT, but the same as healthy controls for psychosocial impact (emotional well being) on QOL. Increased age at transplant (>2 years), being from a lower socioeconomic background and receiving an unrelated bone marrow transplant, result in a poorer quality of life, as measured by the CHQ, than healthy peers (Kunin-Batson, Shapiro et al. 2015). However, children with MPS I who have been treated with HSCT have better adaptive scores and psychosocial scores than children who are managed by ERT alone (Ahmed, Zuck et al. 2012, Kunin-Batson, Erickson et al. 2012).

The drawbacks of these studies though are that the CHQ is not disease specific and although the Vineland II is validated for assessment of adaptive behavior of healthy individuals based on caregiver reports, it has not been validated for the MPS population and as it is not disease specific, limiting its sensitivity in measuring the impact of disease and treatment in this population. Also, the Vineland II measures adaptive functioning, rather than the impact of disease on QOL. Does HSCT improve HRQoL to levels comparable with that of healthy children, in comparison with those managed on ERT alone, who seem to continue with a significant burden of disease? Further exploratory work is needed to help answer this question.
Patients with MPS I have similar insecurities as Kuratsubo’s cohort of attenuated MPS II patients, with concerns about their identity, future expectations and social relationships. Parental stress is associated with the ideal of being perceived as a ‘good-parent’ (Lawes 2007). These findings are from a short communication that Lawes published after undertaking a sponsored study. She conducted 22 one-on-one interviews with families of children suffering with MPS I, using discourse analysis. Unfortunately, her brief published report does not provide details of her methodology and whether the interviews were structured or semi-structured. She does not provide a topic guide, patient demographics, treatment or detailed results from the interviews.

There are no other published works exploring the HRQoL of patients with MPS I.

1.3.2.c MPS VI

As with MPS I, very little research work exists examining the impact of MPS VI on the QoL of patients and their carers, hence explaining the brevity of this section.

The ‘TNO-AZL Child Quality of Life Questionnaire’ Child-form for children and ‘TNO-AZL Questionnaire for Pre-school Children’s Health Related Quality Of Life’ are generic HRQoL measures and were used in a
study of the efficacy of Galsulfase ERT for MPS VI in Dutch patients. During the course of treatment with the ERT, the domains: lung problems, social functioning, sleeping, liveliness, positive mood and communication improved significantly. In the older children anxiety and negative emotions worsened showing higher levels of stress as the children got older, highlighting the developmental changes in children that can influence the results (Brands, Oussoren et al. 2013).

No further studies examining the impact of MPS VI on QoL have been published.

1.3.3 ERT clinical trials

ERT has improved the objective clinical and functional outcomes in children with MPS, improving both morbidity and survival. However, its impact on HRQoL remains unclear. The qualitative outcome measures used by the ERT trials in MPS I, II and VI are summarised in Table 2 (Valayannopoulos and Wijburg 2011). However, the ERT trials have not measured the impact of treatment on HRQoL.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study design</th>
<th>MPS subtype</th>
<th>No of patients included in study</th>
<th>Quality of life measures</th>
<th>HRQoL impact assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iduronate-2- sulphatase (Muenzer, Guscavas-Calikoglu et al. 2007)</td>
<td>Phase I/II double-blind placebo controlled RCT</td>
<td>MPS II</td>
<td>12</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Iduronate-2- sulphatase (Muenzer, Wraith et al. 2006, da Silva, Strufaldi et al. 2011, Buesterien 2012)</td>
<td>Phase II/III double-blind placebo controlled RCT</td>
<td>MPS II</td>
<td>32</td>
<td>AHUM CHQ</td>
<td>Significant improvement over 53 weeks in all domains, with the most benefit seen in the dimensions of self-care and bodily pain</td>
</tr>
<tr>
<td>α-L-Iduronidase (Wraith, Clarke et al. 2004)</td>
<td>Double-blind placebo controlled RCT</td>
<td>MPS I</td>
<td>22</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>α-L-Iduronidase (Clarke, Wraith et al. 2009)</td>
<td>3.5 year open-label extension study</td>
<td>MPS I</td>
<td>45</td>
<td>CHAQ/HAQ disability index</td>
<td>Disability index remained stable or improved over 3.5 yrs (mean 1.91)</td>
</tr>
<tr>
<td>α-L- Iduronidase(Wraith, Beck et al. 2007)</td>
<td>Open-label study of patients &lt;5yrs</td>
<td>MPS I</td>
<td>20</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Galsulfase (Brands, Oussoren et al. 2013)</td>
<td>Open-label study</td>
<td>MPS VI</td>
<td>11</td>
<td>TNO-AZL children (TACQOL), preschool (TAPQOL) versions</td>
<td>Domains; lung problems, social functioning, sleeping, liveliness, positive mood, communication and social functioning improved significantly. In the older children anxiety and negative emotions worsened showing higher levels of stress as the children got older</td>
</tr>
</tbody>
</table>

Table 2; Subjective outcomes used in the ERT clinical trials for MPS I, II and VI
1.4 Head and neck symptoms in Mucopolysaccharidoses and their impact on HRQoL

1.4.1 Deafness

Hearing loss is a universal finding in MPS, with a third of patients suffering with severe-profound hearing loss (≥61 decibels (dB) pure tone average threshold) (Napiontek and Keilmann 2006). More is known about the hearing loss in MPS type II, in comparison with the other sub types, due to the publication of an observational study; The Hunter outcome survey (HOS) (Keilmann, Nakarat et al. 2012). At the time of survey, ninety-three percent of the eighty-three children surveyed had a hearing loss; 20% had a mild hearing loss, 31% a moderate loss, 22% a significant loss and 7% a profound loss (WHO-ICIDH criteria). One third had a sensorineural hearing loss (SNHL) with a further third a mixed hearing loss. 16% had a pure Conductive hearing loss (CHL). The survey also reported that bone-conduction thresholds worsened with age by 1dB each year and that eventual SNHL occurred in most patients (Keilmann, Nakarat et al. 2012).

In MPS I, seventy-eighty percent of patients suffer with a mild-moderate hearing loss (mean Air conduction (AC) threshold 33.9dB, mean bone conduction (BC) threshold 12.8dB with an air-bone gap (ABG) of 21dB). This hearing loss appears to remain stable with advancing age. Following a
transplant, the incidence of hearing loss improves and is seen in sixty-three percent of patients. 30% have an SNHL, 31% CHL and 40% a mixed hearing loss (Lin, Shih et al. 2014, Aldenhoven, Wynn et al. 2015, Shapiro, Nestrasil et al. 2015).

No data has been published on the natural history of hearing loss in any of the MPS sub-types. All sub-types appear to have a higher incidence of CHL in early childhood, which then changes to higher levels of SNHL with advancing age (Pentek, Gulacsi et al. 2016).

The conductive element of their hearing loss may be attributed mainly to otitis media with effusion (OME) and recurrent acute otitis media (rAOM). OME and rAOM are commonly seen in well, young children without MPS, with peak incidence at 2 and 6 years. In MPS, GAG deposits within the Nasopharynx and Eustachian tube, along with adenoidal hypertrophy and rhinosinusitis contribute to persistent Eustachian tube dysfunction. Unlike healthy children, the middle ear effusion fails to resolve in childhood, with symptoms occurring into adolescence and adulthood. The CHL may be managed with long and short-term ventilation tubes, which improve both AC and BC hearing thresholds (Peck 1984, Motamed, Thorne et al. 2000, Napiontek and Keilmann 2006, Pentek, Gulacsi et al. 2016). Temporal bone studies in MPS show that GAG containing vacuoles develop within the middle ear cavity and mastoid air cell system, alongside replacement of the ossicles with mesenchymal tissue. For this reason, children may require hearing aids to supplement the improvement seen with the ventilation tubes.

The underlying cause for the sensorineural component of the hearing loss in MPS is less well understood. No degenerative loss of the hair cells within the organ of Corti has been noted in either human or canine models. In the canine and mouse model, progressive vacuoles containing GAGs are seen within otic capsule structures, the spiral ligament and stria vascularis, with increasing age of the animal (Schachern, Cureoglu et al. 2007, Horedeaux, Deniaud et al. 2011). It is hypothesized that this may lead to loss of epithelial cells within both of these supporting structures, with an eventual imbalance in the ionic composition of endolymph, although further neurophysiology studies are required to evaluate this theory further (Horedeaux, Deniaud et al. 2011). Audiometric patterns witnessed in HOS were as follows: 48% had a flat SNHL; 20% a gently sloping high frequency SNHL; 13% had a low frequency ascending SNHL; and 2.6% a mid frequency U shaped loss (Keilmann, Nakarat et al. 2012). Rehabilitation may be achieved by a conventional Hearing Aid. More recent evidence is emerging for implantable hearing aids such as Cochlear implantation in selected children with severe/profound hearing loss, who would obtain minimal benefit from more conventional hearing aids (Saeed, Nichani et al. 2013).

There is a paucity of literature that examines the impact of ERT and HSCT on hearing loss in children with MPS. Lin et al are the first to report pre-
treatment hearing thresholds in patients with MPS. In their cohort of thirty-nine children with different types of MPS sub-types, three with MPS II are followed-up long term after the insertion of ventilation tubes and ERT therapy. These three children show an improvement in both AC threshold (mean 60dB pre-treatment, 33dB post-treatment in the better hearing ear) and ABG (mean 32.8dB pre-treatment, 10dB post-treatment). The authors hypothesise that the improvement in the conductive element of the hearing loss is secondary to the improvement in recurrent URTi’s with ERT but cannot explain why the sensorineural component also improves (Lin, Shih et al. 2014). In contrast, Dualibi et al show that ERT does not change or improve hearing thresholds (reported using speech reception threshold) in children with attenuated MPS I after twenty-two months of treatment (Dualibi, Martins et al. 2015).

Hearing loss has been used as a secondary outcome measure in a handful of trials and longitudinal studies, detailed in table 3. Individual case reports show conflicting results, with very small patient numbers (Tokic, Barisic et al. 2007, Mercimek-Mahmutoglu, Reilly et al. 2009).
<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>MPS sub-type</th>
<th>No of patients included in study</th>
<th>Hearing outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSCT (Krivit, Peters et al. 1999)</td>
<td>Attenuated MPS I</td>
<td>n=12 Hearing was a secondary outcome measure</td>
<td>8 improved to better than 30dBHL (6 conductive and 2 mild SNHL). The remaining 4 children with moderate SNHL remained unchanged</td>
</tr>
<tr>
<td>HSCT (Aldenhoven, Wynn et al. 2015)</td>
<td>MPS I-H</td>
<td>n=217 Hearing was a secondary outcome measure No audiometric data available</td>
<td>Severity of hearing loss and hearing thresholds in dB not provided. 88% had some degree of hearing loss pre-HSCT and 63% post-HSCT. Of this group, a third were sensorineural, a third conductive and a third mixed loss.</td>
</tr>
<tr>
<td>Idursulfase (Muenzer, Wraith et al. 2006, Muenzer, Guscasas-Calikoglu et al. 2007, da Silva, Strufaldi et al. 2011)</td>
<td>MPS II</td>
<td>No clinical trials used hearing loss as an outcome measure</td>
<td></td>
</tr>
<tr>
<td>Idursulfase (Parini, Rigoldi et al. 2015)</td>
<td>MPS II Observational study with 9 year follow-up</td>
<td>n=17 no audiometric data available</td>
<td>12/17 had a hearing loss, 11 severe and 1 moderate. On ERT, 6 improved with a gain of 20-50dB, 4 stabilised and one got worse</td>
</tr>
</tbody>
</table>

Table 3: Hearing outcomes from HSCT and ERT clinical trials
1.4.1. Deafness and its impact on HRQoL in MPS

Specific evidence for the impact of hearing loss on HRQoL in MPS is lacking. Using the HU-13, a health utility index which measures the functional impact of vision, hearing, speech, ambulation, dexterity, emotions, cognition and pain, on a scale of 0-1, on the patient, Needham et al show that hearing and speech have a major impact, causing a severe disability in children with MPS II (Needham, Packman et al. 2014). No other published works exist.

The impact of congenital hearing loss in otherwise healthy children has been extensively researched. In comparison with normal hearing peers, those with congenital hearing loss have mental health and behavior issues along with difficulty with family activities and social interactions. These problems have a linear relationship to the severity of their hearing loss (Wake, Hughes et al. 2004).

Once again, research on children with congenital hearing loss who are otherwise well, shows that the inability to hear during the early language acquisition years will result in poor language skills with a domino effect on reading skills and educational achievements (Phelps and Branyan 1990, Van Eldik 1994, Davis and Hind 1999). This may lead to increased behavior problems and higher levels of parental stress (Meadows-Orlans 1995). The cochlear implant literature recognizes that early recognition and aggressive management of this severe hearing loss, along with appropriate early auditory rehabilitation, will improve the hearing disability and allow good
acquisition of language and speech intelligibility, giving these children the opportunity to attend mainstream education and extend their participation in the world around them (Daya, Ashley et al. 2000, Geers 2004). This will have a positive impact on their quality of life (Lin and Niparko 2006, Morettin, Dias Dos Santos et al. 2013). Speech performance continues to improve with duration of hearing rehabilitation and consistent usage of hearing aids. Non-syndromic children with congenital hearing loss, who have received cochlear implants, will develop seventy-seven percent speech intelligibility in comparison with normal hearing children after ten years of use, allowing independent living (Beadle EA 2005). Also, children who are implanted earlier view the implant as an extension of themselves and report better HRQoL scores (Warner-czyz, Loy et al. 2009).

The applicability of these findings, taken from the congenital hearing loss literature, to patients with MPS is difficult to ascertain. The neurocognitive disease suffered by MPS I and II may contribute and perhaps directly lead to problems with speech clarity, language acquisition, behavior concerns and educational achievements.

Parents whose children have congenital hearing loss, as part of a multi-system problem such as cerebral palsy, do not always view hearing loss as a health related problem (Sach and Barton 2007) and may give precedence to their child’s other needs first, perhaps ignoring early auditory testing and rehabilitation. No research has been undertaken ascertaining the importance that parents with MPS give to their child’s hearing disability in comparison
with their other medical problems. The impact that deafness and perhaps speech delay and loss of speech clarity, if these are truly a problem, may have on their health related quality of life has never previously been quantified.

1.4.2 Recurrent Infections

Frequent URTI’s, both rhinosinusitis and AOM are seen in all sub-groups of MPS. They have been attributed to adenoidal hypertrophy, GAG deposits in the postnasal space (PNS) and an altered immune status (Simmons, Bruce et al. 2005, Clark, Bishop et al. 2013). Alongside the recurrent URTI’s, these young patients also have chronic thick nasal and tracheal secretions (Muhlebach, Wooten et al. 2011, Scarpa, Almassy et al. 2011), the etiology of which is poorly described. These symptoms start in infancy, in many children prior to the establishment of a diagnosis of MPS (Motamed, Thorne et al. 2000). The impact of HSCT and ERT on these symptoms, or the resolution of symptoms with age, has not been reported in the literature.

1.4.2.a recurrent infections and their impact on HRQoL in MPS

No reports could be found within the literature on the impact of recurrent infections on the HRQoL of children with MPS. As with deafness, no research could be identified ascertaining the importance that parents with MPS give to their child’s recurrent infections or thick nasal and tracheal secretions, or how these rate in comparison with their other medical problems.
Research into the impact of recurrent infections on otherwise well children shows that those with rhinosinusitis report low levels of perceived physical health but interestingly do not report a negative impact on their psychosocial health, such as behavior and self-esteem. However, in comparison with other chronic illnesses such as Juvenile Rheumatoid Arthritis (JRA) and Asthma, they have poorer HRQoL, with limitations reported in school and play related activities (Cunningham, Chiu et al. 2000).

1.4.3 Airway Disease

GAG’s are ubiquitous and children with MPS may develop disease at multiple sites within the upper airways, anywhere from the lips to the lungs. The sites predominantly affected are the tonsils, adenoids, pharynx, larynx and trachea (Simmons, Bruce et al. 2005). This may give rise to multi-level upper airway obstruction and progressive severe obstructive sleep apnoea (OSA). OSA is a disorder characterized by a reduction or cessation of airflow in the presence of breathing effort and in children with MPS is due to anatomical variations and pathological upper airway disease.

The enlargement of the adenoids and tonsils is a universal finding in MPS. It is made worse by the presence of chronic upper respiratory tract infections, reported in seventy percent of children with MPS (Moreira, Kyosen et al. 2014). This may lead to snoring and sterterous breathing by
the age of 2 (Papsin, Vellodi et al. 1998, Yeung, Cown et al. 2009). Snoring whilst asleep is commonly reported by parents of children with MPS with rates of 100% in the published literature (Lin, Chen et al. 2010). Unlike healthy non-syndromic children with OSA, most of these children have a body mass index within the normal reference range (average BMI 20.6) (Moreira, Kyosen et al. 2014).

If the disease is affecting the Larynx, with prolapse of GAG deposits into the glottis on inspiration, these children may develop stridor. Alongside GAG deposits within the trachea, these patients may have a variable degree of underlying Tracheobronchomalacia, compounding the multi-level airway obstruction (Simmons, Bruce et al. 2005).

Anatomical changes such as narrow nares, macroglossia, a short immobile neck, stiff temperomandibular joint, craniofacial anomalies and skeletal abnormalities of the thoracic wall and abdominal organomegaly limiting diaphragmatic movement, may also contribute to this progressive upper airway obstruction (Walker, Darowski et al. 1994, Muenzer, Wraith et al. 2009).

Reported rates of OSA in children with MPS are between 77-100%, with moderate disease in up to 7% of those with MPS I and 33% of those with MPS II (AHI 5-10/hr) and severe disease in up to 86% of MPS I and 45% of MPS II (AHI >10/hr), reflecting a trend towards more severe disease in MPS I but equal overall prevalence in both sub-groups of patients (Nashed,
The severity of the OSA worsens with age with the worst polysomnography scores in post-pubescent patients (Lin, Chen et al. 2010). Twenty percent of surgery associated deaths in MPS I are secondary to airway obstruction due to multi-level airway disease (Arn, Bruce et al. 2015).

Management of the airway in these children is challenging. In the presence of enlarged adenoids and tonsils, an adenotonsillectomy may be performed to improve the symptoms of obstructive sleep apnoea. Surgery improves the severity of disease, although symptoms may recur or progress with age in fifty-six percent of patients (Gonuldas, Yilmaz et al. 2014) (Wooten, Muenzer et al. 2013). Pharyngeal and laryngeal disease may require a rigid airway endoscopy (DLTB) and surgical removal of the thickened diseased tissues (Simmons, Bruce et al. 2005). However, if the obstructive picture is due to multi-level disease, extending into the trachea, continuous positive airway pressures ventilation (CPAP) or bi-level positive airway pressure therapy (BIPAP) along with supplemental oxygen may become necessary to splint the upper airway (Kamin 2008, Muhlebach, Wooten et al. 2011). A tracheostomy may be life saving if the patient develops acute airway obstruction or severe progressive multi-level disease (Malik, Nichani et al. 2013). A review of the MPS I registry reveals that forty percent of children have had surgery to improve their airway disease, with an adenotonsillectomy being the most commonly performed, followed by a laryngotracheobronchoscopy and then tracheostomy (Arn, Bruce et al. 2015).
Yearly sleep studies along with 6 monthly respiratory function tests in children older than 6-7 years are advocated in these children (Muenzer, Wraith et al. 2009, Scarpa, Almassy et al. 2011).

Children with MPS I-H have a significant improvement in their degree of OSA after an HSCT, with AHI levels improving from 9.5/hour to 4.1/hour. Despite this initial improvement, twenty four percent continue with progressive disease, of which thirteen percent suffer with persistent severe OSA. Negative predictors of outcome post transplant appear to be increased age at transplant, the presence of inhibitory antibodies, and poor substrate clearance. Also, HSCT does not completely protect against the development of OSA but delays its onset, with a second peak of onset seen after the age of ten years. Those with attenuated MPS I, managed on ERT, do not show the same levels of improvement, with progressive disease with increasing severity seen in seventy-three percent of patients and a higher number of patients requiring a surgical intervention to improve symptoms (Moreau, Brassier et al. 2015, Pal, Langereis et al. 2015).

ERT produces a reduction in the apnea-hypopnea index as seen on serial overnight sleep studies in clinical trials but the degree of improvement has not been quantified. No subjective outcome measures have been reported (Wraith, Clarke et al. 2004, Harmatz, Giugliani et al. 2008, Muenzer, Beck et al. 2011).
1.4.3.1 Airway disease and its impact on HRQoL in patients with MPS

Evidence for the impact of OSA on HRQoL in MPS is sparse and reliant on a single study that looks at the impact of OSA on one hundred and twenty-four children with both MPS and Downs Syndrome in India. The authors report that children’s AHI scores improve to within normal levels, following treatment with both adenotonsillectomy surgery and CPAP and that this improvement is sustained for up to a year. Using the OSA-18 outcome measure they show that in MPS children, OSA has a large impact on QOL, as reported by their parents. Following treatment, an improvement is seen in sleep disturbance, physical suffering and daytime problems domains. However, the emotional distress and caregiver concerns domains remain unchanged, with only a marginal improvement in overall QOL scores. Hence, although the AHI returns to normal after treatment, the parents did not feel that this substantially improved their child’s HRQoL secondary to OSA and that OSA-18 has a poor correlation with the AHI (Sudarsan, Paramasivan et al. 2014).

If we turn to the broader literature on the impact of OSA on otherwise well children, it shows that non-syndromic children with OSA have a poorer health status in comparison with healthy children (Baldassari, Mitchell et al. 2008). The child health questionnaire (CHQ) is a validated generic QOL outcome measure that may be used to measure global health in children. When used to assess the difference between children with OSA and well controls, it shows that those with OSA have a significantly poorer quality of life, mainly in the areas of general health perception and emotional parental
impact. Other subsets affected are bodily pain, physical functioning and family activities. They also score worse than children with JRA and asthma, significantly in the subsets parental impact-time and parental-impact emotional, with some impact on behavior and social limitations. Lack of parental sleep and constant worry about the health of the young child may be a source of stress for many parents of children with OSA (Rosen, Palermo et al. 2002, Georgalas, Tolley et al. 2004, Stewart, Glaze et al. 2005, Baldassari, Mitchell et al. 2008).

The broader literature also reveals that fragmented sleep and recurrent hypoxia induced arousals in younger children may cause symptoms of hyperactivity, inattention, poor concentration, disruptive behavior such as fighting, bullying and being quarrelsome, labile emotional behavior and poor school performance (Chervin, Dillon et al. 2003, O'Brien 2011). Studies of young children with attention deficit disorder (ADHD) have found levels of mild sleep related breathing disorder to be five times higher than otherwise healthy children (Corkum, Tannock et al. 1998). Along with behavioral disturbance, studies have reported cognitive impairment with a reduction in intelligence quotient scores and working memory (Gottleib, Chase et al. 2004). Working memory is essential for problem solving and normal psychological development in children. In the older adolescents OSA may cause hyper somnolence in the day, poor concentration and lead to depression (O'Brien 2011). There are no published studies looking at OSA related behavior disturbance in MPS, although we do know that
children with MPS I and II may have neurocognitive disease, which may lend itself to behavior disturbance in its own right.

1.5 Research Aims

The primary aim of this study, using patient and parent interviews and a grounded theory approach to data analysis, was to identify the experience patients and their parents have of living with MPS (I, II and VI) in an attempt to determine the subjective social, functional and psychological impact of the disease.
2.0 Methodology

Disease modifying treatments have had a positive effect on the life expectancy of children with Mucopolysaccharidosis, with many now successfully reaching early adulthood. As these children, with multiple comorbidities, live longer, understanding the challenges that they face in their daily lives becomes increasingly important. As highlighted earlier, to date, there is a lack of research examining the impact of head and neck disease, or indeed global health on the HRQoL of these children and their families.

Much of the literature on HRQoL, summarised in the introduction section of this thesis, has been obtained through the completion of generic QoL questionnaires, used as secondary outcomes in published ERT clinical trials. These questionnaires are not sensitive for MPS and do not always include domains pertinent to our population of patients. This may be overcome by combining these with disease specific questionnaires (Eiser and Morse 2001, Eiser 2004). However, disease specific questionnaires do not currently exist for MPS, highlighting the need for future instrument development.

Early in the process of developing a new disease specific questionnaire, the researcher is advised to explore the patient’s perception of their health and the impact of the disease on this, which may be done through exploratory interviews and grounded theory research (Brod, Tesler et al. 2009).
data may then be combined with expert opinion and the existent literature, to identify domains for inclusion in the new instrument. It also means that further construct validity is more straightforward (Fayers and Machin 2007, Brod, Tesler et al. 2009).

Further, a qualitative approach was used so that participants could narrate their stories and identify what was important from their own point of view about their health and the impact of MPS on the lives of the families. This type of qualitative research begins with the expressed stories of individuals, defined as ‘the spoken or written text giving an account of an event/action or series of events, chronologically connected’ (Czarniawska 2004, Creswell 2007). This approach was appropriate because it allowed participants to describe how their experiences had changed, as children with MPS grew older and developed the impact of the disease on families and the challenges they faced on a daily basis.

My previous exposure to children with MPS has been through interaction with the families as their clinician. This interaction is usually short and conversation limited to the clinical problem. Hence, in order for me to better understand the parents and children’s perception of the impact of disease on their lives, I wanted to spend a longer period of time in dialogue with them, most suitably through conversational interviews (Roulston 2008).
Of the different qualitative research methods available, both Phenomenology and Grounded theory would allow me to explore the lived-in experience of MPS in greater detail. Phenomenology is a research method used to extract the ‘essence’ or experience of a certain phenomenon and can generate a descriptive text about the lived-in experience of the individuals interviewed, in this case the parents. Although children would be involved in the interviews as far as possible, parents would form the principal data source, particularly for young children and those with cognitive impairment.

Through this study I wanted to explore the experience and perspectives of the family and not just the parents. An approach drawing on grounded theory would be better than Phenomenology in facilitating this. This descriptive text will also attempt to explain why the disease or certain aspects of it have an impact on HRQoL for these families, providing a framework for future research to develop theory (Creswell 2007) as well as informing clinicians about families’ perspectives of the condition and its management. Grounded theory is also considered the best approach for collecting data with a high content validity for development of new disease specific quality of life outcome measure (Brod, Tesler et al. 2009).

There are two broad approaches that may be used to generate grounded theory. The ‘systematic approach’ described by Strauss and Corbin or the more modern ‘constructivist approach’ defined by Charmaz (Charmaz
Theoretical sampling, proposed by Strauss and Corbin, underpins the sampling strategy employed in grounded theory research. Unlike quantitative research where sampling is intended to represent statistically the properties of a larger population group, in qualitative grounded theory studies, a range of characteristics found in the population are represented to test the applicability of interpretation of meaning and theory as it is generated. Data collection and analysis go hand in hand and are a continual process. Data analysis generates new concepts and more questions. Further data collection and sampling is used to answer these questions, becoming increasingly focused. This cyclical process continues until no further questions arise and ‘saturation’ of the concept being explored has occurred. I used this principle of theoretical sampling. Once an interview took place, it was coded and analysed. Emergent themes were incorporated in my topic guide and then tested and explored in subsequent interviews. No new data emerged which could not be tested in an interview.

Purposive sampling of families with MPS, attending the Willink metabolic and genetics unit in Manchester for treatment, provided access to a sample of patients with the same disease but varying disease severity, patient age, treatment and family dynamics, hence introducing heterogeneity. This maximum variation allowed testing of concepts generated, true in different conditions, in order to achieve “saturation” (Corbin and Strauss 2008, Flick 2006) (Strauss and Corbin 1990). During this research, I drew on both of these approaches where they were consistent with each other.
2009). Our sample of patients interviewed was reflective of the variation seen in the patients with MPS I, II and VI. Perhaps further saturation could be achieved but we were limited by the number of patients available for recruitment, reflective of the rare nature of this disease. Time constraints limited the same sample being interviewed for a second time.

Qualitative research may rely on data in the form of interviews, observations, documentation and audiovisual materials (Creswell 2007). Corbin and Strauss suggest that researchers use unstructured interviews, giving respondents space to talk about subjects important to them (Corbin and Strauss 2008). Interviewees have a complex and intimate knowledge of the subject being considered, in this case the impact of MPS on HRQoL, and they are able to provide spontaneous, explicit answers to open questions. However, if structure is introduced to the open questions, using a semi-structured approach, it can focus the subjective theory towards the issue being studied (Flick 2009). The semi-structured approach also allows a novice qualitative researcher such as myself to have an outline of open but focused questions to direct the interview, allowing good utilization of time. Initial questions included within my topic guide were drawn from the published literature and my personal experience of MPS. However, the topic guide was reactive and continuously evolved as data analysis proceeded, incorporating new themes and questions that arose during the previous coding cycle in this project.
Coding is the process by which data, in my case transcripts of interviews, are broken down, conceptualized and then put back together in order to build a theory grounded in the data (Strauss and Corbin 1990). The systematic approach to grounded theory coding is a more structured approach to coding and data analysis and for a novice researcher such as myself provides a clearer framework to follow. It has three distinct phases although researchers move freely between phases and may also combine them (Flick 2009).

2.1 Open Coding

This is the earliest phase of data analysis and starts once the first interviews have been conducted. The transcript is re-read multiple times to build an overall picture and to allow the researcher to familiarise themself and reflect upon the ideas being expressed by the interviewee. Smaller segments of data, representing ideas or phenomenon are then given ‘codes’ or units of meaning. Whilst coding my data I found it helpful to code using ‘in-vivo’ codes that were a reflection of terms or phrases used by the interviewees. I found it easier to code entire sentences and in some cases entire paragraphs if they were describing a specific phenomena. This process produced dozens of primary codes. Codes that reflected similar phenomena, events or incidents were then grouped together in primary descriptive ‘categories’(Creswell 2007, Corbin and Strauss 2008, Flick 2009).
2.2 Axial Coding

In this stage a key central phenomenon is identified, generally one that is being discussed extensively by the research participants or seems key to the research topic being explored. The sub-categories that relate to the cause or consequence of this central phenomenon are added to this new category. Both inductive and deductive thinking are involved. Not all primary categories will be used. As a researcher you reflect upon the emergent data and decide which axial category is central to the story unfolding and will form the central category, to which all others may be linked. This central category is then developed further until theoretical saturation is reached, where further coding does not add to new knowledge acquisition. Theoretical sampling continues in order to further explore the central phenomenon. Through this process we obtain theory grounded in rich data. Writing memos whilst coding assists in this process, where the researcher reflects and questions the emerging data. A coding paradigm is then created, which presents the early theory to emerge from the study (Creswell 2007, Corbin and Strauss 2008).

2.3 Selective Coding

The categories identified in the axial coding phase are now all linked to each other through a single story or central phenomenon/category that attempts to explain the research question being explored. The researcher can now generate a hypothesis that links together the different spokes of the axial coding wheel, giving rise to theory (Creswell 2007, Flick 2009).
2.3.1 Reflexive coding in my study

1. Whilst following Corbin and Strauss’s systematic method, I found that during the axial coding phase, I moved away from the rigid axial coding suggested by the authors, as it was very forced and perhaps a bit artificial. I opted to follow Glaser’s coding families in which he groups similar codes together although eventually leaning much more heavily towards the focused coding in Charmaz’s constructivist theory approach (Glaser 2001, Charmaz 2006). I ended up with a few key phenomena, which I then linked together in a subsequent stage, just before the final selective coding phase.

2. During my initial coding, I was identifying ‘topics’ and not ‘actions and processes’ and hence not truly analysing the data. My supervisor reflected upon this when he read the first coding transcript. I then re-analysed the data and performed more inductive coding, using phrases and words used by the interviewees themselves.

3. I was aware that my own personal beliefs, clinical, cultural and social, have shaded my analysis of the data and also my ideas of why some interviewees behave in a certain way.

It is suggested that qualitative researchers leave their pre-conceptions behind and approach the fieldwork and analysis with a fresh, open perspective, so that their personal ideas do not influence the interviews or the coding of emerging data. However, I found that in the early stages of my research, my own clinical preconceptions were important as they allowed a level of understanding of the phenomena I wanted to explore,
giving me a starting point for my research. They provided a shared experience or phenomenon with the interviewees, on the basis of which I could build a relationship with the first few families that I interviewed. My medical background, specifically my chosen discipline of head and neck surgery, will have provided a framework for the study design forming the backbone of much of my early questioning. Partaking in this grounded theory research made me continually question and challenge my personal beliefs and perspective on chronic illness, disability and death (Charmaz 2006). I developed a reflective practice during data collection and analysis, a concept foreign to my practice beforehand.
3.0 Method

Prospective national research and ethics committee (NREC) opinion (appendix 1) and local research and development (R&D) sponsorship approval were obtained at the outset of the study in September 2013 (appendix 2).

Mucopolysaccharidosis is a very rare disorder, managed in the United Kingdom by a handful of internationally renowned, tertiary pediatric metabolic medicine and genetics units. I felt that the best way to obtain access to these patients would be through one of these units and hence approached the metabolic and genetics team in Manchester. I had previously been involved in retrospective research with the metabolic team, building a positive research relationship with them. The metabolic consultants and specialist nurses are familiar with the families of children with MPS and have a long professional relationship with them. The specialist nurses manage their multi-disciplinary care. Many families travel long-distances for investigations and treatments at the unit. Children attending this unit include families living across the United Kingdom and inclusive of a diverse, multicultural population.

3.1 Patient recruitment

The specialist nurses are informal gatekeepers to these families and correspondence or access to the families is through them. There is a
specialist nurse for each sub-group of MPS under study. I met with two of these nurses regularly through the study period, discussing patients with upcoming hospital appointments, who would be suitable research candidates. The nurses approached the families on my behalf to see if they would participate in the study. This was done via telephone. They told the families about my study and my medical and research backgrounds. The research study and what it would entail were discussed in great detail. Interested families were sent copies of the patient information leaflet and consent or assent forms to read a few weeks in advance of our meeting. They were presented with the opportunity to speak with me over the telephone for further clarification or details, if they so wished.

The specialist nurses, with their intimate knowledge of the families and access to the children’s appointment diaries, were invaluable. However, one of the drawbacks of gatekeepers is their informal vetting of suitable candidates. I was sensitive to this and worked hard to gain the trust of the specialist nurses. Also, purposive sampling and later theoretical sampling, from a very small pool of families, served to ensure that a range of families were included.

I opted to interview patients at the hospital when they were attending a routine visit. I was performing this research part-time and was available to interact with the families only during my fixed research sessions. Hence, interviews could only be conducted when both the interviewee and I were available at the same time. Owing to patient and researcher availability, I
sometimes had to interview two or three families consecutively. Sometimes patients failed to attend their appointment or cancelled on the day. Sometimes patients became acutely unwell and were no longer willing or medically fit for participation in the study.

3.2 Inclusion Criteria

Patients with MPS type I, II and VI were prospectively recruited over a twelve-month period, between December 2013 and November 2014. Inclusion criteria were as follows;

a) Children aged sixteen years or under at the time of interview
b) MPS I children with both Hurlers and non-Hurlers variants
c) MPS II children with both attenuated and severe variants
d) MPS VI children
e) Children of both sexes in the MPS I and VI study, whilst only males for the MPS II study (MPS II is an X-linked disorder)
f) Both English and Non-English speaking families and children (interviews were conducted through a translator)
g) Single and dual parent families
h) Children attending both mainstream and special needs schools

Patients were recruited either until data saturation occurred, or alternately no further participants were available for interview (in-keeping with the rarity of the disorder) within the time frame of my research degree.
MPS I, II and VI represent a heterogeneous group of patients with varying phenotype and severity and therefore purposive sampling was used to recruit a varied cohort of children likely to represent this heterogeneous condition. Children with different disease severity, physical limitations and variation in age were approached. I hoped this would allow a developmental theory to develop with maximal variation. Initial sampling was the outcome of planning meetings between the nurse specialists and me, but also dependent on availability of families in the first few months of recruitment. Further sampling was theoretical, based on emergent questions and themes, following data analysis and coding.

### 3.3 Semi-structured Interviews

Being a novice interviewer and qualitative researcher, I practiced my interview techniques and open conversational style, prior to meeting my first research patient. I approached a close group of friends, all of who are working mothers with young children, and interviewed them on their experience of achieving a work-life balance. With their consent, I video recorded these interviews and analysed them with my educational supervisor. This technique was invaluable and provided positive reflexive feedback.

The research interviews were conversational and semi-structured. In contrast to Phenomenology where the researcher may use open-ended interviews, the standard approach in grounded theory research is to use semi-structured interviews. Interviewees have a complex and intimate
knowledge of the subject being considered, in this case the impact of MPS on HRQoL, and they are able to provide spontaneous, explicit answers to open questions. However, if structure is introduced to the open questions, using a semi-structured approach, it can focus the towards the issue being studied (Flick 2009). The semi-structured approach also allows a novice qualitative researcher such as myself to have an outline of open but focused questions to direct the interview, allowing good utilization of time. Initial questions included within my topic guide were drawn from the published literature and my personal experience of MPS. However, the topic guide was reactive and continuously evolved as data analysis proceeded, incorporating new themes and questions that arose during the previous coding cycle.

I invited both parents (mother and father) to participate in the interview process and the children to participate in the interviews. At the beginning of each interview, I introduced myself as a research student from the University of Manchester, with an interest in MPS. Some of the families were previously aware of my medical background as an Ear Nose and Throat (ENT) surgeon, and enquired if the interview would be more like an ENT consultation. I reassured them that the interviews were an opportunity for them to speak about the impact of the MPS on their lives, with further discussion to be had about the impact of their head and neck problems. This was not meant to be an exclusive discussion about just the head and neck problems.
An open, conversational style was adopted for the interviews. I sat in a circle of chairs alongside the parents and children, allowing face-to-face conversation. The children were invited to have interviews independently to their parents, allowing their views to be given equal importance. Alternatively they could attend the interviews with the parents if they preferred. Informed consent or assent for those under the age of sixteen was obtained before the interview was conducted. Each interview lasted between forty minutes and an hour and was digitally audio-recorded. At the start of each interview I went through the patient information sheet and consent form at length to clarify any outstanding concerns and obtained their permission to audio-record the interview.

All children declined to be interviewed separately to their parents. Six of the older children (three MPS I and three MPS II) contributed towards the family interview alongside their parents. All of the Family interviews were conducted in the presence of their children. A total of eighteen family interviews were conducted, nine families with MPS I, six with MPS II and four with MPS VI. Three families had multiple affected children and hence twenty-two children were present and included in this study. Although both parents were invited to participate in the interviews, only three interviews included couples. The remaining fifteen was conducted with one parent. Further details have been provided in the demographics results section under each sub-group.
Fifteen interviews took place in a clinical consultation room within the outpatient clinic at the Willink metabolic and genetics unit. The room was large with space for multiple chairs to be placed in a circle. A play assistant was available in the clinic setting, to assist with the younger children, freeing the parents up for the interview. The play assistant was intermittently present during the interviews within the clinic room, with the consent of the parents. Two families were interviewed on the day case surgery unit whilst their children were having ERT. This is an open eight bay ward and the curtains can be drawn round the bed to allow some privacy. On one occasion the ward was busy with three occupied bays and hence was noisy. On the second occasion, the family in question was the only patient on the unit. Also, the nurses were frequently entering the clinical area to monitor the child’s ERT infusion, which meant pauses in the interview. One family was interviewed in the side room on the high dependency unit, during their child’s post-operative stay in hospital. This once again was a large room but the child was critically unwell and unable to participate in the interview process. Three of the families had multiple affected children and hence were interviewed as a single-family interview. Three of the interviews were conducted through a certified hospital translator (one in Arabic and two in Urdu).

A few children had multiple appointments on the same day as my scheduled interview and sometimes my research interview with them had been inserted into this hectic schedule. This was not ideal for a number of reasons. Firstly, some parents could not relax into the interview as they were either
late arriving or running late for their next appointment. Secondly, the interview would sometimes be disrupted because a nurse would arrive for a weight measurement or urine sample. I always offered the parents the opportunity to either pause the interview or re-schedule it for a different day. No families took up this offer and instead preferred to carry on through the chaos. I conducted three of my interviews at lunchtime, whilst the parents and children ate packed lunches in my clinic room.

3.4 Topic Guide

With the assistance of my supervisors, I developed a ‘topic guide’ to steer the interviews (Appendix 3a). The subjects for inclusion were guided by clinical experience and a literature review; no other qualitative studies existed at the time exploring the impact of MPS on HRQoL. The topic guide was designed to explore the impact of MPS on the daily routine of the child and their family. It then explored in further detail the functional and social impact of hearing loss, language development, educational performance, sleep quality and nasal discharge. Understanding was also sought regarding the impact of hospital visits, medical and surgical treatments, future expectations and evolution of the disease. As the interviews were semi-structured and informal, I asked broad open-ended questions, allowing the interviewees to steer the interview in a direction important for them. I asked probing question to explore responses given by the interviewees.
The topic guide was fluid and evolved with time, guided by emerging themes and subjects that appeared to be important to the families (appendix 3b). For example; when I conducted the first two interviews with families of children with MPS II, the opening question was, ‘Tell me about a typical day in your household?’ It soon became apparent that the parents wanted to start the interview by talking about the early diagnosis of their child’s illness and then their child’s development in a chronological fashion. They wanted specifically to discuss how the impact of the illness had evolved with time and how their initial aspirations had eventually been replaced by acceptance of the limitations imposed by the disease. Hence, subsequent interviews were started with, ‘How old was your child when they were diagnosed? How did you feel at the time?’ Topics like ‘Education’, ‘Language’ ‘Future’ and ‘Social acceptance’ came to the forefront and these emerging themes were explored in the latter interviews. Other topics, initially felt to be important, such as ‘nasal discharge’ and ‘sleep quality’, were soon dropped from the topic guide, as parents did not give them the same importance. In MPS I, parents wanted to discuss the topics ‘education’, ‘language’, ‘mobility’, ‘pain’ and ‘sleep apnoea’ in further detail. Hence, subsequent interviews took on a different format and parents were asked to describe the main impact of their child’s disease on their lives and how this fit in with education, social integration and future independence. Parents were allowed to steer the direction of the interviews and discuss topics important to them. As theory evolved, further cases were sought to explore and then saturate emergent themes.
When designing the topic guide, I was worried about how parents would react to questions about their child’s future disease development and future independent living. I felt that many of them would be unwilling to discuss these sensitive topics, especially in the presence of their children. However, this was not the case. Parents and older children alike were happy to share stories and talk about the challenges that they faced, including ideas and plans for the future. They discussed limited mobility and dependence on wheelchairs or residence homes, they talked about independent jobs, they worried about not being able to have children due to the chemotherapy and mostly they worried about who would look after the children once the parents had died. The children were present and participant in all of these conversations. I felt that the children were active participants in the management of their own illness. It also came as a surprise when both parents and children talked about the mortality associated with MPS. It was clearly evident that this was something they discussed in their family environment and were comfortable discussing, on their own accord, with me. I did not actively ask any child or family how they felt about death as a question.

At the end of each interview, the parents were asked to complete a short questionnaire, collecting employment information about the mother and father. A section of this form was completed by me and included other demographic information such as disease severity, subtype of MPS, severity
of problems as noted in the medical notes and treatment received by the child to date (Appendix 4).

A third party transcribed the interviews verbatim. One interview was partly in Urdu and was transcribed by myself (I speak fluent Urdu, along side English). Field notes were dictated following each interview to make note of my thoughts and impressions. The transcripts were entered and analysed using the Qualitative software NVIVO for Mac© (http://www.qsrinternational.com).

3.5 Data Analysis

Data collection and analysis went hand in hand and were a cyclical process, where emergent codes and questions determined further patient sampling and guided topics for the subsequent interviews. Following each interview, I either audio recorded or wrote reflective notes, documenting my experience of the interviews, my observations of the family dynamics and other details that I was worried may be lost once the interview had been transcribed into text. Each interview was transcribed and the transcript read through for accuracy but also to obtain an overall sense of the interview. The transcripts, field notes and reflective notes were entered into the NVIVO program. Within the NVIVO program, I created two folders, MPS I and MPS II.

The NVIVO program allows the user to code their data directly within the software platform. Each line, thought or paragraph, is assigned a code,
which could be the actual sentence used by the parent during the interview (in-vivo codes). An example of this was my primary code, ‘hearing has not improved or changed with ERT’. I was very interested in the impact of ERT on hearing in this sub-group of patients and assigned this code for the following extract, ‘he has always been profoundly deaf. His deafness has not changed with age and it has not got any better or worse with the enzyme replacement therapy. The enzyme has had a completely different effect on his body, a brilliant one, with his swollen tummy and joint problems improving very quickly.’ When I coded further interviews, I simply added extracts or lines to this primary code, if they had similar sentiments. When I assigned these early codes, I was very conscious of using descriptive words so that the true meaning/essence of the line or paragraph was relayed rather than my sub-conscious interpretation of it. This process generated an extremely long-list of primary nodes. Many of the nodes had similar meaning or were talking of similar themes and hence I was able to cluster them together into a secondary node or category. For example, I placed the primary node described above into a secondary node titled ‘impact of ERT on hearing’. This secondary node contained five primary nodes, all discussing the relationship between ERT and deafness.

Once a long-list of secondary nodes emerged, I was able to categorise them further into tertiary nodes. The tertiary node for the example above was ‘hearing’ and this contained nine secondary nodes including: ear infections, grommets, hearing aids, impact of deafness at school, impact of ERT on hearing. The MPS I and II interviews were coded as separate files, with
each one generating its own nodal tree, with no influence from the other. Hence theory for each sub-group emerged independent to the other.

Development of the secondary and tertiary nodes was inductive but also reflective, with regular input from my supervisor. As the project progressed and categories began to clearly emerge, we started looking for further cases to saturate them along with deviant cases. Questions were now more focused, primarily based on the preliminary data obtained from the earlier interviews. Further interviews saturated these categories, with fewer new categories emerging with time.

NVIVO was then used to further classify the demographic data of the interviewees and the ‘case classification’ function allowed me to develop files describing ‘parental employment’, including the sub-categories father employed, mother employed, full time employment, part time employment, loss of family earnings, and ‘person specification’, including the sub-categories age, chronic rhinosinusitis, deafness, MPS subtype, presence or absence of neurocognitive disease, presence of OSA, disease severity and sex. Populating these groups also allowed comparisons to be made between these characteristics with the emerging codes and categories.

The next phase was the axial coding phase in which Strauss and Corbin (Strauss and Corbin 1990) recommend identifying a central core category, one that is being discussed extensively by the research participants. Once immersed in the data, I found this rigid axial coding system difficult and a bit artificial, almost forcing the data to conform. Hence, I began to follow
Glaser’s (Glaser 2001) coding families in which he groups similar codes together. Towards the end of the process my way of analyzing the data was primarily constructivist, following the process defined by Charmaz (Charmaz 2006). I had identified a few key phenomena within the data, which recurred in consecutive interviews. My supervisor and I spent many an hour, reflecting on these emergent categories, both objectively but also subjectively. We were then able to inductively analyse these phenomenon, linking them together to give rise to theory.

In MPS II, the smaller of our two studies, this process was seamless and the core phenomenon of ‘fitting-in’ was seen to emerge independently from each of the categories, and seemed to link the categories together. However, in MPS I, a core phenomena did not clearly emerge in the same way, where true saturation of the themes did not occur as it did with MPS II. The theory in this group was much more interpretive. Whilst interpreting the data, diagramming was used. This was done via pen and paper, with reflection from both my supervisor and myself. This was an extremely useful exercise as it allowed one to visually focus on all of the emergent themes in a schematic manner. It easily allowed the relationship between categories to be seen and a theoretical framework to be drawn.

### 3.6 Ethical standards

As detailed, national research and ethics committee opinion was obtained before commencement of the study (appendix 1). Research and
Development team approval and sponsorship were obtained from the Central Manchester Foundation Trust and University of Manchester (appendix 2). A consent form (Appendix 5) was used for children sixteen years of age and over. The same consent form was also used for the parents of the children participating in the study. For children between the ages of five and fifteen years, an assent form was designed that the child could sign (Appendix 6). This was offered to all children but only taken up by the older children in our group. One copy of the consent form was placed in the main trial folder, one copy was filed within the patient’s notes and a third copy was given to the patients to take home with them. Age specific patient information leaflets were designed, using language appropriate for the age of the child (Appendix 7a-d). These were sent out by post to the family a few weeks prior to the interview, allowing them to read the information, making an informed choice about participation in the study.

Following recruitment, patients were assigned a unique research number, along with a pseudonym, used to identify them within the study. A research folder was created and copies of the signed consent forms, patient identifiers and completed demographics questionnaires were stored within this. This folder was stored safely within the academic offices of the metabolic team, ensuring patient confidentiality, in line with NHS and University policy.

With parental consent, all of the interviews were digitally audio-recorded. Parents understood that the data would be treated with the utmost confidentiality and anonymity. They also understood that they could
withdraw consent and participation in the study at any point during the interview process. The patients’ names within the transcripts were manually replaced by pseudonyms. The anonymised transcripts were then stored, using the pseudonyms on my personal computer, within the NVIVO software program. With the assistance of the University information technology department, my computer and the NVIVO files were password encrypted.

Parents participated in this study of their own free will and no coercion occurred to ensure participation. They also understood that participation was to improve our understanding of the disease process and participation would not secure any enhanced medical treatments or services for their child. Parents and children were aware that the interview could be terminated whenever they wished. If they felt distressed by the questions being posed, they were free to end the interview. The specialist nurses, with who they have a supportive relationship, would be at hand to provide support if they felt confused, worried or simply wanted to discuss an aspect of the interview further.

In extreme cases of emotional distress, provision was made for them to be referred to a clinical psychologist. A clinical psychologist works with families having treatment at the Willink metabolic and genetics unit in Manchester. Access to this service was available to the families participating in this project as part of their standard care.
Ethical approval was sought for the adjunctive use of subjective disease specific head and neck QoL instruments. However, we felt it appropriate to spend the study period exploring the lived-in experience of patients with MPS using a pure grounded theory approach, largely because the existent questionnaires are not sensitive for MPS. Hence, these questionnaires were not administered to our patients and have not been included in the text or the appendix.
4.0 Results

4.1 Demographics

4.1.1 MPS II

The department has twelve registered children with MPS II, with most of them attending once a year for review. Over the eleven-month period, all twelve children with MPS II were due to attend the unit for review of treatment and agreed to participate in the study. Five of the children with the severe variant of MPS II did not attend their designated appointment (some due to unforeseen illness or need for unscheduled treatment) or declined to participate on the day, hence seven patients and their parents were interviewed.

As expected, all children were male. Six of the children had the attenuated variant of MPS II and one child had the severe form. The attenuated and severe forms can have markedly different systemic multi-organ disease burden. Also, the attenuated form has mild-moderate, static neurocognitive disease whereas in the severe form it is progressive, with gradual loss of neurocognitive function and overall decline. Hence, it was not appropriate to group them together and each sub-group was analysed independently.

As only one family from the severe group participated in the study, theory could not be generated following the initial coding process. However, primary coding from the interview highlights some pertinent issues
important to this family and as this is such a rare illness, I have presented these results.

The mean age was 12 years, range 7-16 years. There were no children with a new diagnosis of MPS II in our unit during the study period and the age range interviewed was broadly similar to that of our registered patient cohort. During the interviews, parents described the developmental story from initial diagnosis to the age of sixteen. All six children with attenuated disease started in mainstream primary school but those older enough subsequently progressed to special needs secondary schools. Three children were in primary school and three within secondary school, providing information about the differing challenges faced by each age group. The child with severe MPS II disease had severe neurodevelopmental delay and marked multi-organ end stage disease. He has limited communication (no language) and mobility (cannot walk). He attends a special needs care facility in the day, when both parents are at work, where he is provided with sensory stimulation, physiotherapy and care.

All children declined to be interviewed separately to their parents. Of the children with attenuated disease, the three teenagers in our cohort participated in the group interviews alongside their parents. The younger three children simply observed the interviews. Two of the teenagers were siblings and participated in a joint interview. All attenuated MPS II interviews were with a single parent, four of them with a mother and one with a father. Of the five families interviewed, four of them were dual
parent families and one a single parent family. All of the dual parent families had both parents in employment whilst the single parent was unemployed, by choice.

The interview with the family of the child with severe MPS II was with both of his parents. They live in Israel, with both parents in full-time employment. All interviews were conducted in English.

Pseudonyms have been given to the children to protect their identity.
<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Severity</th>
<th>Treatment</th>
<th>Developmental Delay</th>
<th>Speech Delay</th>
<th>Hearing Loss</th>
<th>Hearing aid</th>
<th>Musculoskeletal disease</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>James</td>
<td>7</td>
<td>Male</td>
<td>Attenuated</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mainstream primary then special needs Secondary</td>
</tr>
<tr>
<td>Jack</td>
<td>10</td>
<td>Male</td>
<td>Attenuated</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mainstream primary then special needs Secondary</td>
</tr>
<tr>
<td>Mark</td>
<td>14</td>
<td>Male</td>
<td>Attenuated</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mainstream primary then special needs Secondary</td>
</tr>
<tr>
<td>Simon</td>
<td>16</td>
<td>Male</td>
<td>Attenuated</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mainstream primary then special needs Secondary</td>
</tr>
<tr>
<td>Adam</td>
<td>15</td>
<td>Male</td>
<td>Attenuated</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mainstream primary then special needs Secondary</td>
</tr>
<tr>
<td>Brian</td>
<td>10</td>
<td>Male</td>
<td>Attenuated</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
<td>Child refuses</td>
<td>Yes</td>
<td>Mainstream primary then special needs Secondary</td>
</tr>
<tr>
<td>Gerhard</td>
<td>14</td>
<td>Male</td>
<td>Severe</td>
<td>ERT</td>
<td>Severe</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>No school – severely dependent</td>
</tr>
</tbody>
</table>

Table 4: Demographic details MPS II
4.1.2 MPS I

There are approximately seventy children with MPS I (fifty patients are post-HCT with a further 20 patients maintained on ERT) registered with the metabolic and genetics unit, with most of them attending once a year for review. Over the eleven-month period of my study, nineteen of these families agreed to participate in the study and were available on one of my research days for interview. Unfortunately, eight of them did not attend their designated appointment with me and hence eleven patients were interviewed.

Seven children were female and four were male. Six children (one male and three female) had an attenuated (Non-Hurler) variant of the disease whilst the remaining five children had the more severe (Hurler) form of the disease. The age range interviewed was 6 months to 16 years, mean age 7 years. Two of the children had recently been diagnosed with the illness and were aged 6 months and 18 months respectively. Both of them were female and had Hurler’s syndrome. Both had been started on ERT on diagnosis and were awaiting HSCT at the time of interview. This age range interviewed was important in providing an accurate developmental story covering the journey from initial diagnosis to the age of sixteen, highlighting issues that each group may face.

Within the Hurler group (n=5), the two aforementioned newly diagnosed children were awaiting an HSCT, two children were post-transplant (5 & 10
years) and one was on long-term ERT (age 16 years). He was of Kuwaiti descent and had severe neurodegenerative disease. Within the attenuated Non-Hurler (n=6) group, four children were on long-term ERT (12, 12, 15 and 15 years) and two children were post-HSCT (age 18 months and 2.5 years). Both of the transplanted non-Hurlers were diagnosed in the prenatal period, as they had older affected siblings. Both families opted for their second child to undergo a transplant, rather than be managed on ERT alone.

Three children with Hurler’s were in a special needs educational facility. They all suffered with pronounced developmental delay and varying degrees of neurocognitive disease. Four of the Non-Hurler’s children attended mainstream school, of which two had mild learning difficulties. Four children (2 Hurler and 2 non-Hurler) were under the age of five at the time of interview and did not attend a full-time educational facility.

All children declined to be interviewed separately to their parents. The older children in our cohort participated in the group interviews alongside their parents. The younger children simply observed the interviews. One of the interviews was conducted in Urdu and a second in Arabic, with translation into English by a professional language interpreter. Two of the interviewed families had two affected children each and hence were interviewed as a single interview. All interviews were conducted on the day with a single parent, six of them with a mother and three with a father. Of the nine families interviewed, all of them were dual parent families. Eight
of the nine interviewed families had at least one parent in full time employment.

Pseudonyms have been given to the children to protect their identities.

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Severity</th>
<th>Treatment</th>
<th>Developmental Delay</th>
<th>OSA</th>
<th>Hearing loss</th>
<th>Hearing aid</th>
<th>Musculoskeletal disease</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amanda</td>
<td>12</td>
<td>Femal</td>
<td>Hurler -Sheie</td>
<td>ERT</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Main stream</td>
</tr>
<tr>
<td>Andrew</td>
<td>12</td>
<td>Male</td>
<td>Hurler -Sheie</td>
<td>ERT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Main stream</td>
</tr>
<tr>
<td>Maya</td>
<td>6 months</td>
<td>Femal</td>
<td>Hurler -Sheie</td>
<td>HSCT</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Ramona</td>
<td>18m</td>
<td>Femal</td>
<td>Hurler -Sheie</td>
<td>HSCT</td>
<td>Moderate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Mallika</td>
<td>9</td>
<td>Femal</td>
<td>Hurler -Sheie</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Main stream</td>
</tr>
<tr>
<td>Sheena</td>
<td>2</td>
<td>Femal</td>
<td>Hurler -Sheie</td>
<td>HSCT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ayesha</td>
<td>15</td>
<td>Femal</td>
<td>Hurler -Sheie</td>
<td>ERT</td>
<td>Mild</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Main stream</td>
</tr>
<tr>
<td>Rubaiya</td>
<td>2</td>
<td>Femal</td>
<td>Hurler -Sheie</td>
<td>HSCT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Steven</td>
<td>10</td>
<td>Male</td>
<td>Hurler -Sheie</td>
<td>HSCT</td>
<td>Moderate with autism</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Special needs</td>
</tr>
<tr>
<td>Milo</td>
<td>5</td>
<td>Male</td>
<td>Hurler -Sheie</td>
<td>HSCT</td>
<td>Moderate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Special needs</td>
</tr>
<tr>
<td>Mohamed</td>
<td>16</td>
<td>Male</td>
<td>Hurler -Sheie</td>
<td>ERT</td>
<td>Severe</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Special needs</td>
</tr>
</tbody>
</table>

Table 5; Demographic details MPS I
4.1.3 MPS VI

Children with MPS VI suffer with similar head and neck problems to children with MPS I and II and within the original study design, this sub-group of children were to be included in this study. There are presently nine of these children registered with the metabolic unit. The parents of four children with MPS VI were interviewed as part of this study. The children were all female, mean age 8 years, range 3-10 years. All children declined to be interviewed separately to their parents. Two of the children were siblings and participated in a joint interview with their parents. All three families interviewed were dual parent families with at least one parent in full time employment.

During the course of this MPhil, I ran out of time and further patient recruitment and data collection could not occur. This aspect of the project is currently on going, separate from this research study.

Hence, MPS VI will be excluded from this study and no further data will be presented in this thesis.

4.2 Parental Employment

Fifteen families of children with MPS I and II participated in the interviews. Participating parents completed simple questionnaires, designed to enquire
about their level of education and employment status both before and after the diagnosis of MPS in their child. The aim of this questionnaire was to establish if having a child with MPS had an impact on their employment status.

Two interviewed families had a single parent (both single mothers) with the remainder consisting of both parents (a husband and wife unit). Twenty-nine of the thirty parents completed the questionnaires and a summary of the results is outlined in Table 6.

The parents, who were unemployed prior to the birth of their child, remained unemployed after the diagnosis was established. This cohort of parents stated that there was a high likelihood that they would be unemployed regardless of the diagnosis of MPS.

Most fathers continued in employment, of which two reduced their working hours and went part-time after the diagnosis was established and two others stated that they had moved into more flexible full-time jobs, which allowed them to take time off for regular hospital appointments. Four mothers continued in full-time work, four reduced to part-time working and two gave up working altogether. The main reason cited for this was the diagnosis of MPS and the amount of time they spend caring for their affected child. One couple, both in full-time employment, stated that although they were able to hold down full-time jobs, they were unable to dedicate the required hours for appropriate career progression, and hence
this was a sacrifice they both decided to make quite early after the diagnosis had been established in their son.

Thus, in our group of eighteen employed parents, thirteen of them had been affected professionally by the diagnosis of MPS.
<table>
<thead>
<tr>
<th>Name</th>
<th>MPS Subtype</th>
<th>Severity</th>
<th>Mother Education</th>
<th>Father Education</th>
<th>Mother Employment Status</th>
<th>Mother Employment Status Prior to Diagnosis</th>
<th>Would your employments be different if your child did not have MPS? (Mother)</th>
<th>Father Employment Status</th>
<th>Father Employment Status Prior to Diagnosis</th>
<th>Would your employments be different if your child did not have MPS? (Father)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amanda</td>
<td>I</td>
<td>Hurler-Sheie</td>
<td>Higher Education - Business</td>
<td>Higher Education - Physics</td>
<td>Unemployed</td>
<td>PR in a music firm</td>
<td>Yes, would still be in full time education</td>
<td>Corporal Physicist</td>
<td>Corporal Physicist</td>
<td>N/A</td>
</tr>
<tr>
<td>Andrew</td>
<td>I</td>
<td>Hurler-Sheie</td>
<td>Higher Education - Podiatry</td>
<td>Higher Education - Speech and Language Therapy (SLT)</td>
<td>Part-time Podiatrist</td>
<td>Full-time Podiatrist</td>
<td>Yes, would work full-time</td>
<td>Part-time self-employed SLT</td>
<td>Full-time hospital SLT</td>
<td>Yes, would work full-time</td>
</tr>
<tr>
<td>Mallika</td>
<td>I</td>
<td>Hurler-Sheie</td>
<td>Primary School (age 11)</td>
<td>Secondary School (age 16)</td>
<td>Unemployed</td>
<td>Unemployed</td>
<td>No – five other children</td>
<td>Unemployed (visually impaired)</td>
<td>Unemployed (visually impaired)</td>
<td>No</td>
</tr>
<tr>
<td>Sheena</td>
<td>I</td>
<td>Hurler-Sheie</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Ayesha</td>
<td>I</td>
<td>Hurler-Sheie</td>
<td>Secondary school (age 16)</td>
<td>Secondary school (age 16)</td>
<td>Unemployed</td>
<td>Unemployed</td>
<td>No – four other children</td>
<td>Drives a minicab</td>
<td>Drove a minicab</td>
<td>N/A</td>
</tr>
<tr>
<td>Rubaiyat</td>
<td>I</td>
<td>Hurler-Sheie</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Steven</td>
<td>I</td>
<td>Hurler</td>
<td>Higher Education (BSc, MSc, MA)</td>
<td>Higher Education (Engineering, MBA, MA, PhD)</td>
<td>Metho-dist Church minister</td>
<td>Metho-dist Church minister</td>
<td>N/A</td>
<td>Metho-dist Church minister</td>
<td>Metho-dist Church minister</td>
<td>N/A</td>
</tr>
<tr>
<td>Milo</td>
<td>I</td>
<td>Hurler</td>
<td>Secondary School (age 16)</td>
<td>Secondary School (age 16)</td>
<td>Unemployed</td>
<td>Unemployed</td>
<td>No</td>
<td>Unemployed</td>
<td>Unemployed</td>
<td>No</td>
</tr>
<tr>
<td>Molhemed</td>
<td>I</td>
<td>Hurler</td>
<td>Higher Education - Teaching</td>
<td>Higher Education - Law</td>
<td>Unemployed</td>
<td>Teacher, secondary school</td>
<td>Yes, would work full-time</td>
<td>Solicitor</td>
<td>Solicitor</td>
<td>N/A</td>
</tr>
<tr>
<td>Maya</td>
<td>I</td>
<td>Hurler</td>
<td>Secondary School (age 18)</td>
<td>Secondary School (age 18)</td>
<td>On Maternity leave</td>
<td>Full time in the billing department</td>
<td>Would like to go back full-time</td>
<td>Pub-manager</td>
<td>Pub-manager</td>
<td>N/A</td>
</tr>
<tr>
<td>Ramona</td>
<td>I</td>
<td>Hurler</td>
<td>Higher Education (age 16)</td>
<td>Higher Education (age 16)</td>
<td>Unemployed</td>
<td>Unemployed</td>
<td>No</td>
<td>Musician – currently unemployed</td>
<td>Musician – currently unemployed</td>
<td>Would like to work full-time</td>
</tr>
<tr>
<td>Name</td>
<td>Attended</td>
<td>Higher Education - Teaching</td>
<td>Secondary School (age 16)</td>
<td>Part-time teacher</td>
<td>Full-time teacher</td>
<td>No, has another child and chooses to be part-time</td>
<td>Part-time self-employed engineer</td>
<td>Full-time BT engineer</td>
<td>Yes, but found coping with full-time work difficult</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Jame II</td>
<td></td>
<td>Higher Education - Teaching</td>
<td>Secondary school (age 15)</td>
<td>Unemployed</td>
<td>No</td>
<td>Unemployed</td>
<td>Unemployed</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Jack II</td>
<td></td>
<td>Second school (age 15)</td>
<td>Mother single parent</td>
<td>Unemployed</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Simon II</td>
<td></td>
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<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td></td>
</tr>
<tr>
<td>Mark II</td>
<td></td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td></td>
</tr>
<tr>
<td>Adam II</td>
<td></td>
<td>Higher Education - Social Sciences</td>
<td>Social worker full-time</td>
<td>N/A</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
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<td>Full-time</td>
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<td>Full-time</td>
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<td></td>
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<tr>
<td>Gerhard II</td>
<td></td>
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<td>Higher Education</td>
<td>Full-time</td>
<td>Full-time</td>
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<td>Full-time</td>
<td>Full-time</td>
<td>N/A</td>
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Table 6: Parental Employment
4.3 Themes from the analysis of the MPS I and II interviews

Many of the emergent themes, discussed further, appeared across both MPS I and II. However, their impact on both sub-groups differed. In this section, I present the individual cohort findings, but also explore the differences between the two. Interview data, for small patient numbers, should perhaps not be used in this manner. However, the literature implies that the problems faced by these groups of children are the same and presenting data side by side, allows treating clinicians, such as myself, to visualize and understand the differences more clearly.

4.3.1 The acquisition and development of spoken language

Parents of children with attn. MPS II and the more severe MPS I (Hurlers’ and moderate non-Hurler’s) were concerned about their children’s delayed acquisition of language, in comparison with their peers and siblings. Many children did not reach their early speech milestones, with no discernable language at diagnosis of the illness, varying between 18 months and 3 years in MPS I and as late as four years in MPS II.

Parents of children with MPS I felt that this delay was due to a number of things, including physical changes in their child such as a large tongue, poor hearing and in some severe cases, global developmental delay. Similarly, in attn. MPS II, parents felt this was secondary to their child’s severe deafness and static neurocognitive disease.
Ramona’s mother (MPS I-H, age 18 months): ‘during her newborn hearing screening they could not get a consistent reading and diagnosed her with hearing loss. We didn’t know at the time that she had MPS. She was wearing two hearing aids by three months of age. Despite the hearing aids, she could not say any words at all until the ERT was started four weeks ago. It was difficult for her and she used to be quite clingy, with me having to carry her everywhere. Since the treatment, she is making sounds like ‘dada’ and the other day actually said ‘book’. It was such a special moment.’

Mallika’s father (MPS I-H, age 9): ‘She was great at lip reading and would sit on the floor and play with her brother. We never realized she was extremely deaf until they diagnosed her with MPS and tested her hearing. To be honest, she wasn’t speaking at all when she was diagnosed (age 5). They gave her hearing aids and put her on the ERT at the same time. Gradually she started to say single words and then sentences quite quickly.’

It appears that deafness and the delayed acquisition of language were a bigger concern for families with attenuated MPS II than those with MPS I-H. Parents and children with mild Non-Hurlers MPS I (Hurler-Schei) did not express any concern about language and hearing. All of the children with attn. MPS II were diagnosed with deafness very early on, preceding the diagnosis of MPS. They had all received multiple sets of ventilation tubes and hearing aids. One child had had a unilateral cochlear implant inserted prior to being diagnosed with MPS, for the treatment of profound hearing loss.
All the children with MPS II had severe language delay, initially attributed solely to hearing loss, and most had the input of a speech therapist alongside hearing rehabilitation. On reflection, some parents felt that they were actually in ‘denial’ of the extent of their child’s language delay.

*Brian’s mother (attn. MPS II, age 10), ‘we watched a video back. In the video, he runs into the room and literally babbles, and runs out again. He was three and a half and had no speech. I think we were in a bubble of denial.’*

For MPS I, parents commented that the ERT had rapidly improved their child’s speech, with children speaking within weeks of it being started, much to the amazement of their parents, and was now no longer a cause for concern. Those parents with multiple children commented that although the speech markedly improved with the treatment, it was never as good as that of non-affected siblings or peers at school. The mild speech impediment and delayed grammar carried through into secondary school. Two parents, with multiple affected children, felt that their children treated with HSCT had better language than their older children treated with ERT alone. However, despite the HSCT the speech was still mildly delayed and lacking in clarity, in comparison with healthy unaffected children.

*Ramona’s mother (MPS I-H, age 18 months), ‘Since the ERT started four weeks ago, she is now making sounds like ‘dada’ and the other day actually said ‘book’. She is also pointing to things properly if she wants them. Before she just made lots of sounds and was not talking at all.’*
Mallika’s father (MPS Hurler-Scheie, age 9 years, treated with ERT) ‘She still has a delay now. When she is trying to talk and have a conversation she gets stuck with some words and there are others that she can’t pronounce.’ Her sister’s speech (Sheena, MPS Hurler-Scheie, age 2 years, treated with HSCT) is much better than Mallika’s was at that age. At two years Mallika was not speaking any words at all whereas Sheena is speaking sentences now. Although better, Sheena’s speech is not so good as my middle two children who do not have the MPS. It is not as clear.’

This subjective improvement in language and hearing with ERT was not witnessed in attn. MPS II. These parents felt that language development had occurred later at primary school, about age six, whilst surrounded by healthy children. Mainstream school had been a positive influence. However, as these children had grown older, their speech had never really caught up with that of their peers and always remained moderately ‘delayed’ or ‘lacking in clarity’.

James mother (attn. MPS II, age 7): ‘his speech rapidly improved after reception. We think it’s because he was in school now with the other kids’.

Brian’s Mother (attn. MPS II, age 10): ‘he is now ten and my friends still can’t understand what he says as his speech is not very clear.’ ‘The other children are all learning year five adjectives and he has to be taken out of class and taught reception level phonics due to his inability to hear. Also he gets his spelling wrong as he can’t hear the difference between similar sounding words like taught and caught.’
In contrast to MPS I, the parents of children with attn. MPS II felt that their children lacked the capacity to develop a ‘better vocabulary’. They felt that this was a direct impact of the MPS disease affecting their child’s brain, giving them some degree of static cognitive impairment.

James father (attn. MPS II, age 7): ‘I think it’s partly due to his hearing, but I don’t think it’s totally that. I think he can get by even without his hearing aids to an extent. It’s just his understanding of tenses and just general basic language is still quite slow and delayed. I think he’s been put at maybe a mental age of about three.’ ‘We are frequently translating things others people say to him into a more basic language that he can understand’.

This inability to communicate and express themselves was associated with behaviour problems in younger children and feelings of frustration and anger in older children. It also affected the self-confidence of the older children, who, towards the end of primary school were beginning to develop insight into their difference to their peers and siblings.

James’s father describing his behaviour (attn. MPS II, age 7): ‘He’s sociable and loves playing with other kids. He loves people, but he struggles to make himself understood and to understand what other people are saying. So I think he’s developed little ways of coping and sometimes it’s physical. He’ll push or he’ll...you know, and sometimes he’ll shout and pull faces because he’s frustrated so that makes it difficult.’
Brian’s mother describing his frustration with not being able to communicate well (attn. MPS II, age 10): ‘he frequently loses the attention of his audience because it takes him so long to phrase his sentences. If we attempt to translate or speak for him, he gets cross and says no, no, no, that is not what I wanted to say. ‘At home he strops and runs upstairs and hides, ‘you don’t listen to me’ type proper teenage tantrums. It’s different at school, he doesn’t do that. Apparently he just gets frustrated and bursts into tears.’ ‘He’s not as confident to say things and he just hasn’t got the vocabulary to say things. That is MPS, he hasn’t got the brain power to know what to say.’

Analysing the emergent themes with my supervisor, and diagraming, revealed that the parents of children in primary school with attn. MPS II held aspirations for their child’s social and academic achievements, with the belief that they could integrate or fit into normal society. They felt that the acquisition of language was crucial, as it would allow the children to communicate with their peers and teachers in mainstream school and not be perceived as being different, whilst also providing a good education, allowing for future independence. They were very accepting of ventilation tubes and hearing aids, as they felt these treatments would allow their child to achieve these stated communication goals more effectively. They were also positive about sign language, which was the first means of communication used by children with early, severe hearing loss. These children had all gone on to develop spoken language, in some cases as a substitute for the signing, but in other cases as a supplement. The families
attributed the transition from sign language to spoken language to the use of hearing adjuncts and the availability of teaching assistants in mainstream schools. The parental preference was for spoken language as they felt it would allow their child to communicate with a wider audience and also make them feel less different to other children their age, once again highlighting the desire to ‘fit-in’.

Most of the children wore hearing aids from a young age. Parents of children with MPS I described the children as having a very positive relationship with their hearing aids. The younger ones consistently asked to wear them whilst the older children felt that they helped them hear everything in their social environment, both at home and at school, allowing them to achieve an education and communicate effectively with others. Adam, an adolescent with attn. MPS II, with a unilateral cochlear implant (a semi-implantable hearing device for severe/profound hearing loss) had developed claw hands in his early teen years, and hence was finding it increasing difficult to use sign language. His mother was thankful that his cochlear implant had facilitated the acquisition of speech, so he was not entirely dependent on his hands and sign language to communicate, and could communicate with an alternate form of communication, the spoken language. Adam himself felt that the cochlear implant (hearing aids) gave him a shared identity with his new friends at his college for the hearing impaired, as all of the children here wear hearing aids just like Adam.
Adam’s mother giving her views on his cochlear implants that had been surgically fitted at the age of three to facilitate the acquisition of sound for profound deafness (attn. MPS II, age 15): ‘it didn’t change anything in the beginning. It’s only now looking back that I’m glad we did it. Sometimes he struggles with signing because of his claw hands. He struggles with some of the signs and maybe communicating with other deaf people that just sign, that don’t speak, I think having the implant has most definitely been a benefit for him.’

Despite Adam’s very positive response to his hearing aids, other parents of attn. MPS II have a more reserved opinion. Some children with attn. MPS II, when angry, frequently remove or throw the hearing aids away, as an outward display of their feelings. For some children in mainstream schools, the hearing aids can draw unnecessary attention and in one case (Jack, age 10) was a cause for bullying. However, Jack lived and schooled in a deprived neighbourhood and his mother felt that the bullying was, in part, linked to the other social problems of their neighbourhood.

4.3.2 Breathing concerns

A major source of parental concern in MPS I was the development of obstructive sleep apnoea (OSA) in their children at a very young age. This was not problematic for the parents of children with attn. MPS II.

Most of the children had developed it by the age of one year, with some displaying symptoms as early as three to four months old.
Milo’s mother (MPS I-H, age 5): ‘At three months old he developed loud snoring, which was audible over the television downstairs. This progressed to breath holding. No one really thought he could be suffering with sleep apnoea at this young age.’

Yasmin’s father (MPS I-H, age 5): ‘She developed really abnormal snoring at the age of five months. She found it really difficult to breathe at night and would break out into a sweat.’ ‘We felt really scared and did not understand what was happening’.

In many of the children it appears to have been the first cause of concern for parents, preceding the diagnosis of MPS. This was a fearful time for parents, as many could see that there child was not breathing properly. The symptoms were frequently misdiagnosed and labeled as ‘colic’ or ‘adenoid’ and the parents were told that their child would soon improve. Some took to sleeping with their child at night so that they could closely monitor them.

Milo’s mother (MPS I-H, age 5): ‘It used to be a leap of faith putting him to bed. You’d put him to bed and go, god is he going to be there in the morning? It was horrible. I used to sleep with him...well, he didn't sleep a lot 'cause it used to wake him up, and it would happen quite a lot. But I used to sleep with him upright on my shoulder as this stopped him holding his breath as much.’
Ramona’s mother (MPS I-H, age 18 months): ‘She wakes up at least every hour and holds her breath while sleeping. I’ve been sleeping close to her since I’ve had her. I’ve tried to put her in a cot, but it just doesn’t work. It stresses her out’.

The ERT had a positive impact on the symptoms. Within the first few weeks of being commenced on the ERT treatment, the snoring and breath holding had improved and eventually ceased in most children. Those children with more severe MPS I had then undergone an HSCT, which may have contributed to the longevity of improvement.

Milo’s mother (MPS I-H, age 5): ‘He had the chemotherapy, followed by the HSCT, and within three months, the severe snoring and breath holding stopped. We are now four years since completion of the transplant and he has not suffered since.’

From the interviews, it appears that in children with non-Hurlers, a late diagnosis (>5 years of age) is a negative predictor and in these children the early improvement with ERT is not sustained. They continue to suffer with progressive disease, requiring a surgical adenotonsillectomy procedure in their early teens, to produce an improvement in the symptoms.

The children report that the disrupted sleep secondary to the OSA makes them very tired in the morning, affecting their performance in school.
Mallika’s father (MPS I-H, age 9): ‘*She used to have symptoms of heavy breathing, to the point where she stopped breathing for a second or two every night. It did not get better with the ERT. A few months ago she had an operation where they removed her tonsils and it has made a huge difference. The symptoms at night have all gone away and she is so much brighter in the mornings.*’

Three children in our cohort were diagnosed with MPS very early (two in the pre-natal period and one at the age of six months prior to the onset of outward symptoms of OSA). All three were started on ERT on diagnosis and then offered a HSCT by the age of six-nine months. To date, these three children remain free of clinical signs of disease (oldest child in this cohort is age three years).

Our cohort included two children with markedly more severe MPS disease than the others. One had MPS I-H and the other had severe MPS II. They both suffer with progressive severe multi-level airway disease, with a profound impact on their lives. For both, the snoring and OSA had progressively worsened with increasing age, requiring multiple hospital admissions hospital for oxygen and pressure ventilation support. They also required a continuous positive airway pressure (CPAP) machine at home to support their breathing at night.

The parents of these children feel distressed and anxious that their children will soon die from the breathing problems. They are reluctant to take
holidays that are not within easy reach of the hospital. They worry about
general anaesthetics. Parents are very accepting of the need for the CPAP
machine at home as they feel it may improve their child’s symptoms and
life expectancy.

Gerhard, the child with MPS II, does not tolerate his CPAP system as it
makes him feel claustrophobic. His parents know that this technology will
prolong Gerhard’s life and support his breathing but are faced with a moral
dilemma as the technology is having a negative impact on their son’s quality
of life. This highlights a conflict between the child’s need versus his
parents needs.

4.3.3 Musculoskeletal disease, mobility and independence

For many parents and children, pain and stiffness within the muscles and
joints, alongside the outward physical appearance of these musculoskeletal
manifestations, had a large impact on their children’s quality of life. The
parents of the children with MPS I described this as the single biggest
problems for their children with a large impact on their children’s HRQoL.
However, in attn. MPS II, although the burden of musculoskeletal disease
was present, the parents felt that the acquisition of language and hearing
difficulties had a more profound impact on their child’s HRQoL. Hence,
further reference in this section will be from the point of view of parents of
children with MPS I.
Musculoskeletal disease started in infancy, with most children developing curvature of their spine, seen as a lump in the back, or trigger fingers and toes. In many these had led to the diagnosis of the disease. They had also contributed to delayed physical milestones such as crawling and walking and many children were still not mobile into their second year of life. The initiation of weekly enzyme infusions rapidly improved the child’s mobility and energy levels allowing them to catch up with other toddlers their age.

Maya’s father (MPS I-H, age 6 months): ‘we found what we thought was a lump on her back, which we later discovered was curvature of her spine. For the lump we saw a pediatrician who raised the suspicion of MPS.’

Amanda’s mother (MPS I, age 12), ‘within seven days of ERT suddenly she was running around the house...she somersaulted off the back of the sofa. She had never done that in her life ever. She was four and a half.’

Ramona’s mother (MPS I-H, age 18 months): ‘we started the ERT four weeks ago and she has now started walking. Before we came here she couldn’t crawl or stand up on her own.’

Neither ERT nor HSCT were reported to stop or reverse the disease process completely and musculoskeletal problems continued to develop as the children grew. In our cohort even those with the most attenuated form of the disease still had significant disease burden. This had an impact on the child’s ability to participate in the most basic activities such as sitting up.
when laid down, climbing a flight of stairs and walking, perhaps to school.
The persistent curvature in their spine stopped them standing straight and
they had stiffness in their joints, from their fingers and wrists to their
shoulders, neck and lower limbs. This stiffness was also accompanied by
pain, brought on by use, in some cases even after ten minutes of walking or
writing. Many had developed clawing of their hands.

Ayesha (MPS I-H, age 15): ‘I get pain in my legs when I walk to school in
the morning. I stop for a few minutes and then start again slowly.
Sometimes I lose my balance and fall over.’

Amanda’s mother (MPS I, age 12): ‘Even now, from a lying position she
can’t sit up. I have to help her. The walking is an even bigger concern for
us.’

Children with non-Hurlers were able to attend mainstream school.
Climbing up and down stairs was challenging and time consuming and
hence for their own safety they left the lesson five minutes earlier than the
other children and used the stairs or lift to travel up and down. They had
multiple sets of schoolbooks, one at home and one at school to save them
carrying a heavy bag. Some of them had a teaching assistant to write for
them or to carry their books and bags for them. In contrast to children with
MPS II (Soni-Jaiswal, Roberts et al. 2017), many of these children were
intelligent and articulate and did not require the teaching assistants for
academic support.
Ayesha (MPS I-H, age 15): ‘at school, I have a helper to carry my bag and books between my classes. It means that I don’t get as tired and it stops my shoulders and back from hurting.’

Amanda (MPS I, age 12): ‘I don’t want a classroom assistant. I think it will make me less independent and attract attention. It would be helpful with my writing but I manage by just shaking my hands whilst writing to get rid of the cramp. My friends help with my bag and I take the lift instead of the stairs.’

Older children, from the age of eight onwards, found it frustrating that they could not participate in sports or run like their friends. Or if they could manage it, they had to adopt a different technique to accommodate the stiffness and the disability. Although, it was apparent that this frustration with not being able to participate in sport was also linked to culture, with White children and parents reporting it to be a bigger problem than their Asian/Asian British counterparts.

Andrew (MPS I, age 12): ‘I play cricket at school but I can’t raise my arm above my shoulder to bowl and so have had to change the way I bowl. I can’t really play football, as you need to be able to run faster than in cricket to get the ball and I can’t manage that. When I play cricket I find the extra weight of the shin pads difficult to carry.’
Amanda (MPS I, age 12): ‘I get annoyed at not being able to participate in sports or run. I get tired very easily. I cannot stand properly and walking hurts my back and my feet if it is for longer than ten minutes.

Children of the same age had also become self-aware and realised that their physical appearance and physical stamina were both different to other children around them. Teenage girls kept a low profile at school and avoided changing in front of their peers in the changing rooms. They felt sad missing out on social activities such as going shopping with friends, as their restricted mobility would mean the need for a wheelchair, causing them further embarrassment.

Amanda (MPS I, age 12): ‘I don’t want to be different, so I just try to blend in and I don’t tell anybody about my condition.’ ‘I don’t like the way my tummy is swollen and looks so big. Also, the way I stand and walk looks funny. My fingers stick out, people might look at them.’

This idea of difference from one’s peers, despite severe musculoskeletal disability, was not an issue for children who had affected siblings and cousins with MPS I. Perhaps having other children in your immediate surrounding with similar problems normalises the problem, allowing the child to attain a shared identity.

All of the children in our group, including those with an attenuated form of the disease, relied on wheelchairs if they had to walk more than ten-twenty
minutes at a single stretch. Parents described children as accepting of the wheelchairs and some felt the children were sometime too easily ready to sit in them and not exerting themselves to their full physical ability. However, Amanda (age 12) did comment that she did not want to use the wheelchair in front of her peers as it made her stand out, highlighting her difference to them. The interviews highlighted that wheelchair use within a mainstream school facility could be difficult and the children preferred to walk around for the day, albeit with assistance or slowly.

Three children with Hurler’s required a special needs education, primarily due to autism or severe learning difficulties. From a musculoskeletal point of view, the big advantage of the specialist schools was that they were on one level and the children could easily use their wheelchairs to get around if necessary. They also offered allied services such as physiotherapy and access to a hydrotherapy pool.

Most parents worried about their child’s future physical health, with some voicing concerns about the children growing into adults who were wheelchair bound, unable to live independently, perhaps becoming institutionalised.

Milo’s mother (MPS I-H, age 5): ‘we worry most about his independence, whether he’s going to be stuck with his old mum for the rest of his life. I want him, you do for your children, to be educated, independent, working,
house, family, just happy, doing the normal, run of the mill things. I wouldn't want to see him in care homes and institutions.'

Children with severe MPS II and MPS I-H suffered with pain in their joints and muscles, including at night. This kept both them and their parents awake at night, causing daytime fatigue. The parents also expressed feelings of helplessness and frustration when they could not help ease the pain and had to watch their child crying.

Gerhard’s parents (Severe MPS II, age 14), ‘It’s not just the breathing; he has a lot of pains at night in his joints. It affects his quality of life. And we try to treat him by many drugs, including cannabis, but nothing works. He screams all night. He’s suffering and crying, we don’t know what to do; most of the time we don’t know what’s hurting him. And he’s looking at us, in the middle of the night, and crying. It’s very hard.’

4.3.4 Education and independence

For our sub-group of children with attn. MPS II, we were able to generate more complete theory, with saturation of themes. Interpretive analysis of the narrative revealed rich data about the parents’ desire for their child to ‘fit in’ with their peers. In the formative years, they wanted their child to integrate into broader society, achieving the same social, developmental and educational milestones as normal children in mainstream school. On transition from primary to secondary school, the focus had shifted and they were more accepting of their child’s differences and wanted them to be
surrounded by a peer group, with similar needs who may also have
developmental delay, language delay or hearing loss, allowing their child to
feel less ‘different’. Parents felt that acquisition of spoken language
(discussed earlier in 4.3.a) and their child’s education was important in
facilitating this.

As mentioned above, educational expectations, including the desire for
normalcy and ‘fitting-in’ changed with increasing age in attn. MPS II.
Parents with young children were eager for their children to attend
mainstream primary school. At this stage many of the MPS II children
were relatively well and the parents wanted to celebrate their similarities
with other children, allowing them to feel like a part of the wider
community. Parents also commented that at this young age the children
were unaware of their difference to other children their age and hence
thrived in this school environment. However, this ability to integrate well
into a mainstream school seemed dependent on a receptive school, able to
cater for the child’s extra needs, for example; one primary school had a deaf
unit attached to it. All of the MPS II children required teaching assistants,
not for physical assistance, but for educational support.

Brian’s mother (MPS II, age 10) said: ‘His teaching assistant keeps him
back after class to do extra spellings. At the moment he is doing spellings
from year five but is in year six.’
However, this social integration was difficult to achieve if the children were on the autistic spectrum, a normal part of the MPS II disease process in some children with CNS disease. These children appeared to thrive instead in special needs schools with small class sizes and an increased level of support. These schools offered a reduction in background noise and improved one to one interaction with the teacher.

James’s father describing the move from mainstream to special needs school for their autistic son (MPS II, age 7): ‘we think this school is much more suited to him and over a short period of time his concentration and behavior have both improved. There is less background noise and so he is able to hear well. The school has a dedicated room where he can spend time with the lady from the sensory impairment service. But on a personal level the move to a special needs school was a really difficult thing for us to accept.’

Parents felt that towards the end of primary school, the ‘learning’ gap between their children and those without MPS had widened significantly. Although the children did not have progressive CNS disease, their baseline learning difficulties had become more socially problematic as they got older. Parental expectations and aspirations for their child changed at this point and rather than academic achievement, they wanted their child to be happy, safe and develop life skills that would provide them with future independence. It appeared that the parents had come to accept the difference between their child and peers. The older children in our group had moved
away from mainstream education to one more tailored to their individual needs when they transitioned from primary to secondary school.

Jack’s mother (MPS II, age 10) said of his approaching final year in primary school: ‘we have social worries. I couldn’t care less about his education anymore. As long as he’s happy! He’s just very immature for his age.’ ‘When they first gave us the diagnosis of Hunters we never thought he would be able to read or write. He has already achieved so much more than that.’

Adam’s mother (MPS II, age 15): ‘His special needs secondary school primarily caters for children with deafness. It has an enrichment program where he attends a mainstream college one day a week. His support worker comes with him. This will hopefully allow him to get a qualification in catering. He is also taught important life skills at college like budgeting.’

4.3.5 The Emotional Impact of the disease

Our interviews showed that young children with MPS I, age 5-6 years; develop an awareness of their illness and their difference to other children around them. The older children, girls more so than boys, were more acutely aware of this fact, especially their physical appearance and their decreased physical stamina. Their parents suggested many had developed shy, introverted personalities when not in their home environment. They reported wanting to simply ‘blend-in’. One fifteen-year-old girl (Ayesha) during the interview stated that she did not feel different to her peers and
that her physical appearance and severe musculoskeletal disabilities were not a problem for her. However, her mother contradicted this by saying that she was always angry at home, shouting at her mother and siblings and if very frustrated, would resort to deliberate self-harm.

Amanda’s mother (MPS I, age 12): ‘She has a tremendous personality at home but becomes painfully shy when we go out. I’m worried that academically she will be a high achiever but will be an emotional wreck by the time she is in her twenties, burdened down by anxiety and depression, the psychological side of things really.’

Some parents expressed relief at their child looking outwardly normal and not suffering from intellectual impairment. For them, the mental and physical disabilities that may be linked to the illness were hard to cope with. They expressed the desire for their children to be similar to their peers and fit-in with society at large. One mother said that when she was first informed of her child’s illness, she was shown pictures of children with the severe form of the disease. For her this was the scariest part of the diagnosis and she left the hospital appointment that day feeling horrified. They expressed gratitude at their children being given the HSCT as they felt it might allow them to live a healthy life.

Maya’s father (MPS I-H, age 6 months): ‘the worst nightmare for a parent is that you have an unhealthy or a disabled child. There is no option for us
than to go ahead with the bone marrow transplant. It can give her a normal life.’

Time off school for treatments and hospital appointments was a concern for parents. They felt that their child missed a third of their school week secondary to their treatments and hospital appointments and the burden of catching up on missed classes and homework was a real one. Many children required extra tuition or quite heavy parental support and encouragement to stop them falling behind at school.

Ayesha’s mother (MPS I-H, age 15): ‘Despite the tuition classes, she does not achieve the same grades as her cousins. I am worried that without an education she will not have an independent future after we die.’

4.4 Impact of MPS on parental quality of life

Parents described the experience of parenting a child with MPS a largely positive one, with increased family cohesion and time spent together. All the parents in our cohort described nothing but love for their child with MPS.

However, caring for a child with physical and intellectual disability can have a negative impact on the quality of life of the parents themself, with many describing both emotional and physical exhaustion.
Those whose young children had recently been diagnosed with the illness described feelings of sadness, shock and bewilderment. However, they viewed HSCT as a positive treatment that may have the potential to change the outcome of their child’s disease. In the early days after diagnosis, parents stated that they struggled with maintaining a meaningful presence at work as a large amount of their time was spent in the hospital. Many turned to their partners for support as they feel that friends and family may not empathise. They also worried about their other children, who were frequently being cared for by well meaning relatives and friends.

Some parents worried about the outward physical appearance of the disease in their child and how it might make them stand out from their peers. They felt protective of their children, especially if people stared or asked questions. Others struggled with accepting the cognitive aspects of their child’s illness such as developmental delay, autism and behavior problems. Some parents said that they initially feel embarrassed.

Gerhard’s mother (Severe MPS II, age 14): ‘People don’t like difference. They are looking and pointing, and they’re laughing; and for me to go to the park, out after school, I couldn’t do it. I really couldn’t do it because everybody was looking, and the children was looking, yeah, see him, see him, he’s so big …

Parents stated that children with the severe form of the disease might be physically dependent on them, requiring constant support. These parents
frequently carried their growing child or heavy equipment. Those whose children had complex needs or required overnight care, described chronic sleep deprivation and mental exhaustion. They also found it tiresome to concentrate at work through the day.

Gerhard’s father: ‘when he was younger, he was running all over. As the disease got worse, he started walking on tiptoes. Over the last three years, he can’t walk at all. This last year he has been unable to stand. We have to carry him around the house and to the car.’
5.0 Discussion

This is the first study to explore the impact of MPS types I and II on the lives of children and their parents through in-depth interviews, providing information on aspects of the illness that pose important functional, emotional and social challenges. The historical emphasis when treating these children was to improve their life span and decrease their multi-system disease burden, monitored with objective outcome measures. Now that ERT and HSCT have become established treatment modalities, and these children have a longer life expectancy, the focus of treatment, and subsequently research, has moved towards improving their quality of life, reflected by the managed access program instituted by NICE for MPS IV (NICE 2015). This is also the first study to show that the issues important to parents of children with MPS I differ to those of children with MPS II, despite the two having a similar spectrum of head and neck disease.

Families interviewed by us feel that despite ERT and HSCT the children have marked disease burden with a significant impact on their daily functioning. We found that even those with attenuated disease face numerous daily challenges, with difficulties in the most basic activities such as getting dressed, walking to school, participating in sports, being able to hear the teacher and communicate with their peers and fighting exhaustion secondary to poor sleep. They are growing into adolescents and young adults with anxiety about their physical appearance, hospital admissions,
social integration, independence and their ability to maintain future employment and have normal adult lives. Many of these issues will be addressed further in this discussion.

Upper airway disease and obstructive sleep apnoea were a major source of concern for parents of children with MPS I with many voicing fears about their child dying as a direct result. Their concerns are consistent with the findings of the MPS I registry that twenty percent of deaths in children with MPS I are secondary to their upper airway disease (Arn, Bruce et al. 2015). In infancy and early childhood, there was impact primarily on the quality of the parents’ lives, with many reporting high levels of stress and anxiety about their child’s disturbed and worrying sleeping pattern, feeling exhausted from being awake every night and co-sharing their bed with their unwell child and frustration at not being taken seriously by their primary care physicians. However, problems could persist throughout childhood, with adolescents reporting that their sleep apnoea made them feel un-refreshed in the morning, exhausted at school, with a direct effect on their academic performance.

Parents of children with attn. MPS II did not feel that airway disease had a substantial impact on the quality of life of their children. This is surprising as published studies report an equal prevalence of airway disease in both MPS I and II. A retrospective study of seventeen children with MPS I with sixteen children with MPS II in 2014 shows that although the overall prevalence of disease in both groups is similar, the severity of disease is
worse in MPS I with a higher susceptibility to OSA induced hypoxemia (Moreira, Kyosen et al. 2014). One could speculate that because the children with MPS II have a milder degree of OSA, its impact on their quality of life is minimal, overshadowed by other aspects of their disease. However, no prospective longitudinal studies exist to support this or show evolution of disease with age, severity or treatment for patients with MPS II.

In contrast, children with severe variant of the disease (both MPS I and II), airway obstruction had a substantial impact on the children’s and their parent’s quality of life. These children had life-limiting disease, with dependence on machines and oxygen to sustain them in their homes. Their parents reported feelings of helplessness and fear that their child would die at home or during their next general anaesthetic procedure, with reports of exhaustion from being awake at night caring for their child, and stress at being rushed into hospital regularly for worsening symptoms. They stated that it was also physically exhausting carrying the life saving equipment. The families were limited in their ability to take family vacations and also felt that travelling to centers with specialist anaesthetic support was expensive. The parents stated that the children themselves did not like the CPAP, as it was claustrophobic.

The parents of children with both attenuated and severe MPS I reported that the obstructive symptoms started as early as three-six months of age, prior to the diagnosis of MPS being established, earlier than the age of two widely reported in the literature (Papsin, Vellodi et al. 1998, Yeung, Cown}
et al. 2009). They felt frustrated that medical staff did not take their concerns seriously, owing to the fact that OSA is not usually prevalent in healthy children this young. This led to a delay in the diagnosis of their children. Recently published work, aiming to determine an algorithm to predict disease severity in new babies diagnosed with MPS I, shows similar results as ours. They report that children with more severe sub-types display obstructive symptoms within the first month of life, earlier than anticipated or previously reported (Kingma, Langereis et al. 2013).

Parents in our study report that children with MPS I-H, treated with HSCT, seem to have the most marked and sustained improvement in their airway symptoms, with many of them reporting resolution of symptoms after completion of the transplant, in contrast to those managed on ERT alone. These parents also report that those children diagnosed later than 5yrs of age (on ERT due to a delayed diagnosis), have minimal improvement in their symptoms, requiring a surgical intervention for their airway disease, in adolescence. A published multi-variant analysis looking at metabolic, therapeutic and patient correlates that modify long term clinical outcomes in sleep related breathing disorders in MPS I found that although the overall incidence of OSA is similar in both transplant and non-transplant groups, the transplant group had significant improvement in the severity of their OSA after treatment (ODI4% of 9.5/hour to 4.1/hour), with lower rates of progression over three years, 24% compared with 73% seen in children treated with ERT alone. They also found that delayed treatment had a direct correlation with the need for a surgical intervention and that this risk was
also increased in those managed with ERT alone (Pal, Langereis et al. 2015). Interesting recent work looking at levels of sleep apnoea in transplant patients confirms that after the transplant children have sustained improvement in their airway disease until they reach adolescence, when this starts to change, with progressive increase in AHI with age over ten years. They discuss the option of supplementing the HSCT with Enzyme therapy in children, as they get older (Moreau, Brassier et al. 2015). Analysed data from the families interviewed by us shows that early transplants have the potential to improve quality of life in comparison with those transplanted later or managed on ERT alone. Newborn screening for MPS would facilitate this.

The parents of those with milder variants of attenuated MPS IH found that their children’s airway disease responded well to ERT and that the symptoms had not reoccurred with advancing age.

Communication was a major source of concern for the parents of children with attn. MPS II. The parents felt that this inability to effectively communicate with family, friends, peers and teachers, had a large impact on their child’s quality of life. The parents of younger children felt that it prevented integration of their child with other children, was responsible for feelings of frustration and subsequent behaviour problems and precluded achievement of their full academic potential. Parents of older children felt that the ability to communicate effectively would allow their children to obtain employment and financial independence, maintain relationships with
friends and colleagues and prevent social isolation. The parents attributed these difficulties in communication to their child’s deafness, delayed acquisition of speech and language and underlying cognitive disease. This is consistent with the findings of an important paper looking at the functional impact of all aspects of attenuated MPS II, which found that hearing produced the most severe disutility (Raluy-Callado, Chen et al. 2013). The hearing loss does not progress or improve with ERT, supporting our findings that parental concerns with language and communication persist as the child got older (Parini, Rigoldi et al. 2015).

The parents of children with MPS I did not share these communication concerns. This is surprising as up to seventy percent of children with attenuated MPS I and fifty percent of children with MPS I-H may suffer with mild-moderate hearing loss (mean air conduction threshold on PTA of 33.9dB, mean bone conduction threshold 12.8db and mean air-bone gap of 21.1dB) (Lin, Shih et al. 2014), which stabilizes, but does not improve, post-transplant (Aldenhoven, Wynn et al. 2015, Shapiro, Nestrasil et al. 2015).

The parents of children with attenuated MPS II felt that their child’s underlying (non-progressive) neurocognitive disease also played a receptive role in language development and had a negative impact on the overall ability to communicate. In contrast, children with MPS I-H have a normal IQ, which stabilises post-transplant. Negative predictors of cognitive function in MPS I-H appear to be older age at transplant, IQ before
transplant and disease phenotype (Aldenhoven, Wynn et al. 2015). One must be cautious though as some emerging evidence shows that after the age of ten, post-transplant MPS I-H may begin to drop their IQ (Shapiro, Nestrasil et al. 2015). If degree of IQ and hearing loss are linked, owing perhaps to central deposits of GAG’s in the brain, will we begin to see an emergence in the future of SNHL in young adults with MPS IH, requiring auditory rehabilitation and support.

In this study, parents felt that the third contributing factor to poor communication was speech and language delay. Parents of children with MPS II reported that early childhood deafness had an impact on the acquisition of language, causing delayed expressive language and lack of speech clarity. Despite management with ventilation tubes and/or hearing aids, the children continued to struggle with phonetics, word blending and distinguishing similar sounding words. These are consistent with the findings of a mixed methods research study, which shows that the severity of speech delay in MPS II corresponds to both IQ and hearing loss, with severe neurocognitive disease displaying more severe speech delay. The same study also shows that mild-moderate speech delay in those with mild neurocognitive disease responds well to hearing aids and ventilation tubes (mean hearing threshold 45dB) whereas the more severe disease (65dB) does not (Cho, Kim et al. 2008).

Parents in my study felt that this inability to hear, coupled with difficulty in effective communication resulted in frustration and behaviour problems. I
could find no comparable published data examining the impact of hearing loss on the development of children with MPS. The developmental impact of hearing loss in otherwise healthy children has been extensively researched. A child’s inability to hear during the early language acquisition years may result in poor long-term language skills with effects on reading skills and educational achievements (Phelps and Branyan 1990, Van Eldik 1994, Davis and Hind 1999). Also, in comparison with normal hearing peers these children have increased levels of mental health and behaviour issues and difficulties with social interactions. These problems seem to have a linear relationship to the severity of their hearing loss (Wake, Hughes et al. 2004). This supports the parental reports in this study of behaviour problems in children with hearing loss and MPS, once again highlighting the importance of early, appropriate management of the hearing loss.

The parents had very positive views about their children using sign language and adjunctive hearing aids to support their social interactions.

Musculoskeletal disease had an enormous functional impact on the children I interviewed. Parents felt that despite ERT, children had a significant burden of disease, which continued to progress with age, in comparison with those treated with HSCT. Published works, using functional and general QOL measures, have shown that the physical disease burden can inhibit the children’s ability to perform daily activities, with high levels of pain and discomfort, comparable to those seen in juvenile arthritis. It also
shows that using a wheelchair has a significant negative impact on HRQOL (Raluy-Callado, Chen et al. 2013, Hendriksz, Lavery et al. 2014). My data shows that it interferes with the child’s ability to fit in with their peers, secondary to an altered physical appearance, the need for adjuncts such as wheelchairs and exclusion from group activities such as team sports or shopping trips. The physical disability is also responsible for feelings of inadequacy, loss of self-confidence, anger and depression. Along with this worry about physical appearance and fitting in, the children worried about dying in hospital and never seeing there loved ones again. Karutsobu et al, using functional independence measurement tools, that young adults with attenuated MPS II have increased anxiety about their physical disability, carry guilt about the impact of disease on their parents, worry about their physical appearance, have concerns about making friends and also their future employability (kuratsubo, Suzuki et al. 2009). Lawes, using open interviews, described concerns about identity, social interaction and future expectations in young adults with MPS I (Lawes 2007). From my work, we now better understand the functional and emotional consequence of musculoskeletal disease on children with MPS, providing a unique insight obtained from parents and the children themselves.

Parents worry about their child’s future independence, both financial and physical. They would like them to be physically independent and achieve meaningful employment. However they also express in the interviews that their children’s substantial physical, and in some children cognitive disability, would preclude this, despite adequate educational achievement.
With advances in medical treatment, these children are successfully living into their late twenties. Data by Pentek et al, looking at the economic impact of MPS in Europe, shows that out of a cohort of forty-six adult patients with MPS, across nine western European countries, only twenty-percent were employed, with the remainder on disability allowance. Using the EQ-5D utility score, they also showed that these children have poor general health status. Over thirty percent of their adult patients could not walk or perform self-care activities, suffered moderate levels of pain and anxiety and depression and required assistance from a carer (Pentek, Gulacsi et al. 2016). Kuratsubo’s team who showed that children with attenuated MPS II have marked physical and psychological disability, precluding successful employment (kuratsubo, Suzuki et al. 2009). Our work highlights the parental desire for an independent future for their children despite the marked burden of disease. The future multidisciplinary management of these children must improve the support available to these families and children in order to facilitate this.

Analysis of the demographics data collected during this study, showed that caring for a child with MPS has an impact on parental employment for seven out of every ten parents, with a resultant loss in overall family income. This is similar to findings of other studies looking at the financial impact on parents caring for children with neurodegenerative life-limiting illness, although it is the first to explore it in MPS (Davies 1996, Steele and Davies 2016). One of the reasons for this may be the time required to provide care for a child with complex needs, as seen by the results of a
paper published this year shows that parents of children with MPS spend about fifty-one hours a week caring for their child (Pentek, Gulacsi et al. 2016). Other reasons may be physical and emotional exhaustion, as reported by our group of parents. Health care professionals must be aware of the huge emotional, physical and financial burden that parents of a child with MPS may have to endure and systems must be put in place to provide increased support in the form of respite and external care.

In MPS II the issues important to parents of children of different ages varied. When the children were under the age of three, hearing loss was the predominant worry. As the children reached primary school age (5-6yrs), the main concern was delayed acquisition of language. Towards the end of primary school (10-11yrs) the focus had shifted towards the child’s mental capacity and their mild developmental delay. The parents of adolescents (11-16) were focused on preventing social isolation in their child and assisting them in achieving life skills that would promote independent living in the future. Despite the marked physical disease endured by these children it is the learning and communication difficulties that have the greatest impact on their quality of life. For parents it was important that their child achieve social acceptance and integration with their peers, i.e. ‘fitting in’. The parents of younger children wanted to celebrate the similarities their child had with others. They sent them to ‘mainstream schools’, which was possible with teaching assistant support, and wanted them to explore activities normal for their peer group. Young children appeared to have little insight into their difference to other children,
although they became increasingly aware of this by the end of primary school (which is for children aged 5-10 years). However, with increasing awareness of their child’s cognitive disease, in part due to the more apparent learning gap between their children and unaffected peers, this expectation of fitting in changed. The parents of older children (11yrs onwards) wanted their children to be in ‘specialist schools’ (which cater for children with special educational and physical needs) rather than ‘mainstream secondary schools’ (ages 11-18years) so they could make friends with children with similar problems, such as deafness or mild learning difficulties. The parental focus shifted from academic achievement to acquisition of life skills such as budgeting, allowing their children to achieve independence as young adults. Teenagers were worried about hospitalization, treatment and even death. Autism, a feature of MPS II disease in some children, was associated with poorer outcomes, with these children requiring additional support.

**Strengths and limitations**

Through this work, I have presented detailed information about the aspects of illness that inhibit children from achieving their full potential and the negative impact of this on parental emotional well-being. The data not only highlights the functional impact, as previously described by others (Kunin-Batson, Erickson et al. 2012, Needham, Packman et al. 2013, Needham, Packman et al. 2014), but also shows the marked emotional and social burden of disease. This work has highlighted previously unknown problems, such as the impact of hearing on behavior in this sub-group of
patients. It is also the first to show that in contrast to published quantitative work, not all recognized aspects of illness have an impact on QOL. An example of this is the low priority parents of patients with attenuated MPS II give to their breathing problems, despite the published literature showing an equal prevalence of OSA in MPS I and II. The themes to emerge from this data, in conjunction with a list of quality of life issues obtained through systematic review of published data and interviews with healthcare providers, could form the attributes of a new disease specific questionnaire, measuring HRQOL in children with MPS, with a focus on their head and neck disease burden. Performing the initial stages of questionnaire development with formal qualitative rigour, as demonstrated here, through detailed evaluation of disease specific problems, provides a foundation for identifying the domains to be included in a quality of life measure. It also means that further construct validity is more straightforward (Fayers and Machin 2007).

When designing the study, we considered interviewing patients in their natural environment, allowing the added advantage of witnessing the challenges that they face on a daily basis, corroborating the narrative obtained through the interview process (Epistemology) (Creswell 2007). However, this would not have been feasible within the time constraints or financial resources of this study. It would also have limited the number of patients available for inclusion, as these are individuals from different parts of the United Kingdom/world rather than a group of individuals who all live in the same geographical location. Hence, the study was performed at the
metabolic and genetics unit at the Royal Manchester Children’s hospital, which is one of a handful of national units for the treatment of metabolic storage disorders and provides access to a larger number of patients than would otherwise not be possible.

As MPS is a rare orphan disease, patient recruitment into the study was limited, despite the study being performed at a national center. We managed to recruit all of the children registered at the unit with attenuated MPS II (n=6) and one out of five registered with the severe disease. Access to children with severe disease was difficult as most of them were too unwell to participate in an interview during the study period. Also, despite these small numbers, we were still able to generate meaningful rich data and achieve saturation. In contrast, the MPS I group, although larger in number (n=11), reflected a smaller proportion of the overall cohort available for interview. This may explain why, despite the emergence of many important themes, we could not develop an overarching category to tie in all of the sub-categories and achieve saturation of the data. Future work could overcome this by a longer period of patient recruitment, which was not possible within the time constraints of this research degree. But one must remember that the aim of this exploratory work was to generate important themes for inclusion in a quality of life questionnaire, and for that purpose it has been a success.

When designing the study, I was advised to include sub-groups I, II and VI as they have overlapping head and neck problems. I was advised to pool the
interviews and analyse them as one. However, when performing and
analysing the interviews, it soon became apparent that each sub-group had
varying quality of life concerns and that they should be considered
independently to each other. We then had to recruit larger patient numbers
than that originally anticipated. Hence, the MPS VI sub-group were
excluded from this study and my limited research time was spent improving
saturation for the MPS I and II cohorts. The study exploring HRQoL in
families with MPS VI is currently on going, independently to this MPhil
project.

Much of the data generated was obtained from parental views voiced during
the family interviews, otherwise known as parent-proxy reports. Published
works show that parents underreport the impact of disease on their child’s
quality of life, in comparison to children themselves, primarily with
reference to emotional and social well being (Eiser and Morse 2001).
Further works could be done to facilitate further participation from young or
less cognitively abled children by incorporating a card sort technique in the
interviews (Malcolm, Gibson et al. 2014).

My interview topic guide was broad, open ended and reflexive, allowing
parents to talk about issues important to them. Many of the parents knew
that I was an ENT surgeon and hence it is theoretically possible that they
were more willing to share their child’s ENT problems with me. I hope that
by encouraging them to discuss issues other than their head and neck
disease, ranked as important by them, would have overcome this potential bias.

6.0 Conclusion

Children with MPS grow older carrying a substantial burden of disease, with a consequent impact on their quality of life. This is the first work to explore, in-depth, the perceptions that parents and children have of their quality of life. Important themes to emerge from our grounded theory analysis, reflective of parental concerns are, breathing difficulties secondary to obstructive sleep apnoea, communication difficulties secondary to hearing loss and cognitive impairment and physical disability secondary to musculoskeletal disease burden. These problems and consequent concerns persist despite ERT and HSCT. The study also highlights the emotional and physical burden on parents of caring for a child with MPS and is the first to discuss the socioeconomic burden of disease for the family and state.

Themes to emerge from this qualitative exploratory work will form the basis of a disease specific quality of life measure, the development of which will mark the next phase of this project. A disease specific QOL measure will allow clinicians to monitor treatment, ensuring that it is tailored to the specific needs of the child, producing overall improvements in their health related quality of life.
This work also highlights the importance of early and aggressive hearing and language rehabilitation in children with MPS, optimising their communication skills and ability to achieve social integration, an education and develop independence as an adult through sustainable employment.
7.0 Bibliography


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Appendix

Appendix 1; National Research and Ethical Approval from the NRES committee West Midlands Edgbaston

23 September 2013

Mr Iain Bruce
Consultant in paediatric otolaryngology
Central Manchester and Manchester Children’s University Hospital’s Trust
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL

Dear Mr Bruce

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The Proportionate Review Sub-committee of the NRES Committee West Midlands - Edgbaston reviewed the above application on 18 September 2013.

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 Co-ordinator Miss Andrea Graham, nrescommittee.westmidlands-edgbaston@nhs.net.

Ethical opinion

- The Committee agreed the Study is suitable for Proportionate Review and falls within category 5 of the NMEIT criteria
- This is a rare condition which can alter the appearance of the face.
- The Committee agreed there would not be too much inconvenience for parents
- The Committee noted some Participants will have travelled a long way and involvement in the study could delay their journey home by up to one hour forty five minutes

Re-issue Favourable Opinion with Conditions, 3rd October 2013
Re-issue Favourable Opinion with Conditions, 3rd October 2013

- The Chief Investigator should have ticked the NHS indemnity box at A76 (3) but as the study is not interventional the Committee have no concerns.
- The Committee agreed the sentence “It is nothing to be scared of” should be removed from the Participant Information Sheets for young children.
- Participants over the age of 16 will be able to Consent for themselves, but they are not provided with a separate Information Sheet or Consent Form. However the Adult Information Sheet has been adapted to state Parents/16+
- The Correct Ethics Committee name should be inserted into the “who has reviewed this Study” section of the Information Sheets.

On behalf of the Committee, the sub-committee 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.

Ethical review of research 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).

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.rdsforum.nhs.uk](http://www.rdsforum.nhs.uk).

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.

- You should remove the sentence “there is nothing to be scared of” from the Information Sheet for young children.
- The Correct Ethics Committee name should be inserted into the “who has reviewed this study” section of the Information Sheets.

It is the 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).
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.

Approved documents

The documents reviewed and approved were:

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Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review 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
Re-issue Favourable Opinion with Conditions, 3rd October 2013

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.

Feedback information is available at National Research Ethics Service website > After Review

13/WM/0591 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/hraretraining/

With the Committee’s best wishes for the success of this project.

Yours sincerely

[Signature]

Mr Paul Hamilton
Chair

Email: nrescommittee.westmidlands-edgbaston@nhs.net

Enclosures:

List of names and professions of members who took part in the review

"After ethical review – guidance for researchers"

Copy to: Mrs Lynne Morsa
Dr Lynne Webster, Central Manchester University Hospitals NHS Foundation Trust
Appendix 2; Sponsorship letters

2a; University of Manchester

Thursday, 25 July 2013

To whom it may concern

Sponsor Reference:

Role of the Research Sponsor under the Research Governance Framework for Health & Social Care and the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031)

I hereby confirm that the University of Manchester would be prepared to accept the role of research sponsor as currently defined in the Research Governance Framework for Health & Social Care Version 2 (DoH 2005) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), in relation to the study:

Parent reported outcomes for Ear, Nose and Throat disease in Mucopolysaccharidosis

I have been informed that this study will be led by Mr Iain Bruce of The University of Manchester.

Sponsorship is subject to the following conditions:

1) The lead investigator for the study must be an employee of the University of Manchester. For student research the academic supervisor is considered to be the lead investigator.
2) An appropriate contract must be agreed between the University and the funding body.
3) The research must be reviewed and approved by appropriate ethics, NHS and regulatory bodies and registered in accordance with University insurance requirements.

To enable the sponsor to meet their responsibilities as listed in section 3.8 of the Research Governance Framework, Chief Investigators are asked to adhere to the responsibilities as outlined in section 3.6 of the Framework (available at: https://www.gov.uk/government/publications). In line with this requirement Mr Iain Bruce must ensure that all involved in the research project understand and discharge their responsibilities in accordance with the agreed protocol and any relevant management, ethical and regulatory approvals.

Chief Investigators are also reminded that they must register NHS REC approval with The University of Manchester Research Ethics Office.

If you have any queries about sponsorship of this project then please address them to Professor Nalin Thakker, Associate Vice President for Research Integrity, The University of Manchester, Christie Building, Oxford Road, Manchester M13 9PL, or email research-governance@manchester.ac.uk

Yours Faithfully,

Lynne MacRae

Research Practice Coordinator
Faculty of Medical & Human Sciences

Dated: 25.07.2013
Dr Archana Soni-Jaiswal  
ENT Department  
Central Manchester Foundation NHS Trust  
Oxford Road  
Manchester  
M13 9WL  

Dear Dr Soni-Jaiswal  

PIN: R03412 (Please quote this number in all future correspondence)  
REC Reference: 13WM/0391  
Research Study: Parent and clinician reported outcomes for Ear, Nose and Throat disease in Mucopolysaccharidosis  

Thank you for submitting the above study for NHS R&D permission. University of Manchester is the Sponsor for this study which is not 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:  

• CMFT 70 Day from Valid Submission to 1st Patient Recruited: 02 December 2013  

Further information regarding the NIHR target can be found on the intranet.  

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: 2.2.10  
cc. Alison Robinson Divisional Research Manager  
Mr Iain Bruce – Chief Investigator
Appendix 3

Appendix 3a; Interview Topic Guide

Description of a typical day in the family’s life

What is the child’s daily/weekly routine?

How severe is the child’s MPS

Explore the impact of disease on their daily/weekly routine?

Explore which aspects of the illness interfere with daily functioning and why?

Which aspects of the illness do parents and children feel have the biggest impact on their lives and why?

Discuss and explore the main challenges that they face?

Understand their experience of ERT and HSCT

Identify the impact it (ERT/HSCT) may have had on the disease or on their lives?

Explore their experience of hospital visits, tests, hospital stays and operations?

Is education important?

What are their expectations of the future? What is the parental expectation?

Discuss concerns that they may have with breathing and how this has an impact on their daily lives?

Do recurrent colds/runny nose have a functional or social impact on them

What is the parental experience with language development and hearing in their child and does this have an impact on their daily lives? What do the children think?

Aspects of being the child’s parent that is most rewarding and aspects that are most challenging
Appendix 3b: Topics added on evolution of the topic guide

How was the MPS first diagnosed and how did the parents feel about this

How do they feel about ERT and HSCT?

What do they worry about or find most challenging

How has their child’s disease evolved with age and treatment?

Explore the impact of the illness on the child’s siblings?

Explore if the disease has had an impact on the parents jobs and relationships

Explore how the parents are coping and what support mechanisms families adopt
Appendix 4; Patient demographics questionnaire

Demographics questionnaire

*(For completion by Archana at the end of the semi-structured interview, asking the parents direct questions listed below with their consent)*

<table>
<thead>
<tr>
<th>Name of Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOB</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>MPS Sub-type</td>
</tr>
<tr>
<td>Severity</td>
</tr>
<tr>
<td>ERT/BMT and age it was given</td>
</tr>
<tr>
<td>Known ENT problems from the medical notes</td>
</tr>
</tbody>
</table>

### Parental Education

<table>
<thead>
<tr>
<th>Post-code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment</td>
</tr>
</tbody>
</table>

Was it different before child ‘X’ was born?

Do they think it would have taken a different route if you were not a caregiver for your child?

How much of your time is dedicated to looking after your child?

Do you equate this to a full/part-time job?
Appendix 5: Consent form

Parent/Patient 16+ Consent Form

Title of project: Parent and clinician reported outcomes for Ear Nose and Throat disease in children with Mucopolysaccharidosis

Name of researchers: Archana Soni-Jaiswal, Jane Roberts, Jean Mercer, Simon Jones, Iain Bruce
Institute: Royal Manchester Children’s Hospital, CMFT, Oxford Road, and Manchester
Participant study number:

Patient Statement:

1. I understand that my/my child’s (please delete as appropriate) participation is voluntary and that I am/my child is free to withdraw at any time. This will not affect my/my child’s future medical care or legal rights.

2. I confirm that I have/my child has had the study explained to me in detail and I have/my child has read and understood the provided patient/parent information sheets dated 8th August 2013, version number 1.0, for the above study. I have/my child has had the opportunity to think our decision through and ask relevant questions.

3. I understand that (my child’s medical notes and) relevant sections of data collected during the study may be looked at by responsible individuals from the University of Manchester, from regulatory authorities or from the Central Manchester and Manchester Children’s hospital NHS Trust, where it is relevant to my taking part in the research. I/my child give permission for these individuals to have access to this data.

4. I consent to my/my child’s interviews being recorded and transcribed. I also give permission for anonymised direct quotes from the interviews being published.

5. I give permission for my child’s GP to be informed about my/my child’s participation in this study.

6. I understand that I/my child will not receive any financial payment for participation in this study. I understand that I/we will not be routinely informed of the results of this study.

Name of Patient: ____________________________________________________________

Signature of Patient / Guardian: ____________________________________________Date: _____/_____/___
Relationship to child: __________________________________________

Name of Researcher: __________________________________________

Signature: __________________________ Date: ___ / ___ / ___
Appendix 6; Assent Form

Assent form for children/young person aged 5-15 years (to be completed by child or parent/guardian)

Title of project: Parent and clinician reported outcomes for Ear Nose and Throat disease in children with Mucopolysaccharidosis

Name of researchers: Archana Soni-Jaiswal, Jane Roberts, Jean Mercer, Simon Jones, Iain Bruce

Institute: Willink Unit, Royal Manchester Children's Hospital, CMFT, Oxford Road, Manchester.

Participant study number:

Patient Statement:

Child (or if unable, parent/guardian on their behalf)/young person to circle all they agree with;

Have you read (or had read to you) about this project? Yes/No

Has somebody else explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked all the questions you want? Yes/No

Have you had your questions answered in a way you understand? Yes/No

Are you happy to take part? Yes/No

If any answers are ‘no’ or you do not want to take part, don’t sign your name!

If you want to take part, please write your name and today’s date

Your name ___________________________

Date ___________________________

The doctor/nurse who explained this project to you needs to sign too:

Print Name ___________________________

Sign ___________________________ Date ___________________________
Appendix 7; Patient Information Leaflets

7a; PIF young adults aged 16-18 years and parents

Patient Information Sheet for young adults age 16-18 and parents/carers

Title of project: Parent and Clinician reported outcomes for Ear, Nose and Throat disease in Mucopolysaccharidosis

Name of researchers: Archana Soni-Jaiswal, Jean Mercer, Jane Roberts, Simon Jones, Iain Bruce

Introduction

Children with MPS frequently suffer with Ear Nose and Throat (ENT) problems, which include recurrent colds, breathing difficulties and hearing problems. We do not know if Enzyme replacement therapy and bone marrow replacement improve them or stop them progressing. Also, we do not know how these ENT problems affect the quality of life of children with MPS. There are no specific tools available to the doctors and nurses to directly assess this.

This study aims to answer the above questions. We are looking at children with MPS type 1, II and VI.

We would like to invite you to participate in this study. During the course of the study, your child will not have any extra treatments, procedures, tests or hospital visits. Please read the following information leaflet carefully and discuss it with one of us if you have any concerns or questions. Please take your time deciding if you/your child would like to take part in our study.

Do I have to take part in this study?
Taking part in this study is purely voluntary. If you/your child decide not to participate, it will not affect the current or future care of your child in any way. If you do decide to participate, you/your child may freely withdraw from the study at any point.

What is the purpose of this study?

This study will allow us to determine the effect that ENT disease has on the quality of life of children with MPS. It will also allow us to obtain your views on existing ENT questionnaires and what elements of them you feel are relevant to children with MPS. Parental views on the severity and relative importance of ENT disease in children with MPS will also be sought.

What are the possible benefits of this study?

The study will allow us to better understand ENT disease in children with MPS, increasing awareness amongst clinicians and improving the quality of the care we provide these children. It may also allow us to monitor the effects of enzyme replacement therapy/bone marrow transplant.

What will happen if we decide to participate in this study?

At your next routine outpatient’s appointment, you will be asked to complete three short ENT questionnaires. You may then meet with a member of the research team for half an hour and take part in a structured interview where the interviewer will ask your thoughts about the questionnaires you have just completed and also your views on the ENT symptoms that affect your child’s quality of life. This interview will be recorded and coded. Direct quotes may be anonymously published in the future.

What are the possible risks to my child?

Participating in this study will not add any extra risk to you/your child. There will be no extra hospital visits as a result of participating in this study. However, partaking in the study will incur longer outpatient appointments (approximately one hour) and completing additional paperwork in the form of questionnaires.

Will my details remain confidential?
All information collected during this study will be stored and used with the strictest confidence. The completed forms and consent forms will be stored in a confidential folder in the Willink unit at the Royal Manchester Children’s hospital. Only members of the research team will have access to this data.

All patients are given a unique study ID and all information generated from the study will be stored under this ID. Any information leaving the hospital will have this unique ID and not your identification details. You will not be recognised from this number by people other than the research team.

The recorded interview will be sent out to a coder but will not have your name or personal details on it. The coder will then send the file back to us for further analysis. The researchers and the statisticians at the University of Manchester will process further data generated. Once again we will use your unique ID and not your personal details.

**What will happen to the results of this study?**

The results of the study will be published in the medical literature, perhaps used in further research and presented at medical conferences. This study forms part of a student project, registered with the University of Manchester, and the results will be published as a thesis.

**Who is funding this study?**

This study has not received any extra external funding. The doctors and patients partaking in this study will do so voluntarily. They will not receive any payment.

**Who has reviewed this study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the Edgbaston NRES committee West Midlands.

**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. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University research practice and governance co-ordinator on 01612757583
or 01612758093 or by email to Research-complaints@manchester.ac.uk. Alternately you may go through the NHS complaints procedure. The hospitals ‘Patient and liaison service’ should be able to help you with this on 01612768686 or on email pals@cmft.nhs.uk.

Contact for further information

If you require any further information please speak to one of the researchers who will do their best to answer your questions.

Thank you for reading this information sheet

Best regards,

Dr A Soni-Jaiswal (archana.soni-jaiswal@cmft.nhs.uk)
Patient Information Sheet for children aged 12-16 years

Title of project: Parent and Clinician reported outcomes for Ear, Nose and Throat disease in Mucopolysaccharidosis

Name of researchers: Archana Soni-Jaiswal, Jean Mercer, Jane Roberts, Simon Jones, Iain Bruce

Introduction

Children with MPS frequently suffer with Ear Nose and Throat (ENT) problems, which include recurrent colds, breathing difficulties and hearing problems. We do not know how or if these problems interfere with things like playing sports, concentrating at school, sleeping. Does having these ENT problems generally make it harder to cope on a daily basis or interfere with normal activities?

Some of you may be on enzyme replacement therapy or have had a bone marrow transplant. Have your ENT problems got better since you started these treatments?

We are doing a small research project, in an attempt to answer these unknown questions.

We would like to invite you and your parents/guardians to participate in this study.

What will happen if we decide to participate in this study?

At your next routine hospital visit, your parents/guardians will be asked to complete three short forms. You may help with this if you wish. Your parents/guardians may then be invited to meet with one of us for between half an hour to an hour. We will ask them, and you, what you thought of the questionnaires (forms) and if you felt the content of them were relevant to your disease. We will also ask them how problems like snoring and difficulties in hearing affect you on a daily basis and compare with your other problems.
This meeting will be recorded and the results later coded. Direct quotes may be anonymously published in the future.

**Do I have to take part in this study?**

It is not compulsory for you or your parents/guardians to take part in this study and participation is purely voluntary. If you do take part, you will not have any extra treatments or painful tests. If you do take part and later change your mind, it is ok to tell your doctors/nurses that you no longer wish to be part of the study. This will not affect the care you or your parents/guardians receive.

**What are the possible benefits of this study?**

If we understand a disease better, we can improve the care and treatment we provide to you and other children with similar problems to yours. We can also educate other doctors and nurses.

The results may also us to develop a questionnaire that allows us to see how well you are responding to new treatments (such as enzyme replacement therapy).

**What are the possible risks if I take part?**

If you take part, your parents/guardians may have a longer stay in hospital on the day of your doctor’s appointment. They may have extra forms to fill on that day.

**What will happen to my personal information?**

All information collected during this study will be stored and used with the strictest confidence. Only members of the research team will have access to them.

**What will happen to the results of this study?**

The results of the study will be shared in the medical literature, perhaps used in further research and presented at medical meetings. This study forms part of a student project, registered with the University of Manchester.

**Who is funding this study?**

This study has not received any extra external funding. The doctors and patients partaking in this study will do so voluntarily. They will not receive any payment.
**Who has reviewed this study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the Edgbaston NRES Committee West Midlands.

**Contact for further information**

If you require any further information please speak to one of the researchers who will do their best to answer your questions.

Thank you for reading this information sheet

Best regards,

**Dr A Soni-Jaiswal** (archana.soni-jaiswal@cmft.nhs.uk)
Patient Information Sheet for children aged 6-11 years

Title of project: Parent and Clinician reported outcomes for Ear, Nose and Throat disease in Mucopolysaccharidosis

Dear

We are writing this letter to invite you to help us with a research study.

What is a research study?
Research is a way in which we try to find out the answers to questions. This helps us to understand certain problems better and improve the way we treat them.

What are you trying to find out?
Children with MPS can sometimes find it difficult to hear or breathe at night. They may also suffer with leaky ears or a constantly runny nose. We are trying to find out how much these problems interfere with things such as playing, sleeping and going to school.

Why me?
We are looking at children with MPS types I, II and VI to see how the above problems affect you on a daily basis.

What will happen if I agree to take part?
If you are happy to take part, we will invite your parents/guardians to complete some forms for us, the next time you are visiting your normal doctor at the children’s hospital. We may also sit with them for a while, perhaps half an hour to an hour, and ask them different questions about your hearing or snoring. You are welcome to join in with the discussion or contribute your feelings and ideas.

Are there any risks?
As we don’t have to do any extra tests there are no extra risks.

Do I have to take part?
No. It is up to you and your parents or guardian. If at any time you don’t want to do the research anymore, just tell your parents, doctor or nurse. They will not be cross with you.

Did anyone else check the research is OK?
Before any research is allowed to happen, it has to be checked by a group of people called a Research Ethics Committee. They make sure that the research is fair.

What will I gain?
There will be no benefit to you or your family. However, the information we get from this research may help other children who are sick. We will be very grateful for your help.
What will be done with information you give us?
We will listen to the recording of you and your parents/guardians talking to us and also re-read the forms you fill. Other people who work at the University of Manchester may also look them at. The results will be published in special magazines called scientific journals.

What about my personal information?
We will do our very best to keep your personal information secret.

What happens next?
If you agree to take part in the study, one of the research team will meet you and your parent or guardian when you come to hospital. You can then ask any further questions.

Thank you so much for your time and consideration.

Yours faithfully

Dr A Soni-Jaiswal (archana.soni-jaiswal@cmft.nhs.uk)
Patient Information Sheet for children under and including 5 years

Title of project: Parent and Clinician reported outcomes for Ear, Nose and Throat disease in Mucopolysaccharidosis

Name of researchers: Archana Soni-Jaiswal, Jean Mercer, Jane Roberts, Simon Jones, Iain Bruce

Dear Parent/guardian,

This information sheet is designed for very young children. Please would you take the time to read & explain the content to them?

Children with MPS sometimes cannot hear as well as other children or may have breathing problems or a runny nose. We have asked your mummy and daddy/guardian to meet with us. We would like to talk to them about any problems that you may have with your hearing or breathing. We would also like to ask them if these problems interfere with things like playing, sleeping or concentrating at school.

When you are next in hospital to see your doctor, we will arrange to meet both you and your mummy and daddy/guardian for a short while. You will not have any tests. If you have any questions please don’t hesitate to ask us when we meet you.

We look forward to meeting you soon.

With Best regards,

Dr. A Soni-Jaiswal

(Archana.soni-jaiswal@cmft.nhs.uk)
Appendix 8; Mucopolysaccharidosis 1: Parental beliefs about the impact of disease on the quality of life of their children

A Soni-Jaiswal, J Mercer, SA Jones, IA Bruce, P Callery

Orphanet Journal of Rare Diseases (2016) 11:96

RESEARCH

Mucopolysaccharidosis I; Parental beliefs about the impact of disease on the quality of life of their children

A. Soni-Jaiswal1*, J. Mercer2, S. A. Jones2, I. A. Bruce1,3 and P. Callery4

Abstract

Background: Hematopoietic stem cell transplants, alongside enzyme replacement therapy and good multi-disciplinary care, have dramatically improved the life expectancy in children with Mucopolysaccharidosis (MPS) I, with better objective and functional outcomes. Despite these improvements, children with both the attenuated (non-Hurler) and severe (Hurler) variants of the disease have marked residual morbidity. Children with MPS I suffer with head and neck disease including obstructive sleep apnoea and hearing loss. The impact of these on quality of life has been poorly researched and no previous work has been published looking at patients’ perception of their own health, an important domain when considering the impact of treatment.

Methods: This exploratory qualitative study aimed to discover the effect of head and neck disease, alongside that of MPS I as a whole, on the quality of life of affected children. A grounded theory approach was used to conduct this study. Children and their parents were invited to participate in semi-structured interviews. The transcribed interviews were coded and emergent themes explored until saturation occurred.

Results: The families of eleven children with MPS I were interviewed, five with Hurler’s and six with the attenuated non-Hurler’s. Important themes to emerge were the fear of dying associated with obstructive sleep apnoea, difficulties communicating at school due to the delayed acquisition of language, chronic pain and restricted mobility, physical differences and restricted participation in social activities such as sports secondary to the musculoskeletal disease burden. The overall theme running through the analysis was the desire to fit in with ones peers.

Conclusion: Parents and children with MPS I worry about ‘fitting-in’ with broader society. The presence of airway disease has a profound impact on the emotional well being of parents whilst language delay and musculoskeletal disease have the biggest impact on the quality of life of the children themselves. It is important to understand the impact of MPS I on the quality of life of children and their families so that we may improve future treatment and management of this sub-group of children who have an increasing life span.

Keywords: Quality of life, Qualitative research, Mucopolysaccharidosis I, Otolaryngology, Obstructive sleep apnoea, Musculoskeletal disease

* Correspondence: archanasj@gmail.com

1 Respiratory and Allergy Centre, Institute of Inflammation and Repair, Faculty of Medical and Human Sciences, University of Manchester, Manchester M13 9PL, UK

Full list of author information is available at the end of the article

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BioMed Central
Appendix 9; Attenuated Mucopolysaccharidosis II; Parental beliefs about the impact of disease on the quality of life of their children

Submitted to the Orphanet Journal of Rare Diseases; currently awaiting an opinion.

Attenuated Mucopolysaccharidosis II; Parental beliefs about the impact of disease on the quality of life of their children

A Soni-Jaiswal1, J Roberts2, SA Jones1, IA Bruce3,1, P Callery4

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3Paediatric ENT Department, Royal Manchester Children’s Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester M13 9WL, U.K
4School of Nursing, Midwifery and Social work, University of Manchester, Manchester, M13 9PL, U.K

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Archana Soni-Jaiswal, Post-graduate research fellow, Respiratory and Allergy Centre, Institute of inflammation and repair, Faculty of Medical and Human Sciences, University of Manchester, Manchester, M13 9PL, U.K
Email: archanasj@gmail.com

Word Count: abstract – 244, introduction – 455, full article - 3873

Abstract

Introduction; The availability of enzyme replacement therapy, alongside improved multidisciplinary management, has transformed MPS II from a life limiting illness into a chronic illness with improved functional outcomes. Despite the improvements in life expectancy, children continue to carry a burden of disease, including head and neck disease, into adulthood.
This exploratory qualitative study explores the impact of this disease on the quality of life of the children with the attenuated variant of MPS II and their families.
Methods; A grounded theory approach was used to conduct this study. Children and their parents were invited to participate in semi-structured interviews about their experiences of living with MPSII. The transcribed interviews were coded and emergent themes explored until saturation occurred.

Results; Six families were interviewed. Interpretive analysis of their narratives revealed the parents’ rich desire for their child to ‘fit in’ with their peers and society at large. However, one of the main obstacles to this was hearing loss and delayed acquisition of language. Parents felt that despite their children marked physical disease burden, these had the greatest impact on quality of life.

Conclusion; There is an evolution with time in the issues important to parents and by proxy, their children, at the heart of which is the desire for their children to ‘fit-in’ and integrate with their peers. To achieve this, a high priority should be given to hearing and language soon after the diagnosis of MPS II is established, with intensive rehabilitation of these.

Key words; Quality of life, Qualitative research, Mucopolysaccharidosis II, Deafness, Otolaryngology

Synopsis; This is the first paper to explore the impact of attenuated MPS II on the quality of life of affected children, with themes emerging directly from patient interviews.

Competing interests
All authors declare no competing interests. No external or internal funding was received for this work. The authors confirm that sponsors have not influenced the content of this research.

Author declarations
ASJ designed, collected and analysed the data as part of an MPhil degree. She performed the literature search and wrote the paper. IAB and PC were her academic supervisors and were involved in the design and conception of the study. They also closely supervised and reflected on all stages of data collection and analysis. JR assisted in patient recruitment. SAJ reviewed and edited the paper. PC is final guarantor for the research study and this paper.

Ethical approval
National Research and Ethics Committee review obtained prior to commencement of the study. Informed consent, and assent for those under the age of sixteen, was obtained from all study participants, prior to their participation.
Mucopolysaccharidosis (MPS) II (G309900, http://www.ncbi.nlm.nih.gov) is a rare inherited metabolic storage disorder, caused by a deficiency in the activity of the enzyme Iduronte-2-sulfatase (EC 3.1.6.13, chem.qmul.ac.uk), leading to progressive cellular damage, organ failure and death (Neufield and Muenzer 2001). MPS II has an X-linked inheritance, occurring predominantly in male patients with a reported incidence in Europe of 1.3:100,000 (Muenzer J 2011). Disease severity and rate of progression lie on a continuous spectrum ranging from mild or attenuated disease with slow progress to severe disease that is rapidly progressive. Both attenuated and severe forms have significant disease morbidity associated with them (Clarke 2008).

Expert panel opinion is that all patients with MPS II experience progressive somatic involvement, whilst only those with the severe phenotype experience learning difficulties with neurodegeneration and severe cognitive impairment (Muenzer J 2011). However, in our experience, only a minority of children with the attenuated form has normal intelligence, with most of them suffering static, non-progressive, learning difficulties. We feel it is the progress of the cognitive disease and learning difficulties that differentiates the two forms.

Licensing of enzyme replacement therapy (ERT), alongside better multi-disciplinary management, has transformed attenuated MPS II into a ‘chronic disease’, with improved functional outcomes, although cure is still not possible. The ERT has no impact on neurocognitive disease progression (Muenzer J 2006, Muenzer, Guscavas-Calikoglu et al. 2007, Buesterien 2012). The impact of this chronic illness on the health related quality of life (HRQoL) of these children has been poorly researched. No exploratory work has been published which provides an understanding of the patients’ perception of their own health (Gill and Feinstein 1994). This is an important domain when considering quality of life and the impact of treatments, such as ERT.

Head and Neck disease is common in MPS II, characterized by airway obstruction (which may be multi-level and progressive), obstructive sleep apnoea, recurrent upper respiratory tract infections (URTIs) and hearing loss. Hearing loss is present in 84% of patients with MPS II, with 30% of patients suffering a severe-profound loss (>61dB pure tone average threshold) (Keilmann A 2012) (Napiontek U 2006). This hearing loss is progressive with a 1dB loss for each advancing year (Keilmann A 2012). The impact of deafness on the HRQoL in children with MPS II and the patient’s perception of their own health status have not previously been explored.
Aim; The aim of this qualitative study was to explore in-depth the concerns faced by parents of children with attenuated MPS II (defined as children with MPS II who may have learning difficulties but do not suffer progressive cognitive impairment and neurodegeneration). It also aimed to assess the impact of head and neck disease on health related quality of life (HRQoL) in this sub-group of children.

Materials and Methods

A grounded theory approach was used to obtain an in-depth understanding, of the impact of mucopolysaccharidosis II, with a specific focus on their head and neck disease burden, on the lives of affected children and their families.

We prospectively recruited 6 patients with MPS II from a large, internationally renowned, tertiary pediatric metabolic medicine and genetics unit, between December 2013 and November.

Children were sixteen years or under at the time of interview and of the male sex (MPS II is an X-linked disorder). Purposive sampling was used to recruit a group of children with the attenuated form of MPS II, with representation of variations in somatic involvement, age, ethnicity, socioeconomic background, family structure, education in mainstream and special needs schools. Ethical approval was obtained from the local research and ethics committee. Informed consent, and assent in the case of children under the age of sixteen, was obtained prior to participation in the study.

Data was generated using open, conversational style semi-structured interviews conducted when families attended planned appointments. Each interview lasted about an hour and was digitally audio-recorded.

A ‘topic guide’ was used to steer the interviews including: the daily routine of the child and their family, functional and social impact of hearing loss, language development, educational performance, sleep quality and rhinorrhea; the impact of hospital visits, medical and surgical treatments; future expectations and evolution of the disease. The interviewer asked broad open-ended questions, allowing the interviewees to talk about the topics of most importance to themselves, and probing questions were used to explore responses given by the interviewees and encourage elaboration. The topic guide was revised to include emerging themes and subjects that appeared to be important to the families. Topics like ‘Education’, ‘Language’ and ‘Social acceptance’ came to the forefront and the latter interviews conducted were used to test these emerging themes. The interviews were analysed using the principles of grounded theory, performing open line-by-line coding of the primary data. The emergent codes were grouped into early
conceptual categories and then grouped further into larger, over-arching categories or themes. Emergent themes guided subsequent interviews. Hence, the identification of categories was iterative, occurring over multiple, progressive cycles of interview-analysis-open coding and reflection. We checked for consistency across cases, searched for deviant cases and adapted the developing interpretation to account for variation.

From an early stage in the process, hearing loss, delayed acquisition of language and mild intellectual impairment or learning difficulties emerged as important influences on quality of life. A common theme of ‘fitting-in’ emerged across all of our categories, but held different meaning at different stages of children’s development. The parents of young children with attenuated MPS II held aspirations for their child’s social and academic achievements, with the belief that they could integrate or fit-into normal society. They felt that they could achieve this by improving their hearing and language. In older children, aspiration was replaced with acceptance of children’s learning difficulties, persistent hearing loss and language delay. Parents had reduced expectations. The parents of older children wanted their child to be happy and to fit-in with other children with similar physical, mental and educational needs to theirs.

Results

Over the eleven-month period, twelve children with attenuated MPS II were due to attend the unit for review or treatment and agreed to participate in the study. Six of them did not attend their designated appointment with the researcher and hence six patients were interviewed.

As expected, all children were male. The mean age was 12 years, range 7-16 years. Parents described the developmental story from initial diagnosis to the age of sixteen. Three children were in primary school and three within secondary school, providing information about the differing challenges faced by each sub-group.

All children declined to be interviewed separately to their parents. The three teenagers in our cohort participated in the group interviews alongside their parents. Pseudonyms have been given to the children to protect their identities.

Interpretive analysis of the narrative revealed rich data about the parents’ desire for their child to ‘fit in’ with their peers. In the formative years, they wanted their child to integrate into broader society, achieving the same social, developmental and educational milestones as normal children in mainstream school. On transition from primary to secondary school,
the focus had shifted and they were more accepting of their child’s differences and wanted them to be surrounded by a peer group, with similar needs who may also have developmental delay, language delay or hearing loss, allowing their child to feel less ‘different’. Parents felt that acquisition of spoken language and their child’s education were very important in achieving the above and these were important themes to emerge from the data. A third theme, labeled emotional impact, also emerged from the data. Parents and older children felt that despite the life limiting diagnosis, the illness had had a positive effect on their relationships and attitudes. These three main themes are discussed further detail below.

**The acquisition and development of spoken language**

The development of language in these children was delayed, with the appearance of single words as late as age three or four. Families reported that children were diagnosed with deafness very early on, preceding the diagnosis of MPS. All the children had received multiple sets of ventilation tubes and hearing aids. One child had had a unilateral cochlear implant inserted prior to being diagnosed with MPS, for the treatment of profound hearing loss.

All the children had severe language delay, initially attributed solely to hearing loss, and most had the input of a speech therapist alongside hearing rehabilitation. On reflection, some parents felt that they were actually in ‘denial’ of the extent of their child’s language delay.

*Brian’s mother (age 10)*, ‘we watched a video back. In the video, he runs into the room and literally babbles, and runs out again. He was three and a half and had no speech. I think we were in a bubble of denial.’

Parents felt that language development had occurred at primary school, about age six, whilst surrounded by healthy children. Mainstream school had been a positive influence. However, as these children had grown older, their speech had never really caught up with that of their peers and always remained ‘delayed’ or ‘lacking in clarity’.

*Jack’s Mother (age 10)*, ‘he is now ten and my friends still can’t understand what he says as his speech is not very clear.’

*Brian’s mother (age 10)*, ‘the other children are all learning year five adjectives and he has to be taken out of class and taught reception level phonics due to his inability to hear. Also he gets his spelling wrong as he can’t hear the difference between similar sounding words like taught and caught.’
The parents also felt that their children lacked the capacity to develop a ‘better vocabulary’. They felt that this was a direct impact of the MPS disease affecting their child’s brain, giving them some degree of static cognitive impairment.

*James* father (age 7), ‘I think it’s partly due to his hearing, but I don’t think it’s totally that. I think he can get by even without his hearing aids to an extent. It’s just his understanding of tenses and just general basic language is still quite slow and delayed. I think he’s been put at maybe a mental age of about three.’

This inability to communicate and express themselves caused younger children to have behaviour problems and older children to feel frustrated and angry. It also affected the self-confidence of the older children, who, towards the end of primary school were beginning to develop insight into their difference to their peers and siblings.

*James’s* father describing his behaviour (age 7), ‘He’s sociable and loves playing with other kids. He struggles to make himself understood has developed little ways of coping, sometimes it’s physical. He’ll push or shout and pull faces because he’s frustrated.’

*Brian’s* mother describing his emotions and frustration at not being able to communicate well (age 10), ‘At home he strops and runs upstairs and hides, ‘you don’t listen to me’ type proper teenage tantrums. Its different at school, he doesn’t do that. Apparently he just gets frustrated and bursts into tears.’ ‘He’s not as confident to say things and he just hasn’t got the vocabulary to say things. That is MPS, he hasn’t got the brain power to know what to say.’

The parents of children in primary school with attenuated MPS II held aspirations for their child’s social and academic achievements, with the belief that they could integrate or fit into normal society. They felt that the acquisition of language was integral, as it would allow the children to communicate with their peers and teachers in mainstream school and not be perceived as being different, whilst also providing a good education, allowing for future independence. They were very accepting of ventilation tubes and hearing aids, as they felt these treatments would allow their child to achieve these stated communication goals more effectively. They were also positive about sign language, which was the first means of communication used by children with early, severe hearing loss. These children had all gone on to develop spoken language, in some cases as a substitute for the signing, but in other cases as a supplement. The families attribute the transition from sign language to spoken language to the use of hearing adjuncts and the availability of teaching assistants in mainstream schools. The parental preference was for spoken language as they felt it
would allow their child to communicate with a wider audience and also make them feel less
different to other children their age, once again highlighting the desire to ‘fit-in’.

All of the children wore hearing aids from a young age. The parents felt that the ERT had
not subjectively improved their children’s hearing loss. Adam, an adolescent with a
unilateral cochlear implant (a semi-implantable hearing device for severe/profound hearing
loss) had developed claw hands in his early teen years, and hence was finding it increasing
difficult to sign. His mother was thankful that his cochlear implant had facilitated the
acquisition of speech, so he was not entirely dependent on his hands to communicate.

Despite Adam’s very positive response to his cochlear implant, others parents had a more
reserved opinion. Some children, when angry, would frequently remove or throw the
hearing aids away, as an outward display of their feelings. For some children in
mainstream schools, the hearing aid sometimes drew unnecessary attention and in one case
(Jack, age 10) was a cause for bullying.

Education and independence

Educational expectations, including the desire for normalcy and ‘fitting-in’ changed with
increasing age. Parents with young children were eager for their children to attend
mainstream primary school. At this stage many of the MPS II children were relatively
well and the parents wanted to celebrate their similarities with other children, allowing
them to feel like a part of the wider community. Parents also commented that at this young
age the children were unaware of their difference to other children their age and hence
thrived in this school environment. However, this ability to integrate well into a
mainstream school seemed dependent on a receptive school, able to cater for the child’s
extra needs, for example; one primary school had a deaf unit attached to it. All of the MPS
II children required teaching assistants, not for physical assistance, but for educational
support.

Brian’s mother (age 10) said, ‘His teaching assistant keeps him back after class to do extra
spellings. At the moment he is doing spellings from year five but is in year six.’

However, this social integration was difficult to achieve if the children were on the autistic
spectrum, a normal part of the MPS II disease process in some children with CNS disease.
These children appeared to thrive instead in special needs schools with small class sizes
and an increased level of support. These schools offered a reduction in background noise
and improved one to one interaction with the teacher.

Jacks father describing the move from mainstream to special needs school for their autistic
son (age 8), ‘we think this school is much more suited to him and over a short period of
time his concentration and behavior have both improved. But on a personal level the move to a special needs school was a really difficult thing for us to accept.’

Parents felt that towards the end of primary school, the ‘learning’ gap between their children and those without MPS had widened significantly. The children did not have progressive CNS disease, but simply that their baseline learning difficulties had become more socially problematic as they got older. Parental expectations and aspirations for their child changed at this point and rather than academic achievement, they wanted their child to be happy, safe and develop life skills that would provide them with future independence. It appeared that the parents had come to accept the difference between their child and peers. Hence, all 6 children with attenuated MPS II in this study moved away from mainstream education to one more tailored to their individual needs when they transitioned from primary to secondary school.

James’s mother (age 10) said of his approaching final year in primary school, ‘we have social worries. I couldn’t care less about his education anymore. As long as he’s happy. He’s just very immature for his age.’

**Emotional impact**

Overall the illness had had a positive impact on family cohesion. Parents described growing closer to one another and more appreciative of the time with their children. The parents felt that they had become better, more selfless people.

Adams’ mother (age 15), ‘It just makes you more appreciative. We probably spend more time playing with the kids now than we would have done if he hadn’t had Hunter’s.’

The younger children’s attitudes towards the illness were positive and most were unaware of their difference to other children until the age of ten-eleven, where they seemed to develop increasing levels of self-awareness. They enjoyed hospital visits because of the positive attention they received and didn’t mind ERT as most of them were allowed to watch TV and relax. However, the adolescents found admission to hospital for tests and procedures difficult. They disliked the time away from friends and family and the side effects of treatments offered to them. Many had developed an awareness of their own mortality.

Adam (age 15), ‘I don’t want to die because I want to stay alive. I want to stay with my two brothers.’
Meeting other families with children suffering from MPS had been a source of comfort and solace for the parents. It had allowed the families to cope and make friendships with others in a similar situation to themselves.

Discussion

Issues important to parents, varied with the age of their child. When the children were under the age of three, hearing loss was the predominant worry. As the children reached primary school age (5-6yrs), the main concern was delayed acquisition of language. Towards the end of primary school (10-11yrs) the focus had shifted towards the child’s mental capacity and their mild developmental delay. The parents of adolescents (11-16) were focused on preventing social isolation in their child and assisting them in achieving life skills that would promote independent living in the future. Despite the marked physical disease endured by these boys it is the learning and communication difficulties that have the greatest impact on their quality of life.

For parents it was important that their child achieve social acceptance and integration with their peers, i.e. ‘fitting in’. The parents of younger children wanted to celebrate the similarities their child had with others. They sent them to ‘mainstream schools’, which was possible with teaching assistant support, and wanted them to explore activities normal for their peer group. Young children appeared to have little insight into their difference to other children although became increasingly aware of this by the end of primary school (ages 5-10 years). However, with increasing awareness of their child’s cognitive disease, in part due to the more apparent learning gap between their children and normal peers, this expectation of fitting in changed. The parents of older children (11yrs onwards) wanted their children to be in ‘specialist schools’ (which cater for children with special educational and physical needs) rather than ‘mainstream secondary schools’ (ages 11-18years) so they could make friends with children with similar problems, such as deafness or mild learning difficulties. The parental focus shifted from academic achievement to acquisition of life skills such as budgeting, allowing their children to achieve independence as young adults. Teenagers were worried about hospitalization, treatment and even death. Autism, a feature of MPS II disease in some children, was found to predict a poorer outcome, with these children benefitting from additional support.

Parents reported that early childhood deafness had an impact on the acquisition of language, causing delayed expressive language and lack of speech clarity. Despite treatment of this with ventilation tubes and/or hearing aids, the children continued to struggle with phonetics, word blending and distinguishing similar sounding words. This inability to hear, coupled with difficulty in effective communication resulted in frustration
and behavior problems. Despite adequate, early hearing rehabilitation, this continues into adolescence with a negative impact on academic achievement. It may also be that the children’s neurocognitive disease plays a receptive role in language development.

No comparable published data examining the effect of hearing loss in children with MPS or histological animal or human studies looking at the effects of MPS on the temporal bones of these patients exists. The developmental impact of hearing loss in otherwise healthy children has been extensively researched. A child’s inability to hear during the early language acquisition years may result in poor long-term language skills with an effect on reading skills and educational achievements (Phelps L 1990, Van Eldik TT 1994, Davis S 1999). Also, in comparison with normal hearing peers these children have increased levels of mental health and behavior issues and difficulties with social interactions. These problems seem to have a linear relationship to the severity of their hearing loss (Wake M 2004).

The hearing loss and subsequent delayed acquisition of language had a major impact on parents’ perceptions of their child’s HRQoL. They felt that it was a necessity to allow their child to attend mainstream school, interact with the other children and achieve their academic potential. The parents of older children felt it would prevent their child from becoming socially isolated and allow them to communicate in a work place, leading towards future independence. The parents had very positive views about their children combining this with sign language and using adjunctive hearing aids. These views are in direct contrast to the views of parents whose children have hearing loss, as part of a multi-system problem such as cerebral palsy. The parents of children with cerebral palsy do not always view hearing loss as a health related problem (Sach TH 2007) and may give precedence to their child’s other needs first, perhaps ignoring early auditory testing and rehabilitation.

To our knowledge, this is the first study of its kind to explore in-depth the perception of parents on the impact of attenuated MPS II (primarily head and neck disease), on their children and on themselves. Owing to the rarity of the illness, only six patients were interviewed for this study. However, despite this, the data generated was extensive with theory rooted in and emergent from this rich data. Also, we managed to interview a diverse group of patients with varying ages and contrasting social backgrounds.

No children were available for interview without the presence of their parents. Hence, most of the data generated is by the parent proxy. Parents of children with chronic illnesses tend to underreport the impact on the child’s quality of life and hence this must be taken into consideration when using this data (Eiser and Morse 2001).
The findings of this study are important as they provide better insight into the perception that parents have of their child’s illness and children have of their own health and the dysfunction in health that they may attribute to it. It also highlights the importance that parents and children place on their hearing and language skills, in comparison with their other medical problems. We feel a high priority should be given to hearing and language, soon after diagnosis of MPS II is established. Management of the hearing loss should include intensive input from Audiology and Speech and Language therapy services, alongside the early provision of hearing aids, even for mild hearing loss. Audiology appointments must occur at regular intervals.

Health care practitioners may use this information to make better-informed decisions about the long-term management of these complex patients; with emphasis on active surveillance of hearing and aggressive early management of hearing loss and receptive/expressive speech delay. They must also be sensitive to the emotional impact of the disease and the desire for parent’s to want their children to ‘fit-in’.

This exploratory work may guide the future development of a patient reported outcome measures for children with attenuated MPS II, specifically focusing on the impact of deafness, the central phenomenon of ‘fitting-in’, spoken language, education and emotional impact. Due consideration must be given to the evolution of parental perspectives and expectations with their child’s development.

**Conclusion**

With advances in medical treatment and subsequent improvements in life expectancy, it is important to understand the impact of attenuated MPS II on the quality of life of affected children. This qualitative research shows that there is an evolution with time of the issues important to parents and by proxy, their children. Those with young children in kindergarten or nursery worry primarily about hearing loss, whilst those with children at primary school worry about delayed language acquisition. Parents of teenagers worry about promoting social integration and independent adult living. All of these themes are linked together by the parents desire for their children to ‘fit-in’ and integrate with their peers and society at large.

Despite the physical disease endured by these boys, it is the learning and communication difficulties that have the greatest impact on their lives. We feel a high priority should be given to hearing and language, soon after diagnosis of MPS II is established.
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