

**A Feasibility Study: Psychodynamic Interpersonal Couple  
Psychotherapy in Mild Cognitive Impairment- and fMRI  
study of changes in brain function.**

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## **Abstract**

The University of Manchester

Name : Dr Arunraj Kaimal

MPhil in the Faculty of Medical and Human Sciences

### **Title : A Feasibility Study: Psychodynamic Interpersonal Couple Psychotherapy in Mild Cognitive Impairment- and fMRI study of changes in brain function**

**Aim:** to study the feasibility of development and evaluation of a new model of psychotherapy for people suffering from Mild Cognitive Impairment and their spouses or partners through a modelling exercise of Randomised Control Trial in addition to generating theoretical and practical knowledge about the methodology

#### **Methods**

1. Development of a new model of Psychotherapy for people with Mild Cognitive Impairment and their partners or spouses
2. Studying the feasibility of evaluation of this intervention by adopting an exploratory RCT methodology
3. Studying the feasibility of application of Functional Magnetic Imaging to understand the biological mechanism of Psychotherapeutic interventions in older people with cognitive impairment.

**Results:** The study identified number of feasibility issues in terms of recruitment , resources as well as tolerability of interventions and other challenges in conducting controlled trials of complex interventions in older people with cognitive impairment . It was also identified that with modifications in the methodology it is feasible to conduct controlled evaluations of complex therapeutic interventions in older population with cognitive impairment

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## **Declaration**

No part of this work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other University

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# **Chapter 1 Background and context**

## **1.1 Introduction**

It has been well recognised that the UK's ageing population has considerable consequences for public services as the latest population projections indicate that the number of people over the age of 65 will have nearly doubled by 2050 (Key issues for the New Parliament 2010). With the elderly being the fastest growing population in the UK, increasing pressure is being put on healthcare and social services to meet this population's care needs. However it is important to understand that a substantial proportion of the older people with good health enjoy their lengthy retirement lives. In the aging society older people increasingly contribute to the economic and social development and it is important to develop cost effective health care interventions to aid older people to have quality in their lives whilst actively contributing to the roles they take in the society.

As an inevitable consequence of aging increasing number of age associated health conditions have been recognised to cause burden on patients and their carers. As a result of this aging has been a priority in the political and social agenda in the United Kingdom and it has stimulated huge research interest. Key issues for the New Parliament 2010 document states that 65% of Department for Work and Pensions benefit expenditure goes to those over working age, equivalent to £100 billion in 2010/11 or one-seventh of public expenditure (Cracknell 2007).

Memory loss has been reported as a consequence of aging. Cognitive changes in later life may indicate an underlying neurodegenerative disease. Age associated disorders of cognitive function such as Alzheimer's disease, and Vascular Dementia, produce distressing effects on sufferers and their carers. Many studies have recently described the impact of these diseases on patients and their

families and there has been an increased interest in detecting these conditions early on as well as to develop interventions to slow or delay its progression.

The national dementia strategy ((Department of Health 2009) identified that two-thirds of all people with dementia live in their own homes in the community with many people in the early stages of their illness, and the others near the end of their lives. The strategy recommends that the right support at the right time and in the right place is important for people with dementia. It has been identified that giving them choice and control over the decisions that affect them can improve their quality of life as well as independence. It was also recognised that the impact on those with the illness and on their families is also profound particularly because of the fact that family carers of people with dementia are often old and frail themselves. High levels of depression, physical illness and a diminished quality of life have been reported in carers of people with dementia (Department of Health 2009). The National Dementia Strategy highlighted the shortcomings in the provision of dementia services in the UK. It was recognised in the strategy that diagnosing dementia early on will help to improve the quality of life for the people suffering from dementia as well as for the people caring for them.

In terms of societal cost, dementia posed one of the greatest economic burdens the country is facing at present. Informal care is estimated to involve 1.5 billion hours of unpaid care provided to dementia patients living in the community, amounting to £12 billion. Productivity losses due to dementia account for £29 million. Overall, dementia is found to cost £23 billion in terms of health and social care, informal care and productivity losses in 2008. Although dementia accounts for over 50% of the combined health and social care costs among the four major diseases (cancer, stroke, cardio vascular diseases, dementia), it only receives 6% of combined research funding (Dementia 2010, Alzheimer's Research Trust 2010).

There is a recent growth in the research interest on the grey zone between normal aging and dementia. Although there were various attempts to develop the concept, definitions and classification; there is a clear consensus about the use of the term Mild Cognitive Impairment [MCI] to delineate the transitional state between normal aging and dementia.

Research suggests that between 5 and 20 per cent of older people have MCI at any one time. This finding makes the diagnosis of MCI important as people who have MCI are identified to be at an increased risk of developing dementia. It is observed that people with MCI have about 3-5 times higher risk of developing dementia. Diagnosis of MCI will provide the sufferers an opportunity to receive a range of support early on in the illness. In addition to this there is a research interest to identify people with MCI who will progress to a dementia syndrome. Although a range of neuro-imaging techniques including MRI are used in this field, it is identified that ongoing research is needed to develop neuro-imaging techniques to understand the patho-physiology of MCI better. The definition, classifications and clinical presentation of MCI are discussed in detail later in chapter 2, section 2.1.

Attempts are also made to overcome the lack of pharmacological interventions targeted specifically for MCI. The recent work is mainly concentrated on strategies to prevent or delay the progression of MCI to dementia, specifically Alzheimer's disease. In the recent years focus on psychological interventions for people with cognitive impairment and their carers by provision of cognition-based therapies as well as psychotherapeutic interventions has been increasing. Although the effectiveness of these approaches was examined in different clinical contexts like Alzheimer's disease and vascular dementia, it was identified that gaps existed in the current literature, even wider in the category of MCI. Effectiveness of psychological approaches to AD and MCI are discussed in section 2.2.

On clinical and research settings it was observed that psychological interventions can have profound effects on people's emotional states, beliefs and thinking. However the underlying biological mechanisms leading to these changes were not thoroughly studied. With emergence of newer functional brain imaging techniques, the underlying changes in brain function as a result of psychotherapeutic interventions attracted considerable research interest. With the use of techniques for symptom provocation and means for identification of neural correlates of psychological symptoms Functional Magnetic Resonance Imaging [fMRI] is widely used in addressing similar questions in a variety of psychiatric conditions including mood and anxiety disorders. So far no attempt was made to identify the biological correlates of psychotherapeutic interventions in a patient population with cognitive impairment. Use of fMRI in relation to the psychosocial interventions is discussed in detail in Section 2.2.

There were attempts to research different aspects of MCI using various study designs. However it was observed that huge gaps existed in establishing evidence based approaches for non-pharmacological interventions for cognitive impairment as well as in establishing the nature of the biological mechanisms underpinning the effectiveness of the psychological interventions in this clinical population.

A Cochrane systematic review examined the effectiveness of cognition based therapies in early stages of Alzheimer's disease and Vascular Dementia (Clare et al 2003). Research on other psychotherapeutic interventions directed at those with MCI is limited; however most findings suggest that psychotherapy may be beneficial in the early stages of dementia (Brierly et al 2003, Burns et al 2005). The studies focusing on the benefits of these interventions for people with MCI have been limited in number. Identifying the increasing need to develop and evaluate the non-pharmacological interventions in older people suffering from memory problems and those who care for them, we have designed this research

project as a feasibility study. The principal aim of this study is to inform large scale research projects to evaluate complex interventions in a challenging population of older people with cognitive impairment and their carers who predominantly are older people through a modelling exercise.

It is also recognised that increasing number of people present to the health services in the stage of Mild Cognitive Impairment, which highlights the need for planning health care interventions for that group. With the lack of evidence base in understanding the patho-physiology, effectiveness of the interventions targeted to the symptoms, as well as the ways to improve the quality of life for patients suffering from MCI and their carers, we have identified the need for further research in this field. Viewing the challenges in conducting research in older people with cognitive impairment, it was also identified that there is a need to adopt innovative approaches in developing and delivering psychotherapeutic interventions in this special patient group. It has been well recognised that undertaking large scale definitive evaluations including randomised control trials for novel interventions has been challenging in this population. The possible challenges in conducting research in older people as well as the methodologies to address the problems related to this are discussed in detail later in this chapter.

To better understand and address the challenges in conducting a large scale study in this field , we conducted this feasibility study as an exploratory trial, which is used to provide vital information including defining the intervention, testing the feasibility of key components such as recruitment, retention, randomisation, and acceptability of outcome measurements, acceptability of trial interventions as well as to understand the challenges in adhering to the written methodology of the trial .This study is aimed at collection of information for any larger trials planned in this population .

Viewing the challenges in developing and evaluating a psychotherapeutic intervention in older population, as well as the difficulty in applying experimental neuro-imaging methods we refer to the guidelines on developing and evaluating complex interventions issued by Medical Research Council UK in 2008, to help developing the methodology for our study. The guidance and the approach to the development of methodology are discussed in the next section.

## **1.2 Developing and evaluating complex interventions**

Medical Research Council UK provided guidance on the development, evaluation and implementation of complex interventions to improve health ( MRC 2008 ,Craig et al 2008 ). MRC identified that developing, piloting, evaluating, reporting and implementing a complex intervention can be a lengthy process. The MRC guidance suggests that a predominant focus on the main evaluation, neglect of adequate development and piloting work, or lack of proper consideration of the practical issues of implementation, will result in weaker interventions. As a consequence those interventions are harder to evaluate with a lesser likelihood of implementation. It was recommended that if there is lack of clarity about the theoretical base of the intervention as well as the outcome the researchers are aiming for , there is a need for further development work before the beginning of evaluation .It was also recommended that enough piloting and feasibility work should be done for the researchers to be confident that the intervention can be delivered as intended and safe assumptions about the effect size , variability , recruitment and retention can be made.

### **1.2.1 Complex interventions; Definitions and characteristics**

MRC guidance describes complex interventions as interventions that contain several interacting components. There are several dimensions of complexity

described such as a range of possible outcomes, or their variability in the target population, rather than with the number of elements in the intervention package itself. It follows that there is no sharp boundary between simple and complex interventions.

Some dimensions of complexity in the health care interventions according to the MRC guidelines are shown in the box 1 below.

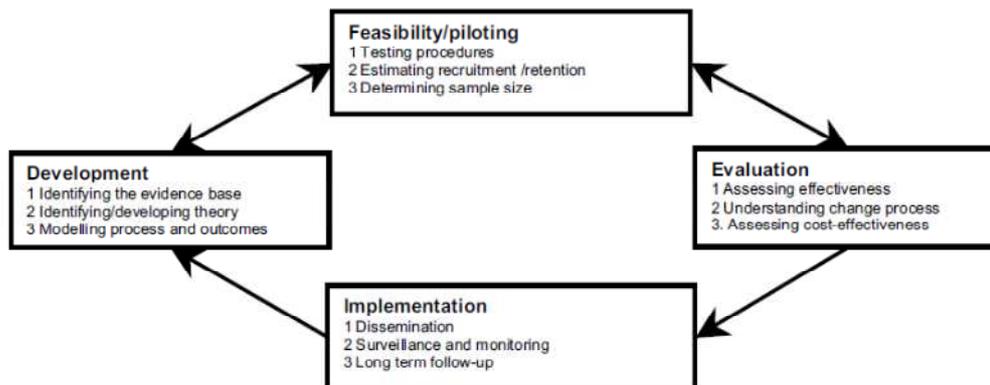
**Box 1. Dimensions of complex interventions**

([www.mrc.ac.uk/complexinterventionsguidance](http://www.mrc.ac.uk/complexinterventionsguidance))

- Number of interactions between components within the experimental and control interventions
- Number and difficulty of behaviours required by those delivering or receiving the intervention
- Number of groups or organisational levels targeted by the intervention
- Number and variability of outcomes
- Degree of flexibility or tailoring of the intervention permitted

In the MRC guidance the main stages , key functions and activities of the development, evaluation and implementation process is summarised in figure 1 below .Although the interaction between these phases are well established it was recognised that they do not often follow a linier or cyclical sequence .

**Figure 1. Key elements of the development and evaluation process** [Figure reproduced from - [www.mrc.ac.uk/complexinterventionsguidance](http://www.mrc.ac.uk/complexinterventionsguidance)]



According to the recommendations the best practice is to develop interventions in a systematic approach. Synthesising the best available evidence and appropriate theory is the first step. A phased approach is recommended to test them. The best practice recommendations is to start with a series of pilot studies targeted at each of the key uncertainties in the design, and then moving on to an exploratory and later on to a definitive evaluation. These recommendations are summarised in a box as well as discussed in detail below.

**Box 2. Recommended steps in the systematic approach to test complex interventions**

- Identifying the evidence base
- Identifying/developing appropriate theory
- Modelling process and outcomes
- Assessing feasibility and piloting methods
- Evaluating a complex intervention

## **1.2. 2. Recommended steps in the systematic approach to test complex interventions**

### **1.2.2.1 Identifying the evidence base**

As the first step in the research process the existing evidence base should be identified. It was recommended that in an ideal situation a systematic review should be carried out. However the existing evidence base related to the planned intervention can be too limited, that the evidence needed to be derived as a part of development as well as evaluation process.

### **1.2.2.2 Identifying/developing appropriate theory**

Research work is available considering the extent to which evaluation reports specify (i) discrete intervention techniques and (ii) psychological mechanisms that account for observed behavioural change (Michie et al 2004). It is concluded that intervention descriptions are often not specific about the techniques employed and that there is no clear correspondence between theoretical inspiration and adoption of particular change in techniques. The review calls for experimental testing of specific theory-based techniques, separately and in combination. It is also observed that understanding relevant theory is important as this is more likely to result in an effective intervention than is a purely empirical or pragmatic approach (Albarracin et al 2005). When complex interventions are developed, a clear understanding about what changes are expected and how the changes are achieved may not be available in the beginning. It was also recommended by MRC that, to develop a theoretical understanding about the likely process of change there may be a necessity to do primary research targeting the population for which the intervention is developed. Conducting interviews with representatives of the targeted population was given as an example to this approach . As there may be several overlapping theories in the already existing evidence, this approach was

observed to be helpful to find the most appropriate one relevant to the target intervention.

### **1.2.2.3 Modelling process and outcomes**

MRC identifies that modelling a complex intervention prior to a full scale evaluation can provide important information about the design of both the intervention and the evaluation (Craig et al 2008). In spite of this recommendation researchers find that there is still an ambiguity about the optimal way to conduct the modelling phase. There are previous studies interpreting the modelling process as a phased approach where Phase 1 involves 'modelling', which requires theoretical and empirical work to 'identify the components of the intervention and the underlying mechanisms by which they will influence outcomes' as described above. The Phase 2 was identified as the process involving an exploratory RCT to test the intervention, examine delivery in routine settings, and provide estimates of key trial parameters such as recruitment rates and estimates of effectiveness, prior to a definitive trial (Lovell et al 2008). The authors found it challenging to develop interventions that are evidence based and patient-centred, regardless of the approach used. MRC identified that, it was important at an early stage in developing an intervention to ask the question 'would it be possible to use this?' before embarking on a lengthy and expensive process of evaluation.

### **1.2.2.4 Assessing feasibility and piloting methods**

MRC recommends that a piloting phase is important to test procedures for their acceptability, estimating the likely rates of recruitment and retention of subjects, and the calculation of appropriate sample sizes. Several systematic reviews suggested that this vital preparatory work is often missed in the RCTs, significantly affecting the quality of research (Eldridge et al 2004, Scheel et al 2003)

A general agreement among the researchers has been observed that when a study's starting point is with the general lack of good evidence for effective ways of application of the planned intervention, and evidence on methods that might be applicable to a disadvantaged population is absent the piloting is essential to make sure that the intervention is feasible in settings accessible to these participants and their families. When the piloting is done retention in the programme appears to be better, with favourable outcomes .MRC also recommends that a pilot study need not be a 'scale model' of the planned main stage evaluation, but should address the main uncertainties that have been identified in the development work. Caution is advised when the pilot studies results are interpreted, particularly when assumptions are made about the required sample size and the likely response rates. It was also identified that there may be a need to use a mixture of qualitative and quantitative methods, to understand barriers to participation and to estimate the response rates. It was suggested that depending on the results, a series of studies may be required to progressively refine the design, before embarking on a full-scale evaluation.

#### **1.2.2.5 Evaluating a complex intervention**

MRC advises that the choice of methodology should be on the basis of specific characteristics of the study, such as expected effect size and likelihood of selection and other biases. As the different designs suit different questions and different circumstances, a range of experimental and non-experimental approaches should be considered to choose the appropriate methodology for evaluation. It is also advised that randomisation is the most robust method of preventing the selection bias and whenever possible it should always be considered in the methodological approach.

## **1.3 Feasibility and Pilot Studies**

In the health and social science research field, there is currently a consensus about the justification for conducting a research project as a pilot study or feasibility study. There are clearer guidelines delineating the content of a pilot or feasibility study as well as the questions that kind of a study should address.

In the UK, NIHR Health Technology Assessment Programme (2011) has defined Feasibility studies and Pilot Studies.

### **1.3.1 Feasibility Studies: definitions and objectives**

Feasibility Studies are pieces of research done before a main study in order to answer the question “Can this study be done?”

NIHR describe that the feasibility studies are used to estimate important parameters that are needed to design the main study.

Like

- standard deviation of the outcome measure, which is needed in some cases to estimate sample size;
- willingness of participants to be randomised;
- willingness of clinicians to recruit participants;
- number of eligible patients;
- characteristics of the proposed outcome measure and in some cases feasibility
- studies might involve designing a suitable outcome measure;
- Follow-up rates, response rates to questionnaires, adherence/compliance rates, ICCs in cluster trials, etc.

It was also identified that feasibility studies are routinely performed in many areas like critical care, diabetes management intervention trials, cardiovascular trials, and primary health care trials to assess the feasibility of conducting a larger scale trial.

### **1.3.2 Pilot studies: definitions and objectives**

According to NIHR definition pilot studies are miniature versions of the main study, conducted to test whether the components of the main study can all work together. The main focus of this has been described as a trial to test the process and the methodology of the main study making sure that the recruitment, randomisation, treatment, and follow-up assessments all run smoothly. It is recommended that the pilot study resemble the main study in many respects. The objective of the pilot study may include an assessment of the primary outcome as well (NIHR 2011).

Two types of pilot studies have been defined - external and internal. External pilot studies were defined as standalone pieces of work planned and carried out independently to the main study. Internal pilot studies were incorporated into the main study design of the RCT (Lancaster et al 2004).

Another review gave narrative descriptions of papers reporting pilot studies in critical care highlighting the need for rigorous pilot studies and pilot trials as the background projects for various study designs (Arnold et al, 2009) .This review suggested that pilot trials are important to ensure that large randomised trials are rigorous, feasible and economically justifiable. This group defined pilot trials as preliminary investigations that were specifically designed to assess the feasibility, safety or acceptability of an intervention, and that included a randomization procedure .Using a narrative format they described the objectives, outcome measures, analytic plan and publication of pilot studies, focusing primarily on pilot randomised trials. It was observed that the overall purpose of a pilot trial is to inform the design and conduct of a larger RCT. As large trials require international and cross cultural collaboration ,with coordinated work by many researchers ,clinicians and patients ,conducting a pilot trial will be a safeguard for investigators and funding agencies that future trials are designed optimally and can be implemented in practice .The objectives

of such sort of a trial were reported as assessment of feasibility ,an evaluation of eligibility criteria planned for a larger RCT, and or a means of understanding mechanisms based on surrogate outcome measures.

The main objectives identified were

- Informing Feasibility
- Examining eligibility criteria
- Assessing mechanisms

The authors observe that, by conducting a pilot trial simulating all aspects of the RCT ,the feasibility can be tested in different aspects of the trial from the allocation process to the outcome measurement and data collection .It also gives an opportunity to test the adherence to the protocol across different centres where the availability of resources is varied .Regarding the examination of eligibility criteria , pilot trials appear to provide valuable data about the impact of inclusion and exclusion criteria on recruitment efficiency .Authors also make an important observation that pilot trials often use surrogate outcomes to inform decisions regarding proceeding to a larger RCT. It was recommended that the results of analyses based on surrogate outcomes should be interpreted with caution as usually pilot trials are not sufficiently powered to detect clinically important treatment effects .Box 3 summarises the main reasons for conducting a pilot study according to a different review (Van Teijlingen et al 2001).

### **Box 3. Reasons for conducting pilot studies (Van Teijlingen et al, 2001 )**

- Developing and testing adequacy of research instruments
- Assessing the feasibility of a (full-scale) study/survey
- Designing a research protocol
- Assessing whether the research protocol is realistic and workable
- Establishing whether the sampling frame and technique are effective
- Assessing the likely success of proposed recruitment approaches
- Identifying logistical problems which might occur using proposed methods
- Estimating variability in outcomes to help determining sample size
- Collecting preliminary data
- Determining what resources (finance, staff) are needed for a planned study
- Assessing the proposed data analysis techniques to uncover potential problems
- Developing a research question and research plan
- Training a researcher in as many elements of the research process as possible
- Convincing funding bodies that the research team is competent and knowledgeable
- Convincing funding bodies that the main study is feasible and worth funding
- Convincing other stakeholders that the main study is worth supporting

#### **1.4 Methodological characteristics of Pilot and Feasibility studies**

Although the literature is limited in this field the attempts to define the methodology and objectives of pilot and feasibility studies recommend that these kind of studies should have explicit objectives .As discussed above there is a need for clearer distinctions between feasibility study and pilot study .

Several authors agreed that one of the main purposes of conducting pilot studies is to test feasibility of conducting a full scale trial and hence the definitions overlap considerably.

There is general agreement that, a pilot study is a miniature version of the main study conducted to test whether all the components of the main study can work together.

It was observed that clinical researchers often propose pilot studies to determine whether a study is worth performing and to guide power calculations (Kraemer et al 2006). This paper observed that this had been resulting in the most likely outcomes of either the studies worth performing being aborted or studies that are not aborted being underpowered. The paper also points out that in medical research Null Hypothesis Significance Testing (NHST) has been the basis of drawing inferences from a sample to population .Even when NHST is correctly applied studies based on these methods are often observed to be underpowered. Because of the smaller sample sizes pilot studies are particularly prone to this issue. The authors make it clear in the paper that the results are statistically non significant not because the hypothesis being tested is untrue or is clinically non significant, but because the sample size is too small. They also report that studies with small sample size are often reported as borderline significant , marginally significant , and trend towards significance etc indicating that the researchers were unable to reject the null hypothesis at the significant level of 5%. Those researchers tend to believe that their hypothesis is true. It was also identified that the post hoc power calculations are undertaken, that is based on the obtained result. In this context the authors advices researchers to take

caution regarding the practice of hypothesis testing studies using pilot studies as 'the previous research' to base the power calculations. The paper endorses that a small inadequately powered pilot study does not fall under the rubric of previous research for the objective of power calculation.

This paper argues about the caution needed against the use of pilot studies for the objective of guiding power calculations. However they identify that pilot studies are important in preparation of proposals for hypothesis testing studies. This group identified that pilot studies should be conducted to test different aspects of feasibility as shown in the box below.

As there is a doubt that whether any effect size estimate from a pilot study represents the true effect size in the main study, the argument is that the pilot studies cannot estimate the effect size with sufficient accuracy to serve as a basis of power computation for that study.

Based on the above arguments it is important to take caution when a pilot study is conducted as a feasibility trial and it may be not necessary to have a power calculation based on a primary outcome .However when the study is conducted as a feasibility trial many researchers still use a power calculation even for the reasons mentioned above including the study of the feasibility of the methodology as well as for training purposes. Even if the power calculation is undertaken, to develop the methodology and the protocol, the adherence to the protocol can be very well tested in the pilot phase rather than an effect size.

It was also recommended that when the objective is to inform a larger trial, the criteria for claiming success should be established before commencement of the study .Although it would be difficult to establish criteria to claim success in feasibility studies, it was observed that establishing feasibility objectives is possible. In pilot and feasibility trials it is allowed to do protocol alterations, whenever the study is observed to be failing to achieve the feasibility objectives. These alterations can be done as corrective actions to achieve success in a full trial and there is an advantage of testing the changes made as

the corrective actions in the pilot phase. When protocol alterations are made it should be fully reported in the pilot trials.

On many occasions in pilot studies particularly when it is conducted as a feasibility study an adaptive trial design is necessary .The adaptive trial design has been described as a methodology which allows modifications to be made to a trials design or statistical procedures during its conduct, with the purpose of efficiently identifying clinical benefits or risks of new drugs or to increase the probability of success of clinical development (Thabane et al 2010) .It was recommended that the adaptations can be prospective or retrospective . the examples of prospective adaption include stopping a trial early due to safety concerns and making changes in the eligibility criteria ,hypothesis or study end points . The example of retrospective adaptation is making changes to the statistical analysis plan prior to locking the data base or revealing the treatment codes to investigators or patients.

This group of researchers also recommended that there should be a predefined analytic plan, specifying primary and secondary analyses, is an important component of a pilot trial protocol .In this analytic plan there is a need to include a strategy for refining the protocol of the full scale trial based on the results of the pilot trial as well as a strategy to address the analytic need of any potential alterations made in the pilot phase. The general recommendation is that in the pilot studies with a specific feasibility objective, the analysis should focus on the feasibility objective rather than treatment effects.

### **1.5 Reporting of pilot studies and analytic plans**

Further to the study described above it was observed that different researchers report that the statistical analysis of pilot studies should be either mainly descriptive or focus on sample size estimation, while results from hypothesis testing must be interpreted with caution (Arain et al ,2010 ; Lancaster et al 2004).Arian et al 2010 revisited the seven journals studied by Lancaster et al

2004 to see whether the subsequent recommendations have changed the practice of reporting the pilot studies .They studied papers from 2007-08 in seven medical journals and retrieved published pilot studies . In addition to that, the authors revisited the reports of registered and completed studies on the UK Clinical Research Network (UKCRN) Portfolio database and the data available were retrieved and scrutinised.

This study concluded that many pilot studies are still poorly reported with inappropriate emphasis on hypothesis testing .They recommend that authors should be aware of the different requirements of pilot studies, feasibility studies and main studies and report them appropriately .It was also observed that the definitions of feasibility and pilot studies vary and there is a need for researchers to explicitly state the purpose of the study.

### **1.6 Quantitative and qualitative phases in pilot studies**

It was identified that pilot studies can be based on qualitative or quantitative methodologies. It was well recognised that larger scale studies would require a number of pilot studies before the main study is conducted.

On many occasions in health research it was necessary to start with a qualitative phase where researchers collect the qualitative data on an unexplored topic as well as collect the data necessary to develop novel interventions for diagnosis and treatment .In this phase it is usual to use in-depth interviews or focus groups to establish the issues to be addressed in the larger clinical study.

In the second phase of piloting, development of the research instruments and testing their adequacy could be carried out. This would include testing the acceptability and the validity of the tools including interventions and the tools for outcome measurement.

In the third phase the piloting could be conducted to test the research process by ‘modelling’ the study as a miniature , to assess whether the research protocol is

realistic and workable , whether the sampling frame and technique are effective, and whether the randomisation ,recruitment , and analysis processes are successful . Issues related to training, resource, logistics, etc can also be studied in detail in this phase.

### **1.7 Feasibility studies and Pilot studies as exploratory trials**

The prevailing view in therapeutic clinical research today is that observational studies are useful to generate new hypothesis and that randomised controlled experiments are the most appropriate method for assessing and confirming the efficacy of interventions. It was also identified that lack of external validity is a drawback of the traditional RCTs as they are conducted on relatively homogeneous population under rigid protocol driven experimental conditions, and it is argued that the results are not always applicable to the heterogeneous patient population seen by clinicians in their everyday practice.

These arguments give more validity to the approach to develop small exploratory trials to test the feasibility of conducting experimental research in clinical population incorporating a pragmatic approach. As discussed above an exploratory trial can include the constructs of feasibility as well as pilot studies and an observational element can be included in this, particularly when the interventions are assessed within the context of routine clinical population. In the below sections we discuss the challenges in conducting research in a complex clinical population as well as the need to develop an innovative methodology to do the piloting of complex health intervention as well as to test the feasibility of applying this methodology in the form of a controlled experimental study in a routine clinical population .

An exploratory trial is used to provide vital information including defining the intervention, testing the feasibility of key components such as recruitment, randomisation, and measurement of outcome as well as unique evidence of

intervention effects for the purposes of calculating the power of a main larger trial. Two major areas of advantage in conducting an exploratory trial are discussed below.

As it is not recommended to modify the intervention in a definitive trial, exploratory trial give the investigator the freedom to test the variations in the intervention to select the most appropriate one for a full scale trial. Exploratory trial also offers the opportunity to generate some qualitative and quantitative data regarding the adaptability and desirability of the intervention, frequencies, intensities and mode of delivery. It also helps to identify the optimal content of the innovative and complex interventions and lead to standardisation of the intervention aiding power calculations. In addition to this an exploratory trial can provide information on training issues, learning curve effects, and helps to develop techniques to adapt analysis to control for variation in the skill mix of providers.

As there is no room for the intervention to evolve in a definitive RCT, an exploratory trial will allow developing mechanisms for monitoring including audio-taping and regular supervision. This phase also used for determining the comparative arm of the main trial particularly to define the ‘standard care’ and determine the necessary monitoring for the main trial.

The exploratory trial is valuable in understanding the methodological challenges as it gives accurate information about the estimates for the sample required for a main trial, preventing the main trial to be under-powered. The exploratory trial also provides the opportunity to “test-drive” the assumptions and strategies including methods of recruitment, randomisation and follow-up. The commitment from participants and compliance can be assessed. This will help to develop innovative strategies to ensure the long-term success of the trial, and the minimisation of the dropout rate.

It has been well recognised that, undertaking large scale definitive evaluations including randomised control trials for novel interventions has been challenging. However it has been very important for the advancement of health science to conduct large scale definitive evaluations and as result it is equally important to understand the complexities involved in such large scale projects. To understand and address the challenges, researchers often propose and funding bodies demand pilot studies. The main intention of performing pilot studies is to understand whether a study is worth performing and also to guide power calculations (Kramer et al 2006).

Medical Research Council [MRC] also recognised that large scale studies that evaluate clinical and healthcare interventions are a complex and significant undertaking for both funders and investigators. Although RCTs are regarded as gold standard method in evaluating health care interventions this has been particularly challenging in the field of complex health interventions. To address the above issues M R C encouraged researchers to design pilot studies as feasibility or scoping studies to gather maximum information to support development of large scale cross disciplinary projects particularly to evaluate novel interventions. In addition to determining whether a study is worth performing and guiding power calculations a preliminary feasibility or pilot work helps to inform the development of a definitive study.

A feasibility or scoping study for an RCT examines issues such as; effective recruitment strategies, the optimal nature of the intervention or outcome measurement, novel analytical modelling etc, particularly in more challenging areas like complex interventions. It is recommended that a scoping study could be hypothesis driven or aimed at developing methodologies to answer a particular research question. It was also highly recommended that novel interventions based on supporting evidence from existing limited literature ,should be developed and tested using small scale ‘platform trials ‘ where the

speculative ,experimental or exploratory nature of the work means that results and outcomes are uncertain or cannot be guaranteed.

MRC's document on 'A framework for development and evaluation of RCTs for complex interventions to improve health' [2000] states 'Complex interventions in health care, whether therapeutic or preventative, comprise a number of separate elements which seem essential to the proper functioning of the intervention although the "active ingredient" of the intervention that is effective is difficult to specify.' The example given in this document is a physiotherapy intervention in which psychotherapy being an essential component making the intervention complex and methodology for evaluation challenging. MRC recommended a framework with a step-wise approach to the evaluation of complex interventions to guide the investigators in determining what the state of knowledge and uncertainty is regarding a complex package at a given time.

### **1.8 Challenges in conducting research in Older People**

The characteristics older population can make conducting a research very challenging in this population. the research settings are understudied in this population and several research projects had to be abandoned because of the difficulties in conducting the research in this population with huge implications for resources allocated to the projects .Generally it was observed that there is an under representation of older people in research studies particularly trials . Older people generally experience a range of physical and psychological symptoms including sensory impairment, pain and fatigue which can have an impact on all aspect of the research studies they take part. It was observed that this can affect recruitment, retention, as well as the quality of data collection. Particular challenges are reported in older population with cognitive impairment and dementia. In addition to the impact on the above aspects, difficulties in getting informed consent were also reported in this group. It was also observed

that older people may readily agree to participate in research studies, with a hope to increase their contact with others, however the practical difficulties can make the participation challenging (Mass et al, 2002).

There are studies detailing challenges in conducting research in older population in the institutional settings. It was reported that poor staff compliance in the institutional settings, inflexibility in established routines, policies and practices in the institutions and the potential gate keeping by family members could create substantial obstacles in to the research process (Hall et al 2009). However the challenges in conducting the research in older people in the community settings were not well studied and we identified increasing scope in studying this area.

Adopting non-pharmacological interventions for people with memory problems and their carers has received increased research interest and there have been successful attempts to conduct randomised control trials in this field. However it was also observed that many of the pilot studies conducted in this field are poorly reported, with inappropriate emphasis on hypothesis testing in the context of lack of methodological rigour.

### **1.09. Development of an exploratory trial using innovative methodology**

The feasibility of a controlled evaluation in the field of psychotherapy is a much debated topic with increasing attention. It was recognised that great deal of commitment and resources are required to develop full scale trial particularly to test a complex psychotherapeutic intervention in special groups like elderly population with cognitive impairment. On the other hand our population is generally aging, which necessitates development of innovative interventions to address their complex psychological needs with sound evidence base. Although there is some preliminary information available in the literature, so far there are no definitive large scale trials to evaluate psychotherapeutic interventions in

elderly population with cognitive impairment. We conducted this study as a formal exploratory trial to identify barriers to research in this population and also to identify ways to address these barriers to facilitate a full scale definitive study.

It is well acknowledged that there is a shortage of well powered RCTs with robust methodology in the field of psychological interventions in older people with cognitive impairment. To date there have been only very few published report on this subject. Although the difficulties in persistence with psychotherapeutic interventions and high dropout rates were thought to be the main reasons behind the lack of large scale trials, there is no formal attempt reported to understand and address the challenges in this field and we designed this exploratory trial to address these issues in addition to generate data for a large RCT. In addition to this we aimed at generating seminal data on biological changes as a result of psychotherapy using an innovative functional neuro-imaging methodology in an observational way.

We adopted the steps to design a formal RCT in this exploratory trial to conduct it in real clinical research setting that we could generate accurate data. The steps we adopted in the design of this exploratory trial are described in the table below.

**Table 1. Aims of an exploratory trial for an innovative complex health intervention**

1. Development of hypothesis and formulation of research question
2. Setting the primary and secondary objectives
3. Using the existing research to define the population and setting up inclusion and exclusion criteria
4. Defining outcomes and determining the primary and secondary outcome measures
5. Propose sample size ,assumptions and power analysis
6. Define the interventions and propose frequency , duration and intensity
7. Plan recruitment rate and feasibility and estimate recruitment and retention rates to devise a strategy for the trial
8. Plan Randomisation methodology
9. Plan statistical analyses
- 10.Propose timetable
- 11.Study governance arrangements
- 12.Data management

### **1.10 Summary**

In summary of the above discussions we have identified that memory impairment usually developing in the later life has a huge impact on the sufferer's life as well as the lives of those who care for them. With the aging demographics in the world there needed to be increased attempts to develop interventions focusing on improving the quality of lives of those people suffering from memory impairment and their carers. However there is huge gap in the research in developing and evaluating interventions focusing on improving the quality of life of people suffering from memory impairment

and this may be due to a variety of reasons including the lack of theoretical knowledge in the this field, difficulties in developing interventions which may be of complex nature , and lack of understanding about the challenges in conducting trials in this population. We proposed a research study to address the above issues adopting the MRC framework to test the feasibility of developing a psychotherapeutic intervention for people suffer from Mild Cognitive Impairment (MCI) and their partners, and evaluating it in an actual trial setting through modelling of a Randomized Control Trial. In addition to this we aim to study the challenges in understanding the theoretical base of the effectiveness of complex interventions by developing a neuro –imaging intervention before and after the therapeutic intervention in the treatment and control groups. We have developed a protocol to set the feasibility outcomes for our study and the primary aim of this study is to understand the feasibility of developing and evaluating complex psychological interventions in older people suffering memory problems and understanding the challenges in applying complex diagnostic interventions as a part of the research study. The primary aim does not include testing the therapeutic effect as the reporting of the study was agreed as more narrative methods rather than a quantitative outcome measurement.

## **Chapter 2; Literature review**

### **2.1 Introduction**

A literature review was carried out as a part of modelling process to generate sufficient theoretical background. Also it was conducted as a part of the principal investigator's educational qualification (MPhil) for which the research study was used.

### **2.1 Mild cognitive impairment**

Mild cognitive impairment [MCI] has been a concept viewed from multiple perspectives since the introduction of the term a decade ago. It has been somewhat controversial and was regarded as a form of incipient dementia or a risk state of dementia by many clinicians and researchers. However it was also argued that MCI could be a variant of normal aging. Numerous studies and conferences attempted to give the clinical entity a syndrome definition with a sub-classification mainly based on the neuropsychological concept of amnesic and nonamnesic presentations. However difficulties remain in defining the boundaries between normal ageing and mild cognitive impairment and between mild cognitive impairment and mild dementia.

In the first epidemiologic studies of dementia many people were observed to be in a group between those who were clearly fitting into to the cognitively normal group or the dementia group (Kay et al 1964). In follow-up studies it was found that a substantial proportion of people from this group progressed to dementia over several years while others continued to have a stable cognitive impairment. Several other studies confirmed this observation later leading to efforts to understand this group better. Many terms were used to describe people whose cognitive functions are in the range between 'normal for age and education' and dementia. Initially several terms like 'benign senescent forgetfulness, 'age associated memory impairment' etc was used to describe this condition.

However it was understood soon that many of these terms were inadequate to define the transitional state between normal aging and dementia (Rosenberg et al 2006).

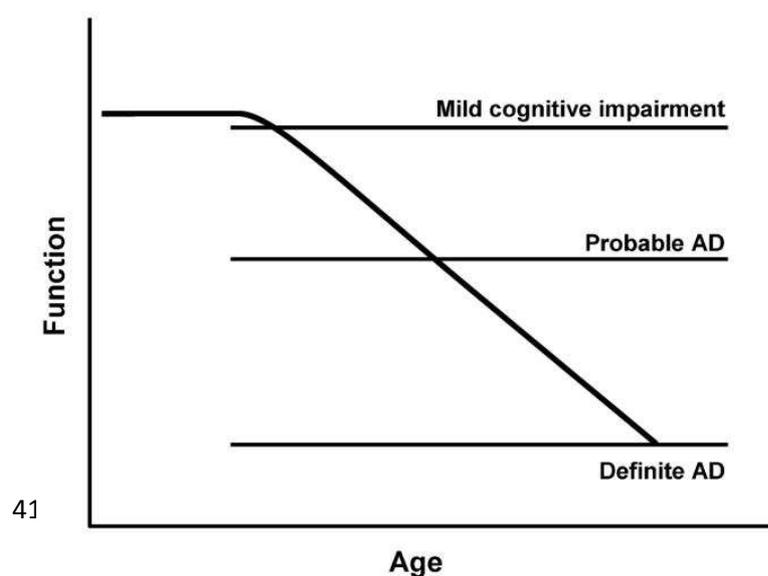
Two decades ago staging systems were published, to assess the boundaries of ageing and dementia. These are the clinical dementia rating (CDR) and the global deterioration scale for ageing and dementia (GDS) (Hughes et al 1982; Reisberg et al 1982). The term mild cognitive impairment was first used in association with stage 3 of the GDS. Although it was argued that the above instruments are rating scales rather than diagnostic tools (Petersen 1999), both scales were helpful in subdividing people to an in-between group whose impairment is regarded as cognitive impairment not amounting to dementia. The concept of age related memory loss was separated from a prodromal manifestation of Alzheimer's disease or other dementias presenting with cognitive symptoms as the first clinical manifestations. The group thought to be in the prodromal stages of Alzheimer's disease was said to have mild cognitive impairment and the term vascular cognitive impairment has been proposed to refer to the prodromal stage of vascular dementia (Gauthier et al 2004, Rosenberg et al 2006) .

An Expert Conference convened by the International Psychogeriatric Association in Bethesda, MD, USA, Jan 21–23, 2005, with the objective of clarifying the diagnosis and management of mild cognitive impairment stated ‘Mild cognitive impairment (MCI) is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life’. It is, thus, distinct from dementia, in which cognitive deficits are more severe and widespread and have a substantial effect on daily function (Gauthier et al 2006).

Mild cognitive impairment with predominant amnesic presentation is observed to have a high risk of progression to dementia particularly Alzheimer's disease. With rapidly aging population globally, the high prevalence of MCI has profound implications especially in the context of a high potential for conversion to a dementia syndrome. (Petersen et al 2001, Grundman et al 2004, Geslani et al 2005) With the emergence of pharmacological and psychosocial interventions for Alzheimer's disease MCI has generated a substantial interest from both clinical and research perspectives. Because of the variety of contributory factors, lack of clear understanding of pathophysiological mechanisms a level of uncertainty is always associated with the diagnosis and management of MCI and the previous research findings indicated the need for methodologically sound research projects with scrupulous use of neuropsychometric assessment tools, cutting edge imaging technology and newer modalities of therapeutic interventions

## Figure 2

*Theoretical progression of cognitive function from normal through mild cognitive impairment to probable and definite Alzheimer's disease (AD) in persons destined to develop AD. Ref – Kelly & Petersen, Neurologic clinics Volume 25, Issue 3, Pages 577-609 (August 2007)*



### **2.1.2 Epidemiology and clinical presentation**

Prevalence in epidemiological studies generally ranges from 3% to 19% in adults older than 65 years. A wide variation is reported in the prevalence and some estimates rise to over 30% [Busse et al 2006]. Currently, attempts are being made to broaden the definition of mild cognitive impairment to include non-memory deficits and impairment in several cognitive domains, with causal mechanisms including degenerative, vascular, and psychiatric factors. When a broader definition is used studies estimated a prevalence of MCI ranging from 3% to 53%. More robust estimates based on population-based samples give a prevalence of 19% among persons over 75 years of age. Incidence rates of MCI are reported at 1 to 1.5% annually in the similar age group. Depressive symptoms, increasing age and decreased educational level were reported as risk factors (Panza et al 2005, Lopez et al 2003, and Barnes et al 2006).

Some people with mild cognitive impairment seem to remain stable or return to normal over time, but more than half progress to dementia within 5 years. Mild cognitive impairment (MCI) can thus be regarded as a risk state for dementia, and its identification could lead to secondary prevention by controlling risk factors such as systolic hypertension. Mild cognitive impairment (MCI) is also described as a transition phase between healthy cognitive ageing and dementia. Although this notion seems to be reasonable, the general nature of the term MCI—including its many definitions—makes accurate accounting of the prevalence, prognosis, and potential benefit from treatment somewhat difficult (Gauthier et al 2006).

The differences in cognitive profile and clinical progression among individuals with MCI are generally recognised. However, recent evidence also suggests that the aetiological heterogeneity among individuals with MCI could be greater than previously reported. For example, cerebrovascular disease seems to be

underestimated as a potential cause of MCI (DeCarli 2003). Clinical subtypes of MCI have been proposed to broaden the concept and include prodromal forms of a variety of dementias (Petersen et al 2008). The amnesic subtype of MCI has a high risk of progression to Alzheimer's disease, and it could constitute a prodromal stage of this disorder. Other definitions and subtypes of mild cognitive impairment need to be studied as potential prodromes of Alzheimer's disease (AD) and other types of dementia (Gauthier et al 2006). In addition to presentations featuring memory impairment, symptoms in other cognitive domains (eg, executive function, language, visuospatial) have been identified. Neuropsychological testing can be extremely useful in making the MCI diagnosis and tracking the evolution of cognitive symptoms over time. Careful assessment can identify subtle deficits that may otherwise elude detection, particularly in individuals of superior baseline intellectual ability. As we move closer to disease-modifying therapy for AD, early identification becomes critical for identifying patients who have an opportunity to benefit from treatment (Nelson et al 2008).

### **2.1.3 Criteria and subtypes**

MCI patients are classified as amnesic (aMCI) if they have a prominent memory impairment, either alone or with other cognitive impairments (multiple domains with amnesia), or nonamnesic (naMCI) if a single nonmemory domain is impaired alone or in combination with other nonmemory deficits such as multiple domains without amnesia (Rozzini et al 2007).

Isolated memory impairment may be fairly uncommon in clinically diagnosed amnesic MCI patients, even when the criteria for amnesic MCI are fairly narrow. Additional cognitive impairments are likely to include fluency and executive functioning. These more diffuse deficits argue for comprehensive cognitive assessments, even when the patient and family are reporting only

memory decline, and are consistent with the increase in attention paid to the heterogeneity of MCI (Kramer et al 2006)

**Table 2 . Criteria for amnesic MCI; Panel - An Expert Conference convened by the International Psychogeriatric Association in Bethesda, MD, USA, Jan 21–23, 2005. Reproduced from Gauthier et al 2006**

Amnesic type of MCI
Memory complaint preferably corroborated by an informant
Memory impairment relative to age amthed and education matched healthy people
Typical general cognitive function
Largely intact activities of daily living
Not clinically demented

An international working group on mild cognitive impairment formulated specific recommendations for criteria, including: (1) the individual is neither normal nor demented; (2) there is evidence of cognitive deterioration, shown by either objectively measured decline over time or subjective report of decline by self or informant in conjunction with objective cognitive deficits; and (3) activities of daily life are preserved and complex instrumental functions are either intact or minimally impaired. These criteria serve to expand the construct of mild cognitive impairment to involve cognitive domains other than memory and make it a prodrome to multiple types of dementia (Winblad et al 2004).

**Figure 3.** Reproduced from Gauthier et al 2006

		Cause			
		Degenerative	Vascular	Psychiatric	Medical disorders
Amnestic mild cognitive impairment	Single domain	Alzheimer's disease		Depression	
	Multiple domain	Alzheimer's disease	Vascular dementia	Depression	
-----					
Non-amnestic mild cognitive impairment	Single domain	Frontotemporal dementia			
	Multiple domain	Dementia with Lewy bodies	Vascular dementia		

**Figure:** Outline of the syndrome of mild cognitive impairment  
 Figure shows mild cognitive impairment with predominantly amnestic versus non-amnestic neuropsychological features, potential prodrome to neurodegenerative disorders such as Alzheimer's disease, frontotemporal dementia, Lewy body disease, or caused by vascular cognitive impairment, psychiatric disorders such as depression, or as a prodrome to other medical disorders, including metabolic and nutritional deficiencies, upper airway obstruction, and head trauma. Figure adapted from reference 35.

### 2.1.4 Pathophysiology

A cholinergic mechanism is thought to be central to the pathophysiology of Amnestic MCI and the neuropathological mechanisms are summarised on table 3. Cerebrovascular involvement in MCI is observed to be intermediate between that seen in ageing and early Alzheimer's disease. Both cerebrovascular disease and neurodegenerative features were shown to contribute to mild cognitive impairment. The importance of white-matter lesions and small lacunar infarcts is becoming increasingly apparent in vascular cognitive impairment. Cerebrovascular disease is frequent in elderly individuals, and treatment of cerebrovascular risk factors constitutes one of the most important prevention strategies for Alzheimer's disease and vascular dementia.

The role of amyloid deposition and neurofibrillary tangle formation in mild cognitive impairment has not yet been studied extensively. Pathological findings of neurofibrillary tangles in the mesial temporal structures do correlate with mild cognitive impairment. Compared with people with dementia and those without cognitive impairment, individuals with mild cognitive impairment have intermediate amounts of Alzheimer’s disease pathological findings with amyloid deposition and tau-positive tangles in the mesial temporal lobes. Mutations in apolipoprotein E alleles clearly raise the risk of progression from amnesic mild cognitive impairment to Alzheimer’s disease (DeKosky 2002, Sperling 2005, Bennett 2005, O’Brien 2003, Galluzi 2005).

***Table 3 Neuropathological findings in MCI***

A central cholinergic deficit
Loss of neurons in the nucleus basalis of Meynert
Upregulation of choline acetyl transferase activity in the frontal cortex and hippocampus.
White-matter lesions and cerebral infarctions
Extracellular amyloid deposition
Intracellular neurofibrillary tangle formation

### **2.1.5 Cognitive and psychological symptoms**

Although cognitive symptoms have been the core features of mild cognitive impairment up to now, it is increasingly recognised that, there is a high prevalence of other neuropsychiatric symptoms including anxiety, depression, irritability and apathy. In a preliminary study to define the neuropsychiatric features of the amnesic-type MCI and compare them with those of mild AD and normal controls, it was shown that MCI patients frequently manifested

neuropsychiatric symptoms. The most common symptoms in the MCI group were dysphoria (39%), apathy (39%), irritability (29%), and anxiety (25%). There were significant differences in apathy, dysphoria, irritability, anxiety, agitation, and aberrant motor behaviour between the MCI and control groups; in contrast, only delusions were significantly less common in MCI compared with mild AD. Psychotic symptoms were significantly more common in the early stage of AD than in MCI. These results were derived from a limited clinical sample and require confirmation in longitudinal community-based investigations (Hawang et al 2004).

In another study (Lyketsos et al 2002) based on ratings on the NPI in the previous month and from the onset of cognitive symptoms, MCI participants were identified to have several psychiatric symptoms, the most common being depression (20%), apathy (15%), and irritability (15%). Frank et al 2006 conducted structured focus group discussions with MCI patients, AD patients, MCI informants, and AD informants to identify key aspects of the impact of cognitive impairment on patients with mild cognitive impairment (MCI) and mild probable Alzheimer disease (AD) and their informants. Seven key themes emerged were uncertainty of diagnosis, skill loss, and change in social and family roles, embarrassment and shame, emotionality, insight, and burden. Patients were able to discuss the impact of cognitive impairment on their lives and reported frustration with recognized memory problems, diminished self-confidence, fear of embarrassment, concerns about changing family roles due to cognitive impairment, and anxiety.

### **2.1.6 Diagnosis**

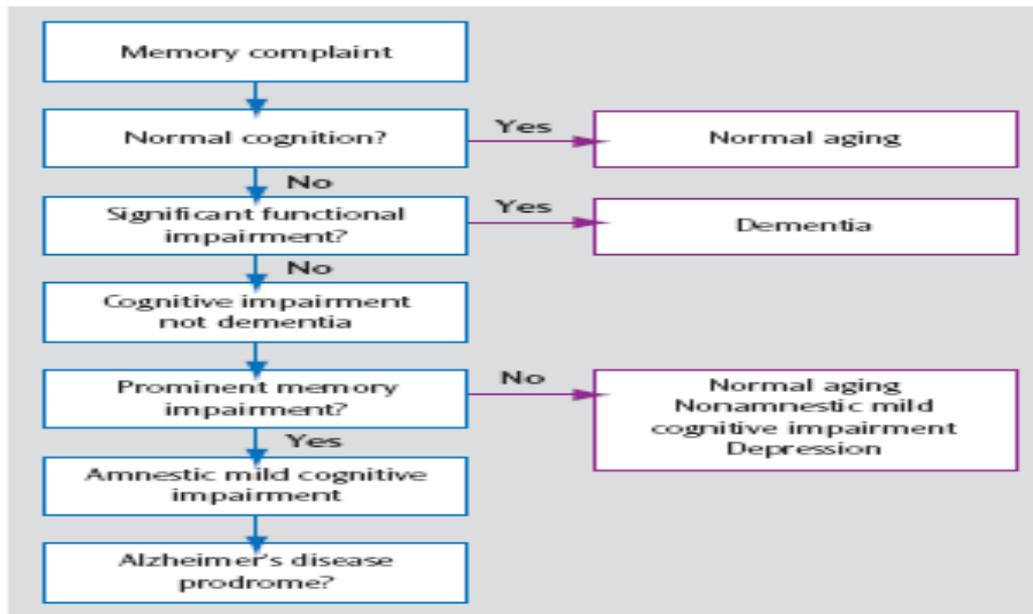
In spite of availability of consensus statements and operational diagnostic criteria for amnesic MCI, difficulties exist in determining a clear demarcation between normal aging and MCI as well as between MCI and mild dementia.

Many of the determinants of this division are linked to the impairment in the level of patient's everyday functioning. Many studies reported existence of minor difficulties in complex activities, financial handling and new learning with increased complexity in subjects with MCI commonly 2-3 years before progression to a dementia syndrome.

However noticeable difficulties in use of the telephone, management of finances, transportation, and management of medication suggest onset of dementia. The lack of awareness of such impairments in people with mild cognitive impairment has been postulated to be predictive of progression to dementia. Individuals with memory complaints and informants should be asked about performance on hobbies, executive level tasks, and instrumental activities of daily life. Informants reported more symptoms and more impairment than did patients and indicated increased dependence on others among patients.

A structured assessment of functional capacities will become increasingly important in determining the point at which people with mild cognitive impairment progress to dementia. However an accurate estimation of patients social and occupational functioning is usually within the realm of an experienced clinician. Neuropsychological tests are helpful but diagnostic of MCI. Usually a variety of cognitive domains tested including delayed recall, semantic fluency, attention, visuo-constructional function, and executive function. A complete metabolic and haematological workup and brain imaging can also aid an accurate diagnostic process. Neuroimaging and electrophysiological tests for the workup of mild cognitive impairment could be the same as those used in early dementia. (Nygard 2003, Franssen et al 1999, Galasko et al 2005).

**Fig 4 . Flowchart for differential diagnosis for MCI-Reproduced from Rosenberg et al A Clinical Approach to Mild Cognitive Impairment Am J Psychiatry, Nov 2006; 163: 1884 - 1890.**



### 2.1.7 Clinical management

There are no pharmacological interventions currently available to prevent cognitive decline or progression from MCI to dementia; however there are symptomatic and preventative therapies that the clinician can consider applying. It was observed that treatment might be symptomatic because of the individual's concerns over memory loss in MCI. Treatment of symptoms must be differentiated from treatment to prevent progression to dementia. It was also argued that treatment of MCI might prevent development of cognitive decline and dementia that often comes with aging. Another valid reason for treating MCI is that it could be the initial presentation of AD (Chertkow 2007).

Cholinesterase inhibitors, Ginkgo biloba, Dietary supplements,, antioxidants, anti-inflammatory agents have been used in MCI, however none of these usually make a significant clinical impact on MCI. The first wave of clinical trials aimed at symptomatic drug treatment for amnestic mild cognitive

impairment over 6 months to 3 years has been largely unsuccessful (Gauthier et al 2004). Results from the Memory Impairment Study showed no significant differences in the probability of progression from amnesic mild cognitive impairment to Alzheimer's disease in patients allocated vitamin E or donepezil, compared with placebo, during the 3 years of treatment, although significant differences were recorded favouring the donepezil group on various measures during the first 12 months of the study including delay of diagnosis of Alzheimer's disease (Petersen RC et al 2005). The management of patients with mild cognitive impairment is currently non-specific control of vascular risk factors; treatment of concomitant disorders such as depression and hypothyroidism; and phasing out anticholinergic drugs. Many people with mild cognitive impairment are very aware of their difficulties and seek information about the nature of their disorder and their outlook. They are also interested in coping strategies, particularly if they are in demanding occupational settings.

Since these patients are at higher risk of dementia and death than usual, they need sensitive counselling about such risks and the current lack of certainty in predicting prognosis. It would not be appropriate to falsely reassure them that they are healthy, since they should have the opportunity to make future plans while fully competent to do so, including advance directives for power of attorney in case of incapacity. A caregiver burden has already been identified for spouses of people with mild cognitive impairment, for which selective preventive interventions to keep psychological wellbeing to a maximum should be considered (Garand 2005). The finding of this research is discussed in detail in the following section.

### **2.1.8. Carer burden in Dementia and MCI**

While the stressors or burden associated with dementia care giving are well-established (Chappell and Penning, 1996; Donaldson and Burns, 1999; Burns and Rabins, 2000).

In a pioneer work it was identified that specific problem behaviours related to the distress experienced by informal caregivers of people suffering from dementia (Chappell and Penning 1996). Using a random sample of distress is measured in terms of both depression and caregiver burden. The findings revealed that specific behaviours on the part of the care receiver were strong correlates of the distress experienced by caregivers. Aimlessness and aggressive behaviours, forgetfulness, and restlessness were correlated with heightened feelings of burden. Apathy or a lack of interest in daily activities was also strongly correlated with both feelings of burden and depression.

It was also observed that caregivers' own characteristics may play a major role in determining how burdensome and stressful they find their role (Donaldson and Burns 1999). These characteristics include such things as gender, availability of support systems, and relationship to patient, as well as the way the caregiver perceives the patient's symptoms (whether illness related or deliberate) and his or her attitude and behaviour toward the patient.

Understanding the origins of caregiver burden has broad implications both in terms of the well-being of caregivers and the quality of support that patients receive.

It was also established that caring for patients with dementia is associated with physical and psychiatric morbidity (Burns and Rabins, 2000). They observed that caregiver interventions can be effective and work is needed to confirm their efficacy when combined with the pharmacological interventions for patients with Alzheimer's disease. The care giving role changes with time, starting with initial adjustment to the diagnosis, help with relatively complex tasks, through the toleration of abnormal behaviours and psychiatric disturbances to helping with the more fundamental activities of daily living. The ultimate aim of intervention is to maintain people as independent as they can be for as long as is possible.

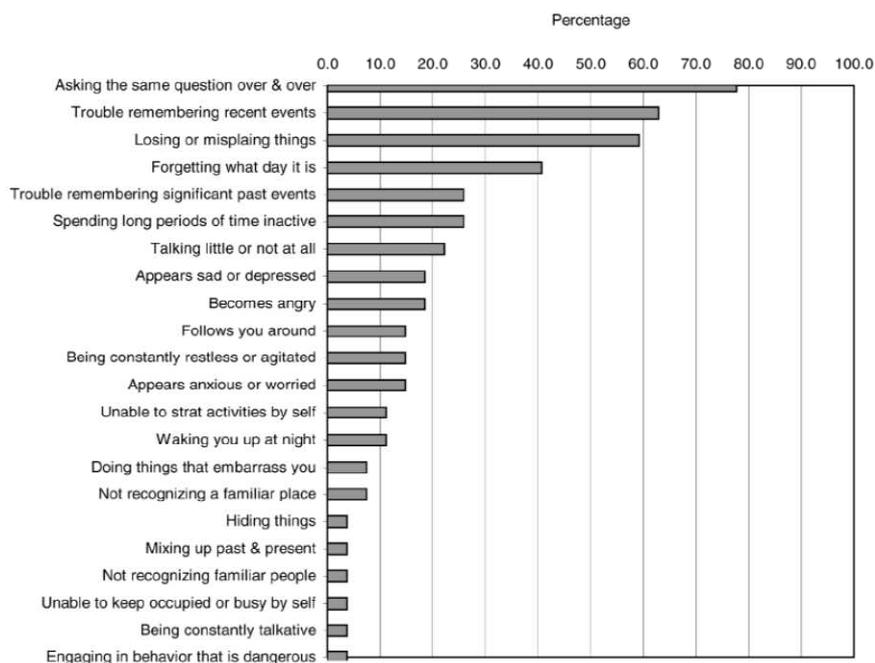
A cross-sectional, descriptive correlational study on spousal caregivers of individuals diagnosed with MCI including spouses or non-married cohabitating partners of the person with MCI, live with the MCI patient in a community (non-institutional and non-assisted) setting reported that little was known about the range of stressors inherent in living with or providing care to a spouse with mild cognitive impairment (Garand et al 2005). Yet, empirical identification of key MCI caregiver stressors is important because the population of elderly individuals with MCI is growing, in part, due to better diagnostic tools for this condition. They observed that Information regarding the burden and the potential mental health impact on spousal caregivers of MCI patients will be helpful to understand if these outcomes were distinct from those observed in spouses of persons with dementia syndromes such as Alzheimer's disease. They suggested that unique aspects of an MCI diagnosis that may provoke distress and perceptions of burden include the prognostic uncertainty of the diagnosis and the caregiver's need to anticipate their spouse's future care needs, ensure the health and safety of their spouse in light of their mild cognitive deficits, and provide emotional support to their spouse. Individuals who may have long provided daily support and advice to their spouse may experience significant emotional upheaval as their 'normal' care for the individual evolves to that required in the face of increasing cognitive limitations.

The above study reported a 13 month period the assessment of 27 patients and their care givers, gathering the data in a structured interview format in the subject's home or other convenient location. Three measures assessed as elements of the care-givers' objective tasks and responsibilities, were care giver responsibilities, life style constrains ,and MCI behavioural stressors . Two measures were used to assess elements of the respondents' burden associated with the samples' new care-giving responsibilities including Subjective

caregiver burden and Burden associated with MCI-related behaviours. To detect psychiatric morbidity symptoms of depression and anxiety were also measured.

The results of this study suggested that even at early stages of cognitive impairment, husbands and wives assume the role of family caregiver and experience caregiver burden and psychiatric morbidity is also associated with the role. The areas of care giving responsibilities included household tasks and some nursing tasks (primarily regarding medications). It was observed that many of these responsibilities were new suggesting that the tasks may have been directly related to the onset of MCI in their spouse. A variety of lifestyle constraints were also reported that the care givers attributed to the cognitive changes in their spouse, and they reported the onset of a variety of behaviours in their spouse that represented changes in functioning [Figure 5]. These changes were distressing, although respondents' subjective perceptions of feeling burdened remained generally low.

**Figure 5. Behaviours in patients with MCI that represented changes in functioning.** Reproduced from Garand et al 2005



The above observations confirms that even in the stage of MCI certain behaviours were already prevalent and were sources of concern, including asking the same question repeatedly, difficulty remembering recent events, and losing or misplacing things. Measures of caregiver burden were significantly associated with depression and anxiety symptoms in this sample.

This research concludes that the care givers for people with MCI may be ideal targets for selective preventive interventions to reduce the psychiatric morbidity that is so commonly observed in individuals with dementia care giving responsibilities. These interventions could be specifically designed to strengthen intrapersonal skills and resources in order to prevent the worsening of psychiatric symptoms as some of these caregivers progress to become dementia caregivers.

## **2.2 Psychotherapy for cognitive impairment**

### **2.2.1 Approaches to psychotherapy**

There are relatively few studies, which have evaluated the benefits of psychotherapy for elderly people with Mild Cognitive Impairment. There is good evidence that interventions for carers of people with Alzheimer's disease (AD) can reduce stress (Mittleman et al 1996; Donaldson et al 1997). Research on psychotherapeutic interventions directed at those with MCI is limited, although most findings suggest that psychotherapy may be beneficial in the early stages of dementia (Brierly et al 2003, Burns et al 2005). Encouraging results have been reported from uncontrolled studies using cognitive training. Large effect sizes have been noted within the range for healthy elderly people, and better than that for patients with Alzheimer's disease. The success of cognitive training seems to be dependent on the level of severity across the range of normal ageing to dementia. These findings in individuals with mild

cognitive impairment need to be confirmed in randomized controlled trials. A recent randomized controlled trial examined the cost effectiveness of a programme of cognitive stimulation therapy for people with dementia (Knapp et al, 2006). The authors found that it was of greater benefit, and might prove to be more cost-effective, than treatment as usual.

A decade ago the American Psychiatric Association (1997) produced practice guidelines for the treatment of dementia. These acknowledged that some clinicians find supportive psychotherapy useful in helping people with mild memory impairment to adjust to their illness, although there had been little research into its effectiveness. Supportive psychotherapy remains widely practiced but seldom studied. A 6 month follow-up study to measure changes in interpersonal functioning following brief supportive psychotherapy (Rosenthal et al. 1999) in an adult psychiatric population provided preliminary experimental evidence for significant and lasting improvement in interpersonal problems after the intervention. In a comparison of supportive psychotherapy and cognitive-behavioural therapy the latter improved symptoms of anxiety in older adults at baseline and 12 month follow-up, but there was no difference in functional ability (Barrowclough *et al*, 2001).

Cheston *et al* (2003) evaluated six 10 week psychotherapy groups for people with dementia and found significant improvement in scores for depression and marginal benefits in anxiety symptoms which were maintained at follow-up.

Fossey and colleagues (2006) went a step further, demonstrating that enhanced psychosocial care can reduce antipsychotic use in care home residents with dementia without worsening behavioural symptoms.

Interpersonal therapy, as the name suggests, examines the individual's distress within an interpersonal context (Weissman et al, 2000). In this sense, there is a great deal of overlap with the person-centred work of Kitwood (1997) and Stokes (2000). It uses a specific framework in which the individual's distress is

conceptualised through one of four domains: interpersonal disputes; interpersonal/personality difficulties; bereavement; and transitions/life events. Despite there being good empirical evidence of the success of this form of treatment with older people (Miller & Reynolds, 2002), it has only recently been used with dementia (James et al, 2003).

Over the past 10 years there has been an increasing interest in applying some of the brief therapeutic frameworks such as cognitive-behavioural therapy (CBT) and interpersonal therapy to dementia. For example, Teri & Gallagher-Thompson (1991) reported positive findings from a clinical trial of CBT with people in the early stages of Alzheimer's disease. Individual and group CBT has also been used by other researchers with some favourable results (Kipling et al, 1999).

### **2.2.2 Reaching the person behind the cognitive impairment**

An important component of cognitive process is language and hence a reduction in language capacity is seemed as an accompaniment to cognitive impairment regardless of its aetiology. Language is regarded as multidimensional in psychotherapeutic process which exists in both cognitive and affective domains. It is not uncommon that family members and friends become detached from the persons with cognitive impairment who have a reduction in their language capacity. Frequently the people with cognitive impairment also tend to choose to be isolated in social situations especially in the context of preserved night into the person's own cognitive, language and emotional barriers. The person with memory impairment and close family members especially spouses go through an intensely emotional bereavement like reaction as the memory impairment is perceived as loss event. In advanced stages of memory impairment like dementias, the emotional detachment may result in emotional abandonment of the person with the cognitive impairment. When this occurs in

patients who are able to connect well with their environment, occurrence of depressive and anxiety symptoms are common (Duffy 1999) .

All loss events generally require a process of grieving, however adjusting to loss in the later life can be a prolonged process, which may result in withdrawal from social activities and emotional situations leading to social and emotional abandonment. Development of cognitive impairment may hasten such a process, as it is a major threat for already compromised developmental issues in late life including independence, body image, sexuality and intimacy. In psychotherapeutic process for an older person with cognitive impairment, a true therapeutic relationship and empathy may only be achieved through an intimate, phenomenological connection with the person's feelings and experiences of surrounding world. While maintaining the objectivity and therapeutic goals an experienced therapist stays within the person's emotional world.

Attention to sub-vocal signals and paralinguistic cues can be important as verbal cues, however identification of a mutually comfortable language early on is the key to the establishment of a therapeutic relationship. While staying within the person's emotional world, significant affective themes existing in the person's inner-world can be traced. Identification of these central themes with significant affective component is an important goal of all psychotherapeutic approaches as it is invariably linked to the conflicts leading to affective and anxiety symptoms in cognitive impairment.

### **2.2.3 Addressing the emotional component**

Several MCI patients express concern about developing AD. MCI informants corroborated this uncertainty over diagnosis. The MCI patients usually recognise that their current level of functioning is significantly worse than before. Many patients described frustration at not being able to do things as they used to. Reading, visiting friends (due to fear of getting lost and fear of not

following conversations), hobbies, and work activities often suffered. Common experiences reported include role change within the family. Some patients attribute their depression to their changing role in life, commonly within their family. MCI patients report more embarrassment about symptoms than patients with AD, and describe more effort in hiding symptoms from others. Many patients feel limited in what they could now manage, partly through fear of getting it wrong.

Several MCI informants describe their concern about changes in normal behaviour and the anger displayed by patients, especially in front of children or grandchildren. Both patients and informants commonly express concern relating to level of burden. Patients may have fear of becoming a burden on family, friends and co-workers. Carers may admit substantial burden associated with interacting with the patient. Frank et al (2006, 2011) studied key aspects of the impact of cognitive impairment on patients with mild cognitive impairment (MCI) and mild probable Alzheimer disease (AD) and their informants, and identify overlap and differences between the groups. Strong emergent themes in patient groups with MCI include frustration with memory problems, diminished self-confidence, fear of embarrassment, concern regarding changing family roles due to cognitive impairment, and anxiety related to uncertainty of prognosis. The main findings from informant groups were discrepancies between patient and informant views of symptoms, with informants seeing patients as more impaired than patients self-report indicated, and reporting increased patient dependence on others.

This study also observed that the patients with MCI were able to engage in-group discussions. They were often able to recall events and relate anecdotes regarding their illness. They usually recognized their problems and the concerns of their family, yet some admitted to not telling friends or family to avoid

embarrassment. Despite this general level of insight, many patients underestimate their impairments relative to informant report.

A cohort study observed that, although caregiver burden and psychiatric morbidity levels were lower than those typically observed in family dementia care giving samples, MCI caregivers have already begun to experience distress in association with elevated care giving burden. The study recommended that these individuals might be the ideal targets for selective preventive interventions to maximise their psychological well being as care-giving burdens related to their spouse's cognitive impairment increase (Garant et al 2005).

#### **2.2.4 Psychodynamic interpersonal therapy**

The principles of the psychotherapy model used in the study are theoretically derived from psychodynamic interpersonal therapy adapted to suit the needs of people with MCI and their carers. Whilst incorporating the main principles of the model as described below, we have focused on specific needs of our population as well as the re-development of the model in a couple therapy form, which is described in section 2.2.5. The principles of the model, draws upon humanistic and interpersonal concepts. In the original conversational model of therapy by Hobson, the main task of the therapist is to develop with the patient 'a mutual feeling language' and a relationship of 'aleness-togetherness' (Hobson 1985). This means the creation of a conversation which is associative, intimate, dependent upon a non linear psychic state, shared by both partners, and allowing free movement and exchange of ideas and feelings. In a shared relationship, individuals move fluidly between a feeling of aleness and togetherness. The principal aim of the therapy (in its brief format) is the identification of interpersonal conflicts or difficulties, which are causing or maintaining emotional distress. Client and therapist work together to find and test solutions to these problems, and both intrapsychic and practical changes are

encouraged (Guthrie 1999).in our model the patient, the carer and the therapist worked together to develop solutions of specific problems identified in the therapy setting.

The main components of the model are given in box 4

#### **Box 4 . The main components of the model**

##### **Exploratory rationale**

Identification of interpersonal difficulties

Provide a rationale for the patient

Linking emotional and cognitive symptoms to interpersonal difficulties or dilemmas

Construction of an interpersonal formulation

##### **Shared Understanding**

Uses statements rather than questions.

Identification of a language of mutuality

Adopting a negotiating style

Use of metaphor

Understanding hypotheses

##### **Staying with feelings**

Focus on here and now

##### **Focus on difficult feelings**

Address the issue of hidden feelings

##### **Gaining insight**

Linking hypotheses

Explanatory hypotheses

##### **Sequencing of interventions**

##### **Making changes**

Psychodynamic interpersonal therapy can be used for either brief or long-term work. When brief psychotherapy is being conducted, it is particularly important that a secure structure is established from the beginning.

### **2.2. 5 Adaptation of the model**

It was necessary to adapt the model in view of patient's and their carer's physical frailty and also the patient's cognitive impairment. The main adaptations of the therapy were under the following domains: home-based treatment; carer involvement; helping people come to terms with AD; using autobiographical narrative and introjection to strengthen self worth; resolution of past conflicts; exploring denial: and improving social relationships. The therapy sessions were carried out at the patient's home, which had the advantage of gaining an accurate picture of patient's level of functioning. In addition to the individual therapy, the therapist spent 10 min each session with the carer, listening to the carer's needs and informing the carer of therapeutic progress. To help people come to terms with AD, the patients were informed of their diagnosis. The therapist gently enquired about the difficulties with memory loss, and then explored their fears. People are allowed to express their feelings in their own pace. The model placed great emphasis on 'staying with feelings' and bringing feelings to 'here and now' to be shared with the therapist. Strengthening the self-worth in these patients, using autobiographical narrative and introjection was an important therapeutic function. Patients were encouraged to recall and focus on the qualities they had shown in their lives that were self specific and revealed character of strength and humanity. The focus of therapy also involved the resolution of past conflicts, sometimes dating back to their childhood. The task of therapy was to help the patients link past and present, and then to explore ways of managing the present in an adaptive and creative manner. For a small number of patients, who were unable to accept

their illness and denied its existence, therapy focused on exploring the denial, without challenging their beliefs in any way (Brierley et al 2003).

In its brief format PIT included strategies to improve social relationships. Practical changes were regarded as being very important, particularly if they enhanced or improved the patient's interpersonal relationships with family and friends. The interpersonal relationship between patient and therapist was used in improving patient's interpersonal contacts outside the therapy setting. One of the aims of therapy was to help the AD sufferer to get as much satisfaction and enjoyment out of life as possible. The model also encouraged statements about not needing to protect or please the therapist and emphasized the non conditional nature of the regard of the therapist.

With the above mentioned adapted model Burns et al conducted a randomised control of brief psychotherapy in patients with Alzheimer's disease. As our study is a further extension of this research, the methodology and findings are described in detail below. The study shows that it is possible to adapt a model of psychotherapy for those with AD.

### **2.2.6 Psychotherapy in Alzheimer's disease –RCT**

Burns et al 2005, assessed in a randomised control trial, whether a psychotherapeutic approach directed towards individuals with AD could benefit cognitive function, affective symptoms and global well-being. The same group of investigators (Brierly et al 2003) conducted a pilot study to evaluate the potential benefits of brief psychodynamic interpersonal therapy (PIT).

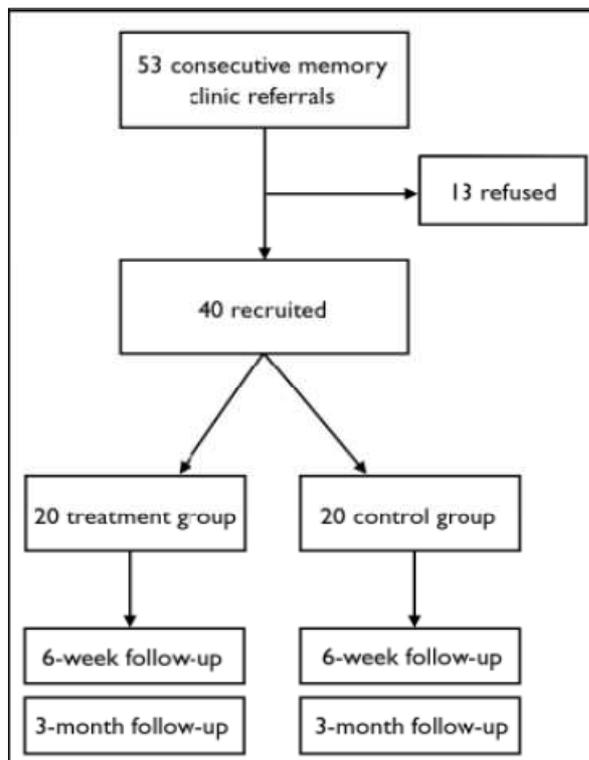
Psychodynamic interpersonal therapy has been used as brief treatment for a variety of disorders including: depression (Shapiro & Firth, 1987; Shapiro et al, 1993), somatisation (Guthrie et al, 1991; Hamilton et al, 2000) and self-harm (Guthrie et al, 2001). It was felt that brief psychodynamic interpersonal therapy may be helpful in the patient group with early AD, as it places particular

emphasis on working with feelings and the therapeutic relationship, rather than cognitive work, which may be difficult for these patients. The model of therapy used and its adaptation for patients with AD are described below.

### 2.2.6.1 Subjects and methods

For the randomised control trial of comparing psychodynamic interpersonal therapy with standard treatment in people with AD, the patients and cares were recruited from referrals to the memory clinic in South Manchester, UK. People living in their own home with a diagnosis of AD according to NINCDS-ADRDA criteria, with the clinical dementia rating of 1, indicating mild dementia and MMSE score of 15 or above were included. A carer in regular contact and the ability to communicate verbally were also requirements. The patients were allocated to one of two groups-treatments or control-using computer generated random numbers.

**Fig. 5 Design of the trial of brief psychotherapy in Alzheimer's disease**



[Figure reproduced from Burns, A., Guthrie, E., Marino-Francis, F., *et al* (2005) Brief psychotherapy in Alzheimer's disease. Randomised controlled trial. *British Journal of Psychiatry*, 187, 143 –147].

#### **2.2.6.2 Therapeutic interventions**

Those in the treatment group received six sessions of psychodynamic interpersonal therapy with an experienced psychotherapist. Those in the control group received standard care, which consisted of general advice regarding the diagnosis and treatment of dementia, with out-patient review. Psychotherapy sessions lasted 50 min. One session from each individual therapy was rated for adherence to the model using the Sheffield Psychotherapy Rating Scale (Shapiro & Startup, 1993). The intervention showed high scores on the psychodynamic interpersonal therapy and generic sub-scales and low scores on the cognitive-behavioural therapy scale, confirming adherence to the model.

#### **2.2.6.3 Assessments**

Independent assessments were carried out at baseline, and after 6 weeks and 3 months. Assessments of patients were done using Cornell Scale for Depression in Dementia, Mini-Mental State Examination, Revised Memory and Behaviour Problems Checklist and Bristol Activities of Daily Living Scale. In addition to assessments of carers using General Health Questionnaire, Beck Depression Inventory and Ways of Coping Checklist, a clinicians interview based global assessment was done to detect change in the patients at 6-week and 3-month follow up.

#### **2.2.6.4 Analysis and Results**

All analyses used the intention to treat principle. Based on a power calculation for a previous study 20 individuals were recruited to each group. Most commonly it was the spouse who cared for the patient; 25% of the treatment

group and 15% of the control group were on antidepressants, and approximately two-thirds of each group were on one of the anticholinesterase drugs for AD. All participants completed the study and follow-up.

There were no significant differences over the course of the study in the outcome measures for the patients, or in the global rating for the outcome measures for the carers. There was a trend towards a slight improvement in the carer's reaction to behavioural problems. There was no difference in the ratings when the patients were divided into two groups by Mini-Mental State Examination score (above or below 24). However, there was some evidence that carers of those with less cognitive impairment (score above 24) benefited more from the treatment in that they blamed themselves less for the problems (section 3 of the Ways of Coping Checklist at 3 months, mean value 0.14 compared with 0.35,  $P=0.031$ ).

On qualitative assessments, every participant agreed with the statement 'I was able to discuss my difficulties with my counsellor and became more clear about what they are'. Eighty-three per cent agreed with the following three statements: 'I find doing things I can do and not thinking too much about what I cannot do, helps me feel less frustrated'; 'Although it sometimes felt painful talking about my past, it felt good to get things off my chest, and I felt calm'; and 'I have been able to talk about some things that have been difficult to talk to anyone else about'. Carers also commented positively about the opportunity they had, to discuss the problems as well as about the positive comments made by the patients.

The study shows that it is possible to adapt a model of psychotherapy for those with AD. No improvement was found on the majority of outcome measures in participants and their carers. However, there was a suggestion that the therapy had improved the carers' ways of coping with some of the symptoms of the

disease. The therapist's experience of working with AD patients suggests that PIT was acceptable and most but not all, were able to work in therapy. The joint sessions with the participants and carers merely helped the therapist to focus on those symptoms that were considered important and distressing. The therapists found that it was possible to explore conflicts arising from the discovery of AD in therapy, using strategies intrinsic to psychodynamic interpersonal therapy.

The finding that the intervention had no effect on measures that reflect the core features of the illness (cognitive function, activities of daily living) is not surprising. Only six sessions were provided which, in psychotherapeutic terms, is a low-dose treatment, and this may partly explain the lack of effect. In addition, a longer study would be needed to assess the more likely benefits in terms of stabilisation of disease. Previous workers have demonstrated a dose response effect with PIT, i.e. the greater the number of sessions, the greater the benefit, up to 16 sessions (Barkham et.al.1996).Further adaptation of this model has been done for our current study, incorporating the carer's needs. The model was developed as Psychodynamic Interpersonal Couple Therapy and the adaptations as well as the rationale for the development of this model are discussed below.

### **2.2.8 Family and caregivers**

Most patients with early Alzheimer's disease live in the community with support from family. High levels of psychological problems and psychiatric symptoms were reported in carers of people suffering from AD. High rates of anxiety as well as depressive symptoms in family caregivers of people with AD, especially in female caregivers was reported in one study and it was observed that Care recipient's and Caregivers' impaired physical health put them at risk for psychological morbidity. A poor-quality relationship between the caregiver and the care-recipient predicted both caregiver depression and anxiety.

Caregivers living with the care-recipient were much more likely to be anxious than depressed (Mahoney et al 2005). Estimated prevalence of depressed mood in caregivers of individuals with mild cognitive impairment (MCI) and attempts to assess whether demographics, stressors, intrapsychic strain, and gain are associated with depressed mood has shown a 25% prevalence of depression in caregivers (Yueh-Feng Lu Y et al 2007). The odds of being depressed were significantly higher in younger, nonspousal caregivers with less education, who cared for MCI patients with lower activities of daily living functioning, and who perceived greater relational deprivation, higher levels of self-loss, and personal gain. Controlling for relevant variables, relational deprivation and caregiver education continued to be significantly associated with depressed mood.

The majority of persons with Alzheimer's disease (AD) are cared for at home by a family member such as a spouse or daughter. Care giving places enormous demands on these caregivers, and the negative consequences associated with care giving are well documented. One paper reported results from the Miami site of the REACH (Resources for Enhancing Alzheimer's Caregiver Health) program that examined the efficacy of a family therapy and technology-based intervention in reducing depressive symptoms (according to the Centre for Epidemiological Studies Depression scale) among family caregivers of AD patients at 6 months and 18 months follow-up. Caregivers in the combined family therapy and technology intervention experienced a significant reduction in depressive symptoms at 6 months. The 18-month follow-up data indicated that the intervention was particularly beneficial for Cuban American husband and daughter caregivers (Eisdorfer et al. 2003).

Another study concluded that the non-cognitive features of Alzheimer's disease are stressful for carers and indicate specific relationships between mood-related and behavioural signs of depression, walking and sleep disruptions and hallucinations in patients and adverse carer outcomes. Patient depression and the mood-related signs of depression in particular were the most consistent and

powerful predictors of psychological morbidity in carers (Donaldson et.al 1998). It was widely recommended that psychotherapeutic intervention strategies needed to identify and target psychological symptoms in patients with AD and their carers. It was also recommended that psychotherapeutic interventions must be based on individual assessment and formulation, with an understanding of the role of the family environment, as well as the carers perspective. Some models of how this might be achieved are already being developed.

### **2.2.9 Couplehood in cognitive impairment and therapy**

The complex nature of late-life marital relationships is increasingly recognised as an important factor contributing to healthy ageing. The long-term marriage relationship is highly relevant in terms of the health and the social, emotional, financial and practical needs of older people, yet the dynamics of this relationship remain poorly understood (Ray 2000). Marital relationships have the potential to influence health, and the onset of ill-health in one spouse can in turn influence the relationship. There is strong evidence that the ways in which elderly couples mutually relate can have a direct influence on health and wellbeing, irrespective of co-existing factors such as education, income and age. The major functions of marriage in old age observed in the previous studies are

listed in the box below  
(Tower and Kasl 1996).

#### **Box 5. Major functions of marriage in old age**

- Communication
- Collaboration
- Companionship
- Continuity and cohesion
- Affirmation
- Support, Protection
- Sexuality and physical touch

It is well documented that older people prefer to remain living in the community as they age, and that spousal

relationships play a major role in the capacity for such independent living, particularly in the provision of informal support. A relationship characterised by synergism and adaptability result in couples developing a supportive relationship involving role reciprocity and interdependence (e.g. one member of the couple preparing the meals, one doing the household chores, and both sharing some tasks such as cleaning dishes and gardening) (Racher 2002). Where friction or the breakdown of relationships was apparent, this was often due to imbalance in the roles or contributions to the relationship, or where cognitive impairment meant that they could no longer communicate as effectively, causing strain and frustration.

## **2.3 How psychotherapy changes the brain function - contribution of functional neuroimaging**

### **2.3.1 Integrating psychotherapy and functional neuroimaging**

It has long been recognised by clinicians that psychological interventions can profoundly alter patients' sets of beliefs, ways of thinking, affective states and patterns of behaviour. Yet the putative mechanisms and underlying changes in the brain have only recently attracted the attention they deserve. Yet the tools of non-invasive functional brain imaging can now reliably detect training- and learning-related changes in brain activation patterns in healthy volunteers, and there is no reason why this should not be possible in those affected by mental disorders as well. Potentially, functional imaging can detect psychotherapy-related changes at the level of brain areas and circuits, and thus contribute to an elucidation at least of the most global neural mechanisms (Linden 2006).

Most functional imaging studies into psychotherapy effects have been conducted with nuclear medicine methods like positron emission tomography (PET) or single photon emission computed tomography (SPECT), and assessed changes in brain metabolism or blood flow between a pre- and post-treatment

scan. The use of functional magnetic resonance imaging (fMRI), which does not expose the patient to radiation, would potentially confer the advantage of more measurement points, including measures of brain activation during treatment or at follow-up. Yet fMRI has traditionally been used to probe the brain activation patterns during perceptual or cognitive tasks, rather than to measure baseline brain metabolism. The use of fMRI for the detection of psychotherapy-related changes thus presupposed two methodological developments, the measurement of the neural correlates of psychopathology and techniques for symptom provocation in the MRI environment. [Dierks et al 1999, Beutel et al 2003] This avenue of research has been particularly successful in obsessive-compulsive disorder (OCD) and simple phobias, and is also being pursued for social phobia, depression, and post-traumatic stress disorder (PTSD).

### **2.3.2 Models and methods**

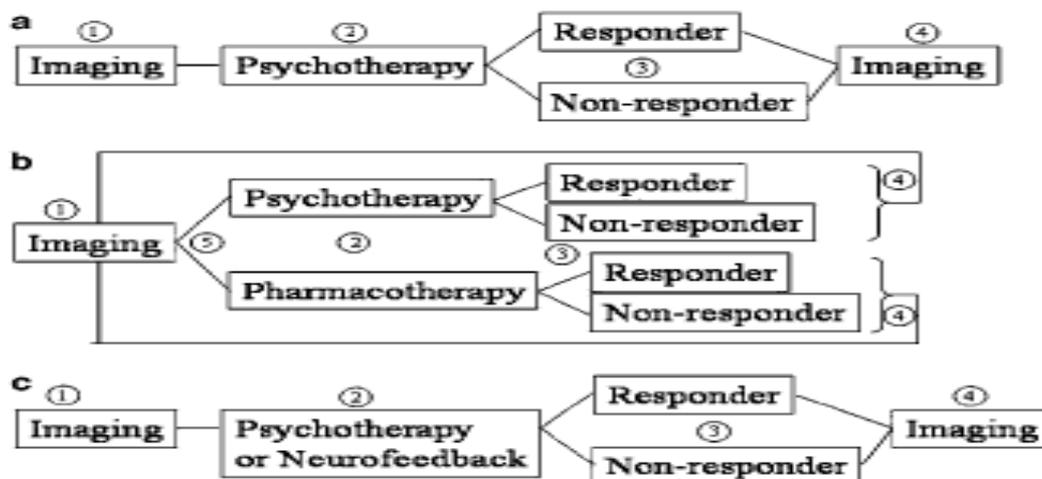
Three possibilities of integrating psychotherapy and functional neuro-imaging with potential clinical implications are described below. As shown in the figure below the first method can be used to identify the brain changes in the responders and non-responders in the psychotherapy and study the differences to understand the biological mechanisms underlying the response observed in one group. The second model can be used in the same way to understand the differences observed four groups of people responded to psychotherapy, not responded to psychotherapy, responded to pharmacotherapy and not responded to pharmacotherapy. The third method shows the use of neuro-feedback in the same way. These are the methodologies to assess psychotherapy targeted to a disease condition and there are no normal control groups to compare. There may a need to conduct an fMRI study to identify the neural activation in the disease before conducting such sort of a trial and normal control group studies can be integrated to the methodology.

Although figure 6 is a good example of some preliminary theoretical models proposed, it was observed that none of those models compares the psychotherapy to an active control, which includes another form of therapy like counselling or contact from a health care or social worker. It was not outlining a model comparing the psychotherapeutic intervention with an inactive control like standard follow up arrangements. As we have recognised that this is a major limitation in identifying the specific changes resulting from psychotherapy leading to causal significance, we have adopted a superior methodology in comparison with the models proposed below. In the study methodology we have compared the psychotherapeutic intervention with the standard follow up from the memory clinic to identify the specific changes in brain function resulting from the psychotherapeutic intervention through functional brain imaging

***Figure 6. Three possibilities of integrating psychotherapy and functional neuro-imaging with potential clinical implications.***

- (a) Baseline imaging measures (with any of the technique discussed in the review) are obtained (1) before a course of psychotherapy (2), after which patients are classified as responders or non-responders based on symptom improvement or other clinical outcome measures (3) and re-examined with the imaging protocol (4). This technique allows for the assessment of psychotherapy related changes in brain activation and their specificity for successful outcome (b) Baseline imaging measures are obtained (1) before a course of either psycho- or pharmacotherapy (2), after which patients are classified as responders or non-responders (3). This outcome information is entered into an analysis of the pre-treatment imaging data (4) with the aim of deriving activation patterns that are predictive of treatment response (5). (c) Imaging identifies abnormal activity in a particular brain area or network in a patient (1).*

*This abnormal brain activity is targeted by psychotherapy (based on information derived from studies of type (a), neuro-feedback, or a combination of both (2). Patients are then classified as responders and non-responders (3). The outcome data can then be compared with standard treatment protocols. Post-treatment imaging (4) will be informative but not mandatory (Reproduced from Linden 2006).*



### 2. 3.3 Clinical implications and biological correlates of psychotherapy

Functional neuroimaging is a promising tool for the investigation of the brain changes induced by psychotherapy. So far, only few studies have used it to assess the effects of CBT in OCD and phobia, and of CBT and IPT in depression. In OCD, psychological intervention led to decreased metabolism in the caudate and a decreased correlation of right OFC with ipsilateral caudate and thalamus. The hyperactivity of the caudate in OCD and its activity decrease after intervention conform to its putative role in the pathophysiology of this disorder. Dysfunctional striato-thalamic pathways have been implicated in inefficient thalamic gating, leading to hyperactivity in orbitofrontal and other cortical areas (Kent et al 2004). Such a scenario would be compatible with the functional neuroimaging findings, especially if increased caudate activity led to

disinhibition of the thalamus by means of the direct pathway, which would indeed increase the correlation between caudate, thalamus and OFC activity.

Finer resolution of functional imaging studies (e.g. in order to look for evidence of suppression of activity at the level of the globus pallidus internus) would be required to further disentangle the differential contribution of the basal ganglia to the pathophysiology of OCD. The prominent reduction of caudate activity after treatment might be explained in the context of the high level of striatal plasticity that has been shown in numerous studies of implicit and associative learning in human and animal models (Linden 2006).

In phobia, the most consistent effect of successful CBT on brain activation was a decrease in limbic and paralimbic areas. It is plausible that decreasing amygdala activation, in particular, should accompany the reduction of phobic symptoms because both mechanical lesions and chemical suppression of the amygdala have consistently resulted in a reduction of both subjective and psycho-physiological measures of fear. (Davis 2004). However, based on these functional imaging findings alone, we cannot determine whether the decrease in amygdala activity after treatment was the cause or rather the effect of symptom reduction. Altered neural processes in other brain areas (which might have been interindividually more variable and therefore not detected in group analysis) could have resulted in the originally offensive stimuli being perceived as less aversive with the consequence of reduced firing of amygdala neurons. Based on these studies the hypothesis generation for brain activity and mind is discussed in the context of development of the methodology for our study in the next chapter.

In both OCD and phobia, similar effects were obtained in the CBT and SSRI-treated groups. These findings, may point to a common final pathway for the neural changes underlying the clinical effects of a biochemical and a

psychological intervention. The difference in the effects between drugs with similar pharmacological effects (fluoxetine and citalopram) across different disease groups (OCD: decrease of caudate activity and OFC-caudate-thalamus correlation; (Baxter et al 1992) phobia: decrease of limbic and paralimbic activity (Furmark 2002) as much more pronounced than between drug and psychotherapy within the same disease group. Thus, the brain changes induced by and underlying the effects of therapy seem to be more dependent on the original dysfunctional area or neural network than on the nature of the intervention. Studies of depression yielded a less consistent pattern than those of OCD and phobia, with reports of both decreases and increases in prefrontal metabolism after successful treatment, and considerable differences between pharmacological and psychological reflect neuronal activity, they are governed by different regulatory system and are thus prone to influences from different confounding variables, for example, changes in neurovascular coupling in elderly patients in the case of fMRI (D'Esposito 2003). Thus, it would be desirable for future functional imaging studies of therapy effects to follow standardised protocols, or at least include a standardised component to which individual research groups could add their own paradigms. Some of these inconsistencies might be attributable to a lack of replicable baseline abnormalities of regional cerebral metabolism in depression.

### **2. 3.4 Application in cognitive impairment**

Functional neuro-imaging techniques have revolutionised research in the field of biological psychiatry recently, however the use of these techniques to understand the underlying mechanisms of clinical changes resulting from psychological interventions for people with cognitive impairment still remain as an untapped area. Functional neuro-imaging studies could further used in this patient population to predict prognosis, to assess the effects of pharmacological

interventions, and to evaluate neuro-psychometric tests in this patient population.

Although fMRI is used to study the neurological correlates of psychotherapy in a range of mood and anxiety disorders, these techniques were not used to identify the same in patients with cognitive impairment. As discussed above in functional neuroimaging, the changes in affect, behaviour, and cognition that are mediated by psychotherapies which have biological underpinnings could be thoroughly evaluated using appropriate symptom provoking techniques and the changes in functional connectivity before and after the structured psychotherapeutic interventions. In addition to this, these types of studies would reveal further knowledge about the possible aetiological links between the mechanisms leading to the impairment in the cognitive process and associated emotional changes.

MR imaging has advanced cognitive neuroscience, particularly our ability to study human memory mechanisms in vivo. Results of functional MR imaging studies in healthy subjects have identified specific regions of the frontal cortex that are involved in both memory formation (encoding) and retrieval and have supported the notion that these regions may jointly participate with the medial temporal lobe (MTL) in human memory processing. Functional MR imaging also has been used to study age-related changes in memory in healthy volunteers, and age-related decreases in working memory retrieval have shown correlation with a reduction in dorsolateral prefrontal cortex activation.

Although there are studies evaluating brain changes in psychotherapy in depression, phobias and OCD there is no published research evaluating changes in brain function in MCI after psychotherapy

## **2. 4. Functional neuroimaging in mild cognitive impairment**

### **2.4.1 Methods of functional neuroimaging**

Neuroimaging techniques, namely positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) are increasingly used to study mild cognitive impairment (MCI) and its conversion to dementia, as well as early Alzheimer's disease (AD).

Despite an important overlap of the various imaging parameter values between MCI, early AD and controls, some markers may help clinical diagnosis in individual patients. For example, the combination of significantly reduced hippocampal volume and brain hypometabolism in a MCI patient establishes the anatomical and functional features seen in dementia. In association with clinical information, the topographic localization of the hypometabolism will help to precise the type of dementia. Functional brain activation studies using functional MRI and PET are not used for clinical purpose, but they allow to determine the differences between control and pathological states and thus to characterize the functional abnormalities specific to the disease. Finally, the use of biomarkers of the neuro-pathological lesions constitutes the most promising tool to accurately diagnose MCI and early AD patients (Johnson et al., 2004, 2008; Machulda et al., 2003).

With the development of the imaging techniques of computerised tomography (CT) and magnetic resonance imaging it was possible to be more specific as to the location of damage in brain injured patients. The measurement of the electrical signals on the scalp, arising from the synchronous firing of the neurons in response to a stimulus, known as electroencephalography (EEG), opened up new possibilities in studying brain function in normal subjects. The advent of the functional imaging modalities of positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional

magnetic resonance imaging (fMRI), that led to a new era in the study of brain function.

## **2.4.2 Functional MRI**

During an fMRI experiment, the brain of the patient is scanned repeatedly while the patient is carrying out some task consisting of periods of activity and periods of rest. During the activity, the MR signal from the region of the brain involved in the task normally increases due to the flow of oxygenated blood into that region. Signal processing is then used to reveal these regions. The function that is mapped is based on blood flow, and it is not yet possible to directly map neuroreceptors as PET scan.

### **2.4.2.1 Blood Oxygen Level Dependent Contrast in MR images**

Since regional blood flow is closely related to neural activity, measurement of the rCBF is useful in studying brain function. It is possible to measure blood perfusion with MRI. However there is another, more sensitive, contrast mechanism which depends on the blood oxygenation level, known as blood oxygen level dependent (BOLD) contrast. It would be expected that upon neural activity, since oxygen consumption is increased, that the level of deoxyhaemoglobin in the blood would also increase, and the MR signal would decrease. However what is observed is an increase in signal, implying a decrease in deoxyhaemoglobin. This is because upon neural activity, as well as the slight increase in oxygen extraction from the blood, there is a much larger increase in cerebral blood flow, bringing with it more oxyhaemoglobin (Figure 3.17). Thus the bulk effect upon neural activity is a regional decrease in paramagnetic deoxyhaemoglobin, and an increase in signal.

### **2.4.2.2 Functional Mapping using the BOLD Effect**

To study brain function using fMRI it is necessary to repeatedly image the brain, whilst the subject is presented with a stimulus or required to carry out some task. The success of the experiment is dependent on three aspects; the scanning sequence used the design of the stimulus paradigm, and the way the data is analysed.

The contrast to noise ratio of the BOLD signal also depends on voxel size and slice thickness. Smaller voxels have fewer protons signal due to the reduced number of spins, however larger voxels may reduce the contrast to noise ratio by partial volume effects. This occurs if the signal changes on activation come from only a small region within the voxel, and so makes less of an impact on the total signal change in that voxel.

During the scanning there are a number of physiological effects that can affect results. These include cardiac pulsation, respiration and general subject movement. All these problems can be dealt with in two ways, either at the time of scanning or in image post processing. Subject movement can also reduce contrast to noise in fMRI images, and introduce artefact in the activation maps if the movement is stimulus correlated. This problem is often solved both by restraining the head of the subject and by using a post processing registration algorithm.

### **2.4.2.3 Paradigm Design**

The choice of stimulus is very critical. For example, to activate the primary visual cortex is straightforward, but to determine the regions responsible for colour discrimination is more difficult. Ideally it is necessary to design the 'on' and 'off' epoch such that there is only one well defined difference between them, which will only activate those brain regions responsible for the single task. This

is not always possible and so a hierarchy of experiments often need to be performed. For example to identify the regions responsible for task A, an experiment can be performed which involves task A and task B, and then one which only involves task B. The regions responsible for task A would presumably be those activated in the first experiment but not the second. This assumes that the system is a linear one, which may not be the case, or there could be some unaccounted for differences in the two paradigms, which could affect the result.

Another problem particularly when dealing with cognitive events such as memory, is that some stimulus must be presented, usually visually, and a subject response given, usually involving motor action. These must either be compensated for by being included in the 'off' period as well, or another experiment must be performed later which involves similar stimulus and response, but not the cognitive task performed in the original experiment. Alternatively the stimulus may be presented in a different way, aurally for example, and response given orally, and those regions common to both stimulus presentation types can be assumed to be responsible for the cognitive task of interest. The subject needs to have good instructions, and be reminded to lie still, and to concentrate. Many stimuli give better activation if a response is required to be made.

#### **2.4.2.4 Analysis of fMRI Data**

The most straightforward way to analyse the data is to subtract the mean 'off' image from the mean 'on' image. This has the disadvantage that any small movement of the head can drastically change the pixel intensity at the boundaries of the image. This can give rise to a ring of apparent activation near the brain boundaries. To reduce this effect, and to give a statistic of known distribution, a student's t-test can be used. This biases the result against pixels in either 'on' or 'off' set with very large variability, and so can reduce movement

artefact. An image where each pixel is assigned a value based on the output of a statistical test is commonly called a statistical parametric map.

Another commonly used technique is that of correlation coefficient mapping. Here the time response of the activation to the stimulus is predicted, usually with some knowledge of the hemodynamic response, and the correlation coefficient between each pixel time course and this reference function is calculated.

Having obtained a statistical map it is necessary to display the regions of activation, together with some estimate as to the reliability of the result. If the distribution of the statistic, under the null hypothesis of no activation present, is known, then statistical tables can be used to threshold the image, showing only those pixels which show strong stimulus correlation.

### **2.4.3 Functional neuroimaging in MCI**

Studies to evaluate brain activation in patients with probable AD, MCI, and controls while performing a working memory (WM) task reported that activation was observed in the parahippocampal region, superior-middle-inferior frontal gyri, parietal region, anterior–posterior cingulate, fusiform gyrus, and basal ganglia. MCI and AD groups showed more activation than the controls in the right superior frontal gyrus, bilateral middle temporal, middle frontal, anterior cingulate, and fusiform gyri. Activation in the right parahippocampal gyrus, left inferior frontal gyrus, bilateral cingulate and lingual gyri, right lentiform nucleus, right fusiform gyrus, and left supramarginal gyrus in the AD group was less than in the MCI group. AD and MCI patients showed an increased extent of activation and recruitment of additional areas (Yetkin 2002).

Functional MR imaging also has been used to study age-related changes in memory in healthy volunteers, and age-related decreases in working memory retrieval have shown correlation with a reduction in dorsolateral prefrontal

cortex activation. Although most functional MR imaging cognitive studies in the literature have been performed with 1.5-T units, there is some evidence that functional MR imaging at higher field strengths enables more sensitivity in the detection of cortical activation during cognitive and motor tasks. For example, in one study of 10 healthy subjects who performed cognitive tasks that required motor decisions, 3-T functional MR imaging, compared with 1.5-T MR imaging, enabled the detection of additional areas of cortical activation (Rypma et al 2000, Gazzaley A, et al 2003, Hoenig et al 2005).

In controlled functional MR imaging studies of memory processing in patients with mild cognitive impairment a reduced activation was observed in MTL regions during a visual memory task involving complex scenes. It was also observed that enhancement of cholinergic activity with Donepezil hydrochloride a cholinesterase inhibitor, resulted in increased activation in frontal regions in nine patients with mild cognitive impairment but not in controls (Machulda et al 2003, Saykin et al 2004, Johnson 2004).

There have been two uncontrolled studies of patients with mild cognitive impairment and two controlled studies of elderly subjects with reduced or declining memory (all performed at 1.5 T) (Dickerson et al, 2004, Goekoop R, 2004, Daselaar 2003, Small 1999). In a study to prospectively assess abnormalities in brain activation patterns during both encoding and retrieval in subjects with mild cognitive impairment by using 4-T functional MR imaging, Petrella et al 2006 observed that brain regions activated by the task (prefrontal, medial temporal, and parietal regions) during encoding were similar to those activated during retrieval, with larger areas activated during retrieval. Subjects with mild cognitive impairment showed decreased magnitude of activation in bilateral frontal cortex regions (during encoding and retrieval), the left hippocampus (during retrieval), and the left cerebellum (during encoding) compared with magnitude of activation in control subjects. Patients with mild

cognitive impairment showed increased activation in the posterior frontal lobes (during retrieval. Lower hippocampal activation during retrieval was the most significant correlate of clinical severity of memory loss in mild cognitive impairment (Petrella 2006).

It is increasingly clear that groups of individuals with MCI are heterogeneous, and this clinical heterogeneity may, in part, explain differences between previous fMRI studies of MCI. If MCI encompasses the entire transitional continuum between normal aging and dementia, as has been proposed, then individuals at the boundary between normal aging and MCI should have less underlying pathology and less memory impairment than individuals at the boundary between MCI and AD (Dickerson 2005)

#### **2.4.4 Functional connectivity in MCI**

A study (Bokde et al 2006) to investigate changes in functional connectivity of the right middle fusiform gyrus (FG) in subjects with mild cognitive impairment (MCI) during performance of a face-matching task, utilized the linear correlation coefficient as a measure of functional connectivity between the right middle FG and all other voxels in the brain. There were no statistical differences found in task performance or activation between groups. The right middle FG of the healthy control and MCI groups showed strong bilateral positive linear correlation with the visual cortex, inferior and superior parietal lobules, dorsolateral prefrontal cortex (DLPFC) and anterior cingulate. The healthy controls showed higher positive linear correlation of the right middle FG to the visual cortex, parietal lobes and right DLPFC than the MCI group, whereas the latter had higher positive linear correlation in the left cuneus. In the healthy controls, the right middle FG had negative linear correlation with right medial frontal gyrus and superior temporal gyrus and with left inferior parietal lobule (IPL), angular gyrus, superior frontal gyrus and anterior cingulate gyrus, but the

MCI group had negative linear correlation with the left IPL, angular gyrus, precuneus, anterior cingulate, and to right middle temporal gyrus and posterior cingulate gyrus. In the negatively linearly correlated regions, the MCI group had reduced functional connectivity to the frontal areas, right superior temporal gyrus and left IPL. Different regions of the cuneus and IPL had increased functional connectivity in either group.. A higher linear correlation in the MCI group in the parietal lobe may indicate the initial appearance of compensatory processes. The results demonstrate that functional connectivity can be an effective marker for the detection of changes in brain function in MCI subjects.

In another study (Teipel et al 2007) analysis of the correlation between fusiform activation and cortical grey matter density identified two distinct sets of brain regions in MCI patients and healthy elderly subjects corresponding to the location of the ventral and the dorsal visual stream and including the prefrontal cortex. This correlation may represent the effect of system specific AD type pathology in MCI or even a primary morphological feature underlying the functional differentiation within the visual system, possibly linked to the distribution profile of neuronal density. There was a further suggestion that the interpretation of activation pattern in fMRI should take into account the degree of cortical atrophy not only at the peak of activation but along the entire functional system underlying the task under study.

## **Chapter 3: Methods for Modelling the RCT**

### **3.1 Introduction to study methodology**

The overall purpose of this study is to assess the feasibility of developing and evaluating a psychotherapeutic intervention for people with MCI and their partners. In addition to that it is aimed at understanding the challenges in exploring theoretical knowledge in the biological mechanisms underpinning the effectiveness of psychological interventions in older people. It also aims at studying the tolerance and feasibility of application of advanced research techniques like functional neuro- imaging to older people with cognitive impairment.

To study the feasibility of testing a complex intervention we adopted the methodology recommended in the MRC framework and the primary aim was to develop a protocol for an exploratory trial and conduct it in the real life scenario (modelling) to inform any future studies planned this field.

### **3.2 Rationale for the study**

As we have observed in the introductory chapters many studies have recently described the impact of cognitive impairment on patients and their families and there has been an increased interest in detecting these conditions early on as well as to develop interventions to slow or delay its progression. It was also observed that gaps existed both in theory as well as evidence base, in the current literature, in the category of MCI particularly in the field of therapeutic interventions. There was also a growing research interest in the use of advancing neuro-imaging techniques in cognitive impairment to contribute to the theoretical as well as clinical aspects. However it has also been identified that conducting research in this population is challenging. We have followed the MRC 2008 guidance to develop this study methodology to identify and develop appropriate theory in the fields of psychotherapeutic interventions for

people suffering from MCI and their carers as well as to test the feasibility of use of fMRI techniques in studying the neuro- biological mechanisms underlying the changes caused by the psychotherapeutic interventions in this complex population through a modelling exercise.

### **3.3 Rationale for adopting an innovative methodology**

As this study is a multi-dimensional piloting work including developing and testing a psychotherapeutic intervention for older people and their carers , and developing a methodology for generating theoretical and practical knowledge in the use of modern neuro-imaging techniques, it is important for us to develop a suitable methodology . As discussed above we have designed the study as a modelling exercise to asses a range of feasibility outcomes.

### **3.4 Hypothesis generation**

From the discussions above we attempt to generate theoretical knowledge in relation to application of a psychotherapeutic intervention to the patients suffering from MCI and their carers (partners or spouses). This include testing the adaptability of the model as well as acceptability of the intervention in this specific population. In addition to this through a modelling exercise by developing an experimental study design we aim to generate theoretical information in formulating a hypothesis both in terms of psychotherapeutic intervention and the neuro-imaging component. However the main aim of the modelling exercise is to study the adherence to the protocol of the experimental design to test the feasibility outcomes as stated above in Table 1. We recognise that the MCI group we are studying is a population with heterogeneous pathophysiology and it has been challenging to understand the theory , that psychotherapy directed to the patients suffering from MCI and their carers will result in emotional as well as cognitive wellbeing in patients and their carers and we aim to generate as much theoretical knowledge as possible in this area to

develop hypothesis for a larger definitive trial planned in this area by the modelling exercise .

With the functional neuro-imaging component added to the modelling exercise, we also aim to generate theoretical knowledge in this area focusing on generating hypothesis for future studies. Functional MR imaging in MCI has shown changes in the activation in dorsolateral prefrontal cortex . Also use of working tasks reported changes in right superior frontal gyrus, bilateral middle temporal, middle frontal, anterior cingulate, and fusiform gyri. Age-related decreases in working memory retrieval have shown correlation with a reduction in dorsolateral prefrontal cortex activation. We aim to study the changes in the activation in these regions using a working memory task, attention and concentration task (n-back) as well as a sociotropy –autonomy task more relating to the emotional aspects in MCI discussed above. As the working memory task and Sociotropy –autonomy tasks were developed in house the preliminary aim was to test the feasibility of administration of these tasks in a population with significant physical as well as cognitive problems in addition to gain the theoretical knowledge.

Outcome assessments are planned statistical approach are discussed in detail below.

### **3.5 Setting the feasibility outcomes**

We have identified three methodological components to study the feasibility outcomes. These are 1) development of trial interventions and examine the suitability of those interventions in the population with MCI and their carers 2) development of a protocol for modelling trial to study the feasibility of different components of an RCT including the efficiency of recruitment, randomisation, adverse events and dropouts 3) Evaluation and qualitative description to generate theoretical as well as practical knowledge.

### **3.6 Development of a psychotherapeutic model**

We have used the existing evidence from the project conducted by the same research group (Brierly et al 2003) in developing a psychotherapeutic intervention for patients with early Alzheimer's disease.

This model of Psychodynamic Interpersonal Therapy was further adapted for patients with Mild Cognitive Impairment and their partners in a couple therapy format. The advantages observed in this model include the emphasis placed upon the identification of underlying interpersonal problem issues, which can be addressed and modified during the treatment even when it is used in the brief form. It was also observed in the previous study that the therapy was well tolerated by people with early Alzheimer's disease, and it was helpful in the patient group as the emphasis was more on working with feelings and therapeutic relationship rather than a cognitive approach.

The patient, patient's partner and the therapist collaboratively to find problem areas and identify solutions to the problems. Therapist also works with the patient and the partner to facilitate both gaining more insight into the problems and encourage them to develop coping strategies through practical changes

#### **Adaptation of the model for people with MCI and their partners.**

It was necessary to adapt the model in view of the specific characteristics of the study population. These characteristics include physical frailty, sensory impairment, and impaired cognitive function sometimes occurring in both the partners. The main adaptations were along the same lines of the trial of psychotherapy for people with Alzheimer's disease .although people with Mild Cognitive Impairment were considered as less cognitively impaired and more functionally able, in comparison with people with early dementia.

The main adaptations were done in the form of therapeutic setting at patient's own home , equal involvement of patient's partner in the therapy ,provision of the therapy in a couple therapy form , focus on linking emotional and cognitive symptoms to interpersonal difficulties or dilemmas and identifying practical solutions , resolution of conflicts from the past and exploration of psychological features like denial which is commonly associated with memory impairment , and improving the patient's as well as partners social function .

To test the adapted model the piloting was done with two couples with early cognitive impairment before it was applied to the exploratory trial.

### **3.7 Treatment setting at patient's own home**

The couples received the pilot therapy were seen in their own homes by the therapist for an assessment before commencing the therapy .The supervision sessions for the therapist was done before and after the assessment sessions. Each therapy session was recorded on a digital recording machine .In the supervision sessions the therapist and the supervisor listened the recordings of therapy sessions together. Based on the model described above a standardization was agreed and procedural framework was developed. Couples were seen in their home for eight therapy sessions and the approach was well received by the patients and their partners because it was identified that frailty prevents many of the couples attending hospital appointments on a regular basis .As patients with memory impairment function better in their familiar environments this setting was identified as optimum . However occasionally telephone calls, pets, and visitors interrupted therapy sessions and allowance of time had to be given for this. Sometimes this approach resulted in the therapist travelling far and there needed to be some flexibility in terms of timing of sessions. It was also important for the therapist to understand the patient's home situation and the level of functioning.

### **3.8 Couple therapy involving the patient's partner or spouse**

In each therapy sessions lasting for 40 minutes the patient and the partner or spouse were seen together by the therapist. Using the framework of the model described above therapy sessions was planned. Interpersonal difficulties were identified using an exploratory rationale and therapist acted as a facilitator in making the patient and the partner or the spouse aware of the interpersonal issues. Understanding the difficulties the patient and the partner were facing as well as assessment of the quality of the relationship between both the patient and partner was important aims of the initial therapeutic sessions.

### **3.9 The frequency, length and arrangements to test the fidelity**

All the therapists were clinicians including senior and junior psychiatrists and psychiatric nurses specializing in dementia care. The therapists had done a PIT course in Manchester University and had had involvement in the development of the model as well as its piloting. The sessions were delivered in the weekly fashion, however because of the annual leave arrangements, patient's and carer's holiday etc. it was delivered as 8 sessions over 12 weeks. All the therapy sessions were recorded in audiotapes and therapists had weekly structured supervisions from research supervisor where the tapes were listened and fidelity was ensured. The necessary modifications in the approach were also made. One session from each individual therapy was rated for adherence to the model using the Sheffield Psychotherapy Rating Scale (Shapiro & Startup, 1993).

Few examples of the application of therapeutic model in the sessions are discussed below. Identification of interpersonal issues was demonstrated in this extract from the therapy session.

*Husband; ...She just fights me all the time when I tell her... , When I try to get her to do things on the right way she fights me..*

*Patient: I don't..*

*Therapist: Mrs..M it seems that.....you wanted to tell us something. . Perhaps you could share your feelings with us..*

*Patient: Well I am in a position of being treated like a girl. Because he shouts at me.. .... don't you?*

On many occasions an approach to provide a rationale for the patient and carer was taken by the therapist .Careful avoidance of confrontational and interrogational approach in exploration was also adopted by the therapist allowing the patient and the partner to express their feelings in their own pace . However the emotions were expressed particularly by the partner the therapist gently attempts to make the partner aware of the issues related to patient's memory impairment by providing a rationale. The model demonstrated 'a here and now 'method and the therapist here demonstrated the component of staying with the patient's feelings. Also a negotiating style was adopted by the therapist and attempts were made to make the partner understand the hypothesis.

*Husband: 'She is as stubborn as a mule'- 'because it is me telling her she fights me' she would take it more easily from somebody else than she would from me,*

*Therapist: Well....I am not sure whether this could be a part of Mrs P's.. memory problem or lack of awareness, you mentioned the word stubbornness, Mr P... Being in an airport perhaps.....you might have felt that it is bit more difficult than what you see inside your house ...*

*Husband: 'it can be embarrassing, when people are looking at your wife, thinking she is not dressed properly, and fighting with me...*

*Wife [Patient]: I can't look back at times .. Why this has happened... I don't understand.*

*Therapist: We both understand that it was very difficult for you...*

*Wife [Patient]: It was a very traumatic time for me ... I could not cope.... I feel quite upset.. I don't know why..*

*Therapist: Perhaps you understood that there is something wrong with your memory...*

*Wife [Patient]: I suppose .... ..yes.. I did not understand what was happening..*

*Therapist: It was particularly upsetting for you*

*Wife [Patient]: Yes, because it was the plainest indication that something was wrong with my mind....*

*Therapist: You feel very sad ...*

*Wife [Patient]: Yes. [Tearful].*

Therapist attempts to link interpersonal difficulties to emotional and cognitive symptoms and use autobiographical narratives and introjections to strengthen self worth. In couplehood when one partner develops memory impairment, the awareness of loss of competence can result in lowered self esteem which in turn results in interpersonal issues. In this model, when ever this is problem is encountered the therapy will aim at helping the patient internalize a new sense of intrinsic self worth. As observed in the previous study the autobiographic memories are used in a constructive way to strengthen their self worth as well as increased insight for partner in understanding and accepting the changes in the patient. The therapist here helps the patient to make links with their life in the past, and enabling them to realize that in many respects they were the same person now that they had always been. An example of using a linking hypothesis to bring past and present together as well as addressing the interpersonal issues is demonstrated below.

*Mr R [husband]: we have been married 55 years. 18 years of that marriage I was in the Navy. .It was very important time because, it was our early*

*marriage. The longest period I was away from home was 9 months. Life goes on and we are getting older and older. You can't keep blaming it on that all the time.*

*Therapist; I am not sure whether Mrs R was blaming it on that..I thought she was just pointing it out that she was very independent when you were away. But you feel that it is bit of a blame..*

*Mr R[Husband] : it is proved that she was a very independent person.....because ...there was not anybody she could turn on when I was away. It was important and it did make a significant mark on our life....I am bit unsure why my wife keeps mentioning this ..It obviously is very much marked in her long time memory ...*

*Therapist : By mentioning this I thought you [Mrs R ] were trying to give me an idea ..About ...how you have changed from a person who was very independent to ...a person who forgets few things..*

*Mrs R [patient] ; yes ...*

*Therapist: when we discussed this last time you became tearful...it is worrying for you ...*

*Mrs R[patient] : yes*

*Mr R[husband] Yes; it gets her depressed..*

To get a dynamic understanding of the issues, the therapist attempts to construct an interpersonal formulation. This model of exploration and formulation helps the therapist to address the interpersonal conflicts between the partners. An example of interpersonal formulation is given below.

*Therapist: what I thought is that ....when things are difficult for you to do .Mr P is particularly happy about you asking him to help you ...however when he gives you suggestions in a good way ...that he is trying to help you ...you would not go along with that ..and perhaps you will tell him that this is not the way to do it....then he is feeling a strong sense of rejection ..and that is putting him off..... that is what I felt..*

*Husband: Exactly..... That is how I feel*

Mostly the therapists uses the statements rather than questions to develop a shared understanding of the feelings . In this way a language of mutuality is created and feelings are brought to here and now to be shared with the therapist, the patient and the partners. Many occasions this approach helped to address the fears and worries particularly related to the future as well as prognosis of the memory impairment.

*Therapist: I get a feeling that the memory problems...and the diagnosis came as bit of a shock for you..*

*Mrs. R: I don't know really*

*Mr R. ...she was little bit frightened.....She did not know what to expect*

*Therapist: Especially after working in a hospital for long time .. ..you might have seen many patients in the hospital*

*Mr R: I think ...one of the fears is..this dreaded word that describes memory loss ..Alzheimer's ..My wife already has had a traumatic experience. She has had cancer.....she knows getting the bad news what it is like*

*Therapist; getting the bad news..... . I also get a feeling that it was particularly upsetting for you as well Mr R..*

*Mr R..it was bit of a shock..to be told that it might be or it could be the early stages of Alzheimer..*

Often use of a metaphor helps the therapist and the other person in the partnership to develop a shared understanding

*Therapist: I feel Mrs P. Is getting increasingly depending on you*

*Husband: Yes she is very*

*Therapist: Bit like children depend on adults*

*Husband: Yes .. You mentioned the word children.. I have observed in the last couple of years ...that ...at times dealing with M and trying to make her do things.. Has been at times trying to persuade a child*

Staying with the feelings is an approach taken by the therapist to understand and address the emotional aspects associated with loss of function as well as role reversal.

*Therapist: I wonder whether we could stay with that feeling for some time ..particularly... for Mrs R.. I am not sure how did you feel when you heard that you have Alzheimer's Disease... Mrs.R..*

*Mrs R; I don't know. I don't really know how I feel to be honest [weeping] ..I don't like being how I am now..[Weeping]... I spent lot of years bringing up my children own my own.. I was really capable..[Crying]... I do forget things ..I don't want to be like that*

The therapist was also able mirror and validate the experiences in the therapy sessions. Understanding the emotions in parallel to the experiences from the past and making links with the current experience is another therapeutic approach in the model.

*Mr J ; one of the saddest things ever happened to me .....is 61/2 years ago when a cat of our's got killed in a car accident right outside our house. And I was responsible for that....it was my fault...I could have stopped it if had seen that car coming..... I was responsible for that.. I failed in my responsibility... to loose a family member suddenly in road accident is devastating.. Especially when you know it is your fault...bit difference in loosing somebody in their old age..... M's Aunty died in last year she was 97.. There is not much sadness in that death..*

*Therapist: R[cat] was young and ....He had a long life to go.. That brings sadness....somewhat the similar feeling to what happened to M...*

*Mr J: yes..Yes...it is more easy to accept it in somebody in the later age.. but M is only 65..I am only 59..*

*Therapist; There are some similarities in that feeling of loss, bit of a shock as well*

*Mr J; Yes...I agree..*

Through the linking as well as the explanatory approaches it was observed that partner is gaining more an understanding about the patient's situations and emotions resulting in less expressed emotions and developing more of a supportive relationship.

Therapist ;I also feel that when Mr J understands more and more about the problems , you are becoming more supportive and encouraging to M.

*Mr J : I think you are probably right in that ,, because I think I have an understanding which I did not have before ..I did not know what was wrong...the diagnosis did not come as a shock to me ..I have known for some time that there was something wrong.. and I have known for some time that I have not handled it very well. I have been impatient with M.....I shouted at her ..now I understand why I was like that ,because I did not understand what was going on ..now I understand it better. I have accepted it. I find it lot easier than I did few months ago. Maybe that is why you getting an impression that I am supportive. I think that is probably the explanation..*

In addition to the above mentioned approaches the therapist actively discuss problem solving approaches as well as provide advises about making practical changes. A number of practical aspects about coping better with memory impairment were also discussed. The examples being,

- Avoiding anxiety and panic when ,the person is not able to remember things use of a diary to aid the memory
- Rehearsing the information to improve memory function

- Developing a routine by keeping things in the same place and getting familiar with it
- Using techniques like labelling , larger images etc
- Being honest with people about the forgetfulness and keeping the pressure away

Therapist also encourages the couple to make positive changes in their social life particularly to strengthen self worth and to improve social relationships. Here the patient, partner and the therapist work collaboratively with evaluation of the plans to make positive change with some therapeutic monitoring. Two examples given below describe how positive changes were achieved in the therapeutic process.

*Mr J: There is some progress to report ,we had contact with C, She is actually coming here on Thursday night , I should be out...*

*Therapist: you mean you thought it is better if M spends some time with C.. on her own..*

*Mr J; I got to go to meeting on Thursday night...M and C can talk..*

*Therapist; it is good that you are getting on with your own things. I feel it would be beneficial for both of you to get on with the things you would like to do.....like Mavis meeting her friends and John taking part in the meeting.*

Also the therapy is aimed at preparing the partner to cope better with the patients cognitive and emotional states that theatre is a less expressed emotion in the relationship resulting in increased quality of life as well as better harmony in the marital or partnership relation.

*Mr P : I am feeling lot more OK with the situation now because I understand it better now..*

*I was under lot of stress , dealing with M's problems.....I needed somebody to talk to ...I did not understand what was going on , in her head.. ...I am feeling of lot more accepting on it ...having been told what the problem is that half the battle I think....I was lot more settled with the problem now than I was few months ago..*

### **3.10 Developing a protocol for an exploratory trial**

To evaluate the intervention we have chosen the development of an experimental method in the form of a Randomized Control Trial . As discussed earlier this was developed as an exploratory trial to study the feasibility of a larger trial with adequate power in the field of evaluation of a complex psychological intervention in the challenging population of older patients with cognitive impairment and their carers. The protocol was prepared as modelling exercise with the methodology of an RCT . This pilot study was developed as a miniature model of an RCT to examine the key uncertainties, as well as to identify and address problems of acceptability, compliance, delivery of the intervention, recruitment and retention.

We have identified the feasibility outcomes for the experimental methodology, which are to be described in an observational way in the quasi experimental design. The importance is given to the process evaluations for the experimental methodology and reporting the outcome evaluations was not included in the primary aim of this study. Although through the modelling exercise it was decided to attempt a power calculation, as the focus of the pilot study was the assessment of feasibility, it was not expected that the study would be powered adequately to assess statistical significance.

### **3.11 Agreed Feasibility outcomes**

It was aimed that the pilot study should be large enough to provide useful information necessary to assess the feasibility.

Criteria for interpretation of success were agreed based on the feasibility outcome .Three possibilities were identified as the outcome of the feasibility trial.

- (1) Study cannot be continued and a main study is not feasible
- (2) A larger scale study can be done with a modified protocol
- (3) A larger scale study can be done with the current protocol

The agreed aspects of the feasibility assessment are described below under four headings.

1. Process: The aim was to assess the process of different components of the RCT design including recruitment rates , retention rates and refusal rates . It was also agreed that any observations should be reported in detail in a narrative way. Also in this aspect of the feasibility study the suitability and implications of inclusion and exclusion criteria; consenting issues, detailed information about the study questionnaire and data collection tools, experimental outcome measurement methods as well as the tolerability of assessment methods were studied .Also the rigor of randomisation, and the adherence to the developed protocol were also looked into.
2. Resources: This aspect of the feasibility study assesses any issues with time and resources allocated for the project particularly to inform any larger trials planned in the future .it determines the capacity and skills , coordination and management of communications , issues with process time , as well as necessity of developing skills in the research team and training and supervision necessary to conduct the trial. It also assesses whether technology available is suitable for the project, as well as addresses questions like do different centres participating perform

differently? Do different researchers have time to perform the tasks they have committed?

3. Trial management and governance: In this section issues related to overall trial management, specific issues related to the study governance, data entry, storage, serious incident management etc are addressed and reported.
4. Clinical and scientific : any issues with the tolerance of the interventions , challenges in developing and implementing the interventions , treatment safety , response ,effect variance etc are studied and reported here.

Development of the neuro-imaging component of the study is well described in the protocol for the experimental study below .

### **3.12 The Protocol for the experimental study**

We developed this protocol based experimental study as a modelling exercise as modelling a complex intervention prior to a full scale evaluation can provide important information about the design of both the intervention and the evaluation. The modelling here is called experimental study as we have taken a stepwise approach similar to the development of a Randomised Control Trial to generate theoretical and empirical work to identify the components of the intervention and the underlying mechanisms by which they will influence outcomes. whilst not intending as a definitive efficacy trial our experimental design used for modelling aim to provide practical knowledge to the principal investigator about developing and conducting an RCT and evaluation of adherence to the protocol ,which was agreed as an educational outcome of this project .

The principle investigator who is the MPhil student developed this trial protocol under supervision following the steps for developing an RCT ,whilst the aims of the study being, to provide vital information including defining the intervention,

testing the feasibility of key components such as recruitment, randomisation, and measurement of outcome as well as unique evidence of intervention effects for the purposes of informing any larger studies planned in the future .

At this stage the student performed a sample size calculation as well , as an educational exercise which is described in the trial protocol

As a modelling and educational exercise the steps of development of the experimental study is described in different subheadings in this section (3.12)

### **3.12.1 Development of hypothesis and formulation of research question**

#### **3.12.1.1 The Hypothesis**

1.The hypothesis is that, structured psychotherapeutic intervention, based on Psychodynamic Interpersonal Therapy principles, directed at sufferers of MCI and their partners/spouses will result in improved well being of sufferers [as assessed by measures of cognitive function, mood, psychological distress, interpersonal functioning and quality of life] and lowered psychological distress in their partners/ spouses, in comparison with controls.

2. The improved well being of sufferers of MCI, as a result of successful Psychodynamic Interpersonal Therapy would result in changes in task induced blood oxygenation level dependant ( BOLD) signal of fMRI.

#### **3.12.1.2 Setting the primary and secondary objectives**

##### **Primary objective**

To test the efficacy of a psychotherapeutic intervention based on Psychodynamic Interpersonal Therapy principles, for people with Mild Cognitive Impairment[ MCI] and their partners /spouses and to study whether psychotherapy changes brain function in patients with MCI , based on functional magnetic resonance imaging assessments of patients' performance on

emotional , episodic memory and working memory tasks before and after psychotherapy.

### **Secondary objectives**

1. The secondary aim is to determine underlying mechanisms of change which result in improvement.
2. To elucidate the neural correlates of symptom reduction and to understand the biological mechanisms of psychotherapy.
3. To investigate changes in functional connectivity in subjects with mild cognitive impairment (MCI) during performance of emotional, episodic memory and working memory tasks before and after psychotherapy.

### **3.12.2 Using the existing research to define the population and setting up inclusion and exclusion criteria**

There are relatively few studies which have evaluated the benefits of psychotherapy for elderly people with Mild Cognitive Impairment. There is good evidence that interventions for carers of people with Alzheimer's disease (AD) can reduce stress (Mittleman et al 1996; Donaldson et al 1997). Research on psychotherapeutic interventions directed at those with MCI is limited, although most findings suggest that psychotherapy may be beneficial in the early stages of dementia (Brierly et al 2003, Burns et al 2005).

Burns et al 2005 , assessed in a randomised control trial, whether a psychotherapeutic approach directed towards individuals with AD could benefit cognitive function, affective symptoms and global well –being. The same group of investigators (Brierly et al 2003) conducted a pilot study to evaluate the potential benefits of brief psychodynamic interpersonal therapy (PIT).

This study shows that it is possible to adapt a model of psychotherapy for those with AD. No improvement was found on the majority of outcome measures in participants and their carers. However, there was a suggestion that the therapy had improved the carers' ways of coping with some of the symptoms of the disease. The therapist's experience of working with AD patients suggests that PIT was acceptable and most but not all, were able to work in therapy. The joint sessions with the participants and carers helped the therapist to focus on those symptoms that were considered important and distressing. The therapists found that AD and the resulting deterioration in cognitive function for the subjects resulted in changes in the usual balance of their interpersonal relationships. For example, previously strong and independent people became dependent on their spouses for many activities of daily living. In many instances both subjects and carers found it difficult to adapt to these changes imposed upon them because of the nature of the disease. The trend towards improvements in both carer and patient outcomes attests to the potential benefit of non-pharmacological interventions in this group. It was recommended that future studies in this area should concentrate specifically on approaches that combine outcomes of carers and those in their care.

### **3.12. 3 Inclusion criteria**

As it was estimated that many older people will have contraindications for MRI scans as well as based on the resources available to do the expensive imaging we did not aim to scan all participants in the exploratory trial phase . We set different inclusion criteria for psychotherapeutic intervention and neuro-imaging with a view to scan a small number of people from the intervention and control groups. The inclusion and exclusion criteria for both psychotherapeutic and neuro-imaging interventions are described below.

## **Psychotherapy**

- a. Diagnosis of MCI according to the criteria suggested by the International Psychogeriatric Association expert conference on mild cognitive impairment (Gauthier 2006). The definitions and classifications are discussed in detail in the literature review section. Patients were recruited from South Manchester memory clinic, Salford memory clinic and Stockport memory clinic with a clinical diagnosis of MCI.
- b. Living with a spouse or partner
- c. Ability to create of a conversation in English aiming to develop ‘a mutual feeling language’ based on psychodynamic interpersonal concepts.
- d. MMSE above 26

## **Imaging**

15 Patients with MCI from the intervention arm and 15 patients with MCI from the control arm as described in inclusion criteria above without any standard contraindications to MR imaging.

### **3.12.4 Exclusion Criteria**

## **Psychotherapy**

- a. Patients/ Spouses suffering from serious physical conditions preventing the regular participation in the project, according to the assessment done by the researcher.

## **Imaging**

1. Patients with standard contraindications to MR imaging, including patients with metal implants, or cardiac pacemakers.

2. Patients with psychological distress (e.g. phobias) associated with MR imaging.

### **3.12. 5 defining outcomes and determining the primary and secondary outcome measures**

#### **3.12. 5 .1 Primary outcome measure for patient and carer [CORE]**

Clinical Outcomes In Routine Evaluation [ CORE OUTCOME MEASURE]

Clinical Outcomes in Routine Evaluation (Barkham *et al.*, 1998, Evans et al 2000) is regarded as a brief user-friendly, questionnaire measure intended to be used at the beginning of therapy to indicate the differences in the severity of problems.

people may have and to be used at intervals thereafter to measure change.

CORE outcome measure (COREOM) used in our study is a self-report, measure . We chose this as the primary outcome measure mainly because in the psychotherapy research it is regarded as short & legible and pan-theoretical with an ability to detect clinical change. Although it is not validated in the older population it appeared to be sensitive to our client groups needs as well as there was a consensus among the clinicians took part in the research that it could relate client input to service output . Also the Minimum administration required as well as easiness to score supported by clinical and non-clinical norms also a factor for consideration.

The 34 items self reported tool is scored by tick box completion on the same five response levels on all items covering four domains as given below.

- 1) Well-being (four items)
- 2) Social functioning (12 items)

3) Problems/symptoms (12 items)

4) Risk: (six items)

(a) To self (harm/suicide)

(b) To others

### **3.12. 5 .2 Secondary Outcome Measures for Patient**

#### **A. Geriatric Depression Scale [GDS]**

The Geriatric Depression Scale (GDS) is a self-report measure of depression in older adults. Users respond in a “Yes/No” format. The GDS was originally developed as a 30-item instrument. Since this version proved both time-consuming and difficult for some patients to complete, a 15-item version was developed. The shortened form is comprised of 15 items chosen from the Geriatric Depression Scale-Long Form (GDS-L). These 15 items were chosen because of their high correlation with depressive symptoms in previous validation studies (Sheikh & Yesavage, 1986). Of the 15 items, 10 indicate the presence of depression when answered positively while the other 5 are indicative of depression when answered negatively. This form can be completed in approximately 5 to 7 minutes, making it ideal for people who are easily fatigued or are limited in their ability to concentrate for longer periods of time.

#### **B. Beck’s Anxiety Inventory**

The Beck Anxiety Inventory is a well accepted self-report measure of anxiety in adults and adolescents for use in both clinical and research settings. It is a 21-item multiple-choice self-report inventory that measures the severity of an anxiety in adults and adolescents. Because the items in the BAI describe the emotional, physiological, and cognitive symptoms of anxiety but not depression, it can discriminate anxiety from depression. The usual age range for the measure is from 17 to 80 .

### **C. Marital Intimacy Scale in Dementia**

Marital Intimacy Scale developed by Schafer and Olson (1981). It comprises five subscales measuring emotional, social, sexual, intellectual and recreational intimacy between marital partners. Each subscale is of six-item five-point interval format. This has been used in dementia research before.

### **D. MMSE**

This is a 30-item measure of cognitive function, with a maximum score of 30 points (Folstein et al, 1975). It normally takes 5-10 minutes to complete.

### **E. DEMQOL**

The DEMQOL system consists of two interviewer administered Instruments used to measure the quality of life in dementia . (Banerjee et al 2006), DEMQOL (28 items) is completed by the person with dementia; DEMQOL-Proxy (31 items) is a proxy report of the person with dementia's quality of life completed by the main carer (score range 31 to 124, with higher score indicating better quality of life). DEMQOL has acceptable psychometric properties for people with mild to moderate dementia (defined as a Mini Mental State Examination (MMSE) score of >10) while DEMQOL-Proxy can be used for mild, moderate, or severe dementia. In this study, we report data for DEMQOL-Proxy only in order to consider the whole range of dementia severity.

### **F. RSQ and RQ-Attachment**

Relationship Questionnaire (Bartholomew 1994) is a single item measure made up of four short paragraphs, each describing a prototypical attachment pattern as it applies in close adult peer relationships .and the Relationship Scales Questionnaire (Griffin & Bartholomew, 1994) contains 30 short statements

drawn . It is possible to administer the RQ and the RSQ and then combine the obtained scores to form a composite measure of adult attachment.

### **3.12.5 .3 Secondary Outcome Measures for Carer**

A. Geriatric Depression Scale [GDS]

B. Beck's Anxiety Inventory

C. Marital Intimacy Scale in Dementia

D. Ways of Coping Checklist

This is a 42-item self-report questionnaire to assess the carer's coping strategies (Vitaliano et al, 1985). It normally takes 15–20min to complete and is rated on a four-point scale, from not applicable to very much used.

E. GHQ

General Health Questionnaire This is a 12-item self-report questionnaire to assess psychological distress and psychiatric morbidity (Goldberg & Williams, 1985). It is completed in 5min or less and each item is rated on a four-point scale.

F. RSQ and RQ-Attachment

### **3.12.6 Propose sample size, assumptions and power analysis & statistical analysis**

With 20 couples in each arm , the study will have 80% power to detect differences in the mean CORE item score overall of 0.85 or more between the groups (assuming a simple t-test is used to compare the groups with common standard deviation of 0.94 and using the conventional 5% significance level).

This relates to an approximate 35% reduction in mean score between the groups (assuming a mean of 2.4 in the placebo group).

Experience has shown that using fMRI paradigms similar to those herein proposed, inter group comparisons with sample as small as n=12 are sufficient to detect activation differences significant at the 5% level (Woodruff et al. 1997).

### **3.12.7 Define the interventions and propose frequency, duration and intensity**

#### **A. Psychotherapy**

In the experimental Group patients and partners will receive Psychodynamic interpersonal couple therapy plus standard clinical care and the control group will receive standard clinical care.

**Experimental Group** – Psychodynamic interpersonal couple therapy plus standard clinical care.

The principal aim of the therapy (in its brief format) is the identification of interpersonal conflicts or difficulties, which are causing or maintaining emotional distress. Clients and therapist work together to find and test solutions to these problems, and both intra-psychic and practical changes are encouraged. With this particular group emphasis will be on role transitions brought about by MCI. Treatment fidelity will be ensured by regular supervision of therapy, the use of a manual and audio taping of sessions for adherence and competency.

**Control-** standard clinical interventions provided from the memory clinic .Usually this is 30 minute follow up assessment from a memory clinic nurse in the 3 months period unless there a clinical indication for outpatient or a community psychiatric nurse follow up .

## **B. Imaging**

Functional images are acquired using the 3 Tesla scanner at Translational Imaging Unit at Hope Hospital in Manchester. Whole brain coverage is achieved using 29 axial slices with 5 mm spacing and a TR of 2.1 seconds. An fMRI scanning session of up to one hour takes place, involving a structural brain scan (6 minutes), a functional resting-state scan (5 minutes) and three cognitive tasks details of which are below:

### **N-back task**

Subjects are to be presented with a series of letters and then asked to identify, via a button press, various patterns depending on which block of the n-back task they are doing: press when see X (0-back block), press when letter same as the letter previously shown (1-back block) and press when letter same as the letter shown before last (2-back block). 35 second task blocks, containing instructions as to which part of the task the subject is to attend to, will be shown in a randomised order. There will be 3 repeats of each 1- and 2-back blocks and 6 repeats of the 0-back block in a functional MR run lasting 7 minutes.

### **Sociotropy /Autonomy task**

This is a task developed in house and aims to investigate the areas of the brain that mediate the processing of Sociotropy (being dependent on others and sensitive to personal rejection) and Autonomy (Reaching personal goals and maintaining independence). This is a passive task where subjects are presented with pictures of people in sociotropic and autonomic situations. One person in each picture is highlighted by a red circle and the subject is then asked to think how they would feel if they were the person in that situation. Example stimuli are: Autonomy - getting an F in an exam (negative valence) or winning a race (positive), Sociotropy – sat apart from a crowd (negative) or being happy in a group (positive). There are four active conditions (Autonomy negative,

Autonomy positive, Sociotropy negative and sociotropy positive) and a two control conditions containing neutral pictures (more than one person for sociotropy and one person only for autonomy). 45 second blocks, containing four pictures from one of the above active conditions, will be presented in a counter-balanced order with 45 second control blocks containing 4 neutral pictures placed in-between. There will be two repeats of the 4 active blocks and four repeats of the 2 control blocks in a functional MR run lasting 12 minutes.

### **Episodic memory task**

This task is developed in Experimental Design and Image Analysis (*EDIA*) Laboratory and NPU in Manchester University. Subjects are shown a series of pictures taken from an angle which make slightly difficult to encode without studying the details (encoding). They are then shown a block of four pictures which are slightly dissimilar to the one originally presented and the original one asked to identify the original one (retrieval). Each picture lasts for 30 seconds with the novel and familiar encoding blocks being followed by the novel and familiar retrieval blocks separated by a 10 second rest. There will be three repeats of this in a functional MR run lasting 14 minutes.

The result will be analyzed based on BOLD signal and functional connectivity and it will be correlated with the changes observed on clinical outcome measures.

### **3.12.8 Proposed duration of treatment period**

Eight 50-minute sessions over 12 weeks.

### **3.12.9 Proposed frequency and duration of follow up**

Baseline assessments at 0 and 3 months, Eight 50 minute sessions over 12 weeks and assessment after therapy and 3 months later. FMRI assessment at 1st month as well as 4<sup>th</sup> month.

### **3.12.10 Plan recruitment rate and feasibility and estimate recruitment and retention rates to devise a strategy for the trial**

Participants will be recruited from patients diagnosed to have MCI, attending memory clinic in south Manchester and living with their partners/spouses. We propose to recruit 20 couple on psychotherapy plus standard care arm [intervention] as well as 20 couple on standard care arm [controls]. From each group a minimum of 15 patients with MCI and 15 controls with MCI without any standard contraindications will be scanned with fMRI.

### **3.12.11 Planned recruitment rate and feasibility**

The patients and their spouses, known to the research team [20 couple on each arm] will be recruited from the memory clinic. Based on our previous experience, we intent to recruit 40 couples over 24 months period. An average of 3-4 couples will be recruited from memory clinic each month.

### **3.12.12 Planned Randomisation methodology**

The patients are randomised, using computer-generated numbers, by a statistician independent of the study.

### **3.12.13 Planned statistical analyses**

The primary analysis will be an intention to treat analysis, using change in mean scores over time and continuous variables (including changes in the symptom severity) will be analysed using analysis of variance, including multivariate repeated measures ANCOVA, taking into account factors known to influence treatment outcome. As numbers of the patients in age groups are relatively small, if the data are not normally distributed, non-parametric measures will be employed.

### **3.12.14 fMRI data analysis**

Analysis of the Fmri data will be carried out using Statistical Parametric Mapping (SPM). Images will be spatially pre-processed to correct for subject motion and to facilitate inter-subject averaging. For each task, responses in the control blocks will be compared to those in the active blocks via regression analysis. This will generate one contrast image per subject per task which is then used as input to the group random effects analysis.

Baseline: We will investigate the main effect of each task for each group (controls and MCI patients) using random effects one-sample t-tests. A two-sample t-test will then be used to investigate any statistical differences between the two groups.

After therapy (MCI patients only): A two-sample t-test will be used to investigate any statistically significant differences between the two therapy groups in brain areas observed to be different between the MCI group and the controls at baseline.

### **3.12.15 Proposed timetable**

0-6 m trial approvals, set up, training, and recruitment

6-12m priming, recruitment

12-24 baseline assessment, continued recruitment of patients, randomisation

24-36 months intervention, assessment and continued recruitment

36-42 months intervention, assessment and follow-up

42-46 months follow-up interviews, analysis

46-48 months final analyses and study close out

## Study time table



### 3.12.16 Study governance arrangements

Overall responsibility for the study will lie with the principal investigator and three supervisors. There will be an independent clinical supervisor for the entire trial period and the principal investigator will have weekly supervisions from all three supervisors.

The investigator will maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

The following points will be scrutinised in weekly supervision.

- patient and spouse/partner- informed consent
- patient recruitment and follow-up
- patient compliance
- accountability
- Treatment fidelity
- adverse event documentation and reporting

### **3.12.17 Serious and unexpected adverse events**

All adverse events occurring in the study will be recorded in the patient's clinical trial notes and forwarded to the supervisory committee. Any events reported by participants or their clinical teams will be followed up according to the local protocol, with guidance from the supervisory committee. The researcher will collect data on adverse events from the participants on a regular basis, which will be scrutinised in weekly supervision.

### **3.12.18 Data management**

The trial data management will be consistent with MRC Guidelines for Good Clinical Practice in Clinical Trials (MRC, 1998) and the Data Protection Act 1998. Principal Investigators will ensure that all personnel are familiar and comply with these guidelines. Data will be stored in case record files in ERC at Wythenshawe Hospital for 10 years. Steps will be taken to safeguard the anonymity and confidentiality of medical and research records.

## **3.13 Methods of exploratory trial**

### **3.13 .1 Aims and ethical approval grant approval and trial registration**

The aims of this part of the study were to conduct a miniature RCT as a modelling exercise, using the hypothesis, primary and secondary objectives described below and using the protocol described in the previous chapter to assess the feasibility of a RCT in the field of complex psychological interventions for people with cognitive impairment. Also the study aims at assessing the feasibility of application of complex neuro-imaging in generating theoretical data about the changes in brain function in people with memory problems undergoing a psychotherapeutic intervention and a control group.

The hypothesis agreed for the modelling exercise is given below. Based on this primary and secondary objectives for the modelling exploratory trial was set .

1. The hypothesis is that, structured psychotherapeutic intervention, based on Psychodynamic Interpersonal Therapy principles, directed at sufferers of MCI and their partners/spouses will result in improved well being of sufferers [as assessed by measures of cognitive function, mood, psychological distress, interpersonal functioning and quality of life] and lowered psychological distress in their partners/ spouses, in comparison with controls.

2. The improved well being of sufferers of MCI, as a result of successful Psychodynamic Interpersonal Therapy would result in changes in task induced blood oxygenation level dependant (BOLD) signal of fMRI.

### **3.13.2 Setting the primary and secondary objectives**

#### **A. Primary objective**

To test the efficacy of a psychotherapeutic intervention based on Psychodynamic Interpersonal Therapy principles, for people with Mild Cognitive Impairment[ MCI] and their partners /spouses and to study whether psychotherapy changes brain function in patients with MCI , based on functional magnetic resonance imaging assessments of patients' performance on emotional , episodic memory and working memory tasks before and after psychotherapy.

#### **B. Secondary objectives**

1. The secondary aim is to determine underlying mechanisms of change which result in improvement.

2. To elucidate the neural correlates of symptom reduction and to understand the biological mechanisms of psychotherapy .

3. To investigate changes in functional connectivity in subjects with mild cognitive impairment (MCI) during performance of emotional, episodic memory and working memory tasks before and after psychotherapy.

### **3.13.3 Ethical Approval and Grant Approval**

NHS Trust sponsorship and approval was obtained from Manchester Mental Health and Social Care Trust. Ethical approval was obtained from South Manchester Ethics committee. Later through Site Specific Information application a SPEAR Trusts approval was obtained to conduct the research in Bolton Salford and Trafford Mental Health Trust, Cheshire & Wirral Partnership NHS Trust, Cumbria Partnership NHS Trust, 5 Boroughs Partnership NHS Trust,> Lancashire Care NHS Trust, Manchester Mental Health and Social Care NHS Trust, Mersey Care NHS Trust, Pennine Care NHS Trust.

To conduct the scan studies an imaging grant of 60 hours of fMRI scanning time on the 3T scanner study time was obtained from Translational Imaging Unit at Salford.

Additional R&D funding for small expenses was granted by Prof Alistair Burns through Old Age Psychiatry research funding.

### **3.13.4 Trial registration**

An ISRCT number was assigned from Current Controlled Trials Limited.

### **3.13.5 Study design**

The study was conducted as a Randomized Controlled Trial in 3 SPEAR centres, the principal one being Manchester Memory Clinic at South Manchester located at Wythenshawe Hospital. The other centres were Salford

Memory Clinic in Hope Hospital and Stockport Memory Clinic in Stepping Hill Hospital in Stockport.

### **3.13.6 Development and delivery of intervention**

We adopted the same methodology of our previous trial described in Burns et al. Psychotherapy sessions lasted 50 minutes and it was delivered at patient's home with patient and carer being with the therapist in a couple therapy form. 8 sessions were conducted by 4 researchers in a 3 month's period. The psychotherapy has been summarised in a manual (Shapiro & Firth, 1987) and treatment fidelity was ensured by regular supervision using audiotapes. One session from each individual therapy was rated for adherence to the model using the Sheffield Psychotherapy Rating Scale (Shapiro & Startup, 1993). This scale allows sessions to be rated according to three main subscales: one for psychodynamic interpersonal therapy; one for cognitive-behavioural therapy and one for generic aspects of psychotherapy. The intervention showed high scores on the psychodynamic interpersonal therapy and generic subscales and low scores on the cognitive-behavioural therapy scale, confirming adherence to the model.

### **3.13.7 Patients**

Eligible patients were those diagnosed of MCI from any of the three memory clinics as per inclusion criteria described above. The principle researcher screened the case notes from the memory clinics with the assistance from the clinical team working in the memory clinics. After obtaining the agreement in the multi disciplinary team the patients and their partners were contacted through telephone and the participant information sheets were sent either by the post or hand delivered to the patients. Later follow up telephone calls were made to see whether the patients were interested in taking part in the study. Those who expressed an interest were visited at home by the researcher and the

details of the projects were discussed with the patients and their partners. In this visit informed consents were taken from the patients and those required further time were revisited for the consenting process. It was aimed to study the feasibility of recruiting 40 couples to the study with 20 couples in the treatment arm and 20 couples in the control arm. It was also aimed to study whether 15 Patients with MCI from the intervention arm and 15 patients with MCI from the control arm could be recruited for the neuro-imaging study as described in inclusion criteria above without any standard contraindications to MR imaging.

### 3.13.8 Randomisation

Those people agreed to take part in the study were randomised using a computer generated randomisation schedule as shown below.

Table 4 randomisation procedure

Subject no.	Allocation	Subject no.	Allocation
1	PIT	21	STANDARD
2	STANDARD	22	STANDARD
3	STANDARD	23	PIT
4	PIT	24	PIT
5	STANDARD	25	STANDARD
6	PIT	26	PIT
7	STANDARD	27	STANDARD
8	PIT	28	PIT
9	PIT	29	STANDARD
10	PIT	30	PIT
11	STANDARD	31	PIT
12	STANDARD	32	STANDARD
13	STANDARD	33	PIT
14	PIT	34	PIT
15	STANDARD	35	STANDARD
16	PIT	36	STANDARD
17	STANDARD	37	PIT
18	STANDARD	38	STANDARD
19	PIT	39	STANDARD
20	PIT	40	PIT

### 3.13.9 Study procedures

Those patients randomised to either arm were evaluated by an experienced researcher independent of the study using the primary and secondary outcome measures. The evaluation was conducted in patient's homes and patient and

carer were evaluated separately taking 40-50 minutes for administration of questionnaire for each participant. For those patients identified for neuro-imaging study was given an appointment for the fMRI and a researcher was present in the scanning centre to guide the patient through the process and take immediate decisions in relation to the procedure. the pre scanning preparations and the time for actual scanning resulted in patient spending up to 2 =-3 hours in the scanning department and the actual scanning time lasted around 50 minutes.

Within few days after the scanning patients allocated to the treatment arm and their partners were visited by the therapists and 8 sessions of psychotherapy were provided. The psychotherapists had regular weekly supervision sessions. Supervision where the recorded therapy sessions were listened by the supervisor as well as therapists and necessary modifications were done to ensure adherence to the treatment protocol.

After finishing the therapy sessions those patients and carers were seen by the independent researcher to repeat the outcome measures. Soon after this neuro-imaging sessions were also arranged for those who agreed for repeat scans.

The patients and carers on the control arm did not receive any form of therapy or equivalent procedures other than standard clinical care from the memory clinic. They were also evaluated by the independent researcher 12 weeks after the initial assessment. Those who agreed for the repeat scans were scanned soon after the assessment by the researcher using the same methodology described above.

### **3.13.10 Analysis**

Qualitative analysis was done by the principal investigator focusing on the feasibility outcomes described above and it was not intended to conduct a statistical analysis for the outcome measurements to study the treatment effect

size. It was also planned to describe the results in a narrative style focusing on the feasibility outcomes.

## **Chapter 4: Results and discussion**

### **4.1 Results**

Between January 2008 and July 2011, 356 case notes were screened by the researchers, from 3 memory clinics. The names of people suspected to have MCI were passed to the research team by the clinicians. Different memory clinics used different assessment tools to conduct detailed cognitive examination like MMSE , ACE-R and KOLT, however all the clinics used MMSE. 126 patients were identified with a diagnosis of mild memory impairment and 42 patients appeared to be meeting the inclusion criteria. Many patients among 126 although had a diagnosis of MCI many had scores in the MMSE below 26 which made them unsuitable for the study. Many patients did not have a partner and they lived either alone or with the support of a family member or formal carer. Few patients screened had progressed to mild dementia and few were troubled by physical problems made them unsuitable for participation .

All those 42 patients were approached by the researcher and 32 couples expressed interest to take part in the research study. On further discussions 16 patients were found unsuitable for the study because of different reasons. Of those 16 patients consented for the study 8 couples were randomised to the treatment arm and 8 were randomised to the control arm. 6 couples from the treatment arm completed the study and all 8 couples from the control arm completed the study. 4 patients from the treatment arm consented for the scan procedure and however only two were able to complete first scans and one completed both scans. 3 patients from the control arm consented for the scan and only one was able to complete both scans.

The characteristics of patients randomized are described in the table below

**Table 5 : The characteristics of patients randomized**

Characteristics	Treatment	Control
n = patients	8	8
male patients	3	5
female patients	5	3
age (years ) ; mean	54-82 ; 74	58-80 ; 76
on antidepressants	2	2
n Partners -spouses	8	8
MMSE ,mean		
Patients	27 (range 26-29)	26 (range 26-28)
Partners	29 (range 27-30)	29 (range 28-30)

#### **4.2 Assessment methods and findings**

All the pre and post treatment questionnaires were well received by the patient and carer population. The demographic characters of the patients and carers were somewhat similar as shown on table above. There were no major differences observed in the assessment scales in the patents or carer population over the time period of study. There were no major differences in the 34 questions answered by the patients and control group when CORE was used an outcome measure to assess generic aspects of psychological wellbeing. The

questions about how they have been feeling over the last week, using a 5-point scale ranging from 'not at all' to 'most or all of the time', on 4 domains including subjective well-being, problems/symptoms, life functioning and risk/harm has shown some difference on scores on domain 2 that is problems/symptoms. The mean score on CORE problems/symptoms (12 items) on both patient groups were 2 and both control groups were 1. The problems appeared to be more related to physical problems in both groups. None of the patients or carers in the treatment or control arm showed any signs of clinical depression although few of them were on anti depressants as shown in the table. Based on the methods described above we took an approach to derive number needed to assess was useful feasibility outcome.

#### **4.2.1 The number needed to screen (NNS) and the number needed to allocate (NNA)**

The number needed to screen (NNS) and the number needed to assess (NNA) are concepts used and described recently in feasibility studies. NNS is a concept originally developed to assess screening programmes (Rembold 1998) This was statically described and used in studies with radiographic assessment of different diseases, presented according to Number Needed to Treat (NNT) analysis terminology Frobell et al 2007 suggested using this concept in clinical trials to estimate how many patients were needed to be screened to include one patient in the trial. The NNS was calculated by dividing the number of patients screened for eligibility with the number of patients included in the trial. According to Frobell et al NNS multiplied with priory determined sample size is an estimate of how many patients needed to be screened.

In addition to this NNA is a concept introduced by Forbell et al. This concept is also similar to NNS and here all the patients eligible for inclusion were regarded as allocated. The NNA was calculated by dividing the number of allocated

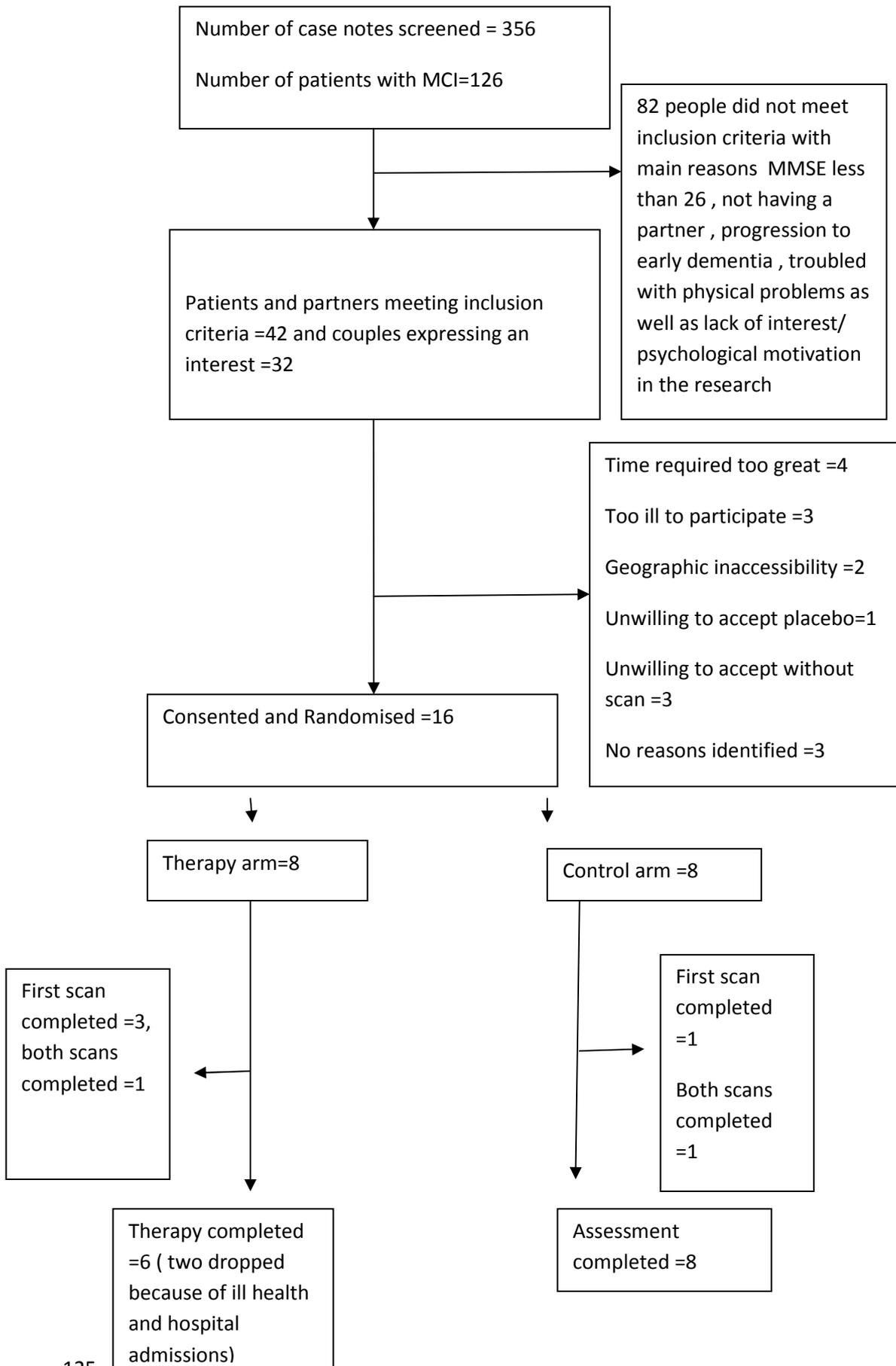
patients with the number of included patients . This gives an estimate of how many patients eligible for inclusion that would need to be allocated in order to include one patient in the trial .the authors argue that with a priory sample size would present an approximation of the total number of patients fulfilling inclusion criteria necessary to allocate.

The NNS and NNA provided an estimate of how many patients were needed to be screened and allocated to include one patient into the trial. The NNS gives an estimate of how many patients needed to be screened and NNA the number of patients needed to have in the initial study to get one completed patient (Frobell et al 2007, Rembold et al 1998, Nelson et al 2002 ).

Using the above concepts we calculated the NNS, that is the number of case notes screened divided by the number of patients allocated. The value of NNS is  $356/16 = 22.25$  (23)

We also attempted to calculate NNA. Although the factor of lack of interest for otherwise eligible participants made this calculation difficult , we included 42 couples who met the inclusion criteria to calculate the NNA and divided it with the total number allocated that is 16. The value of NNA is  $42/16 = 2.6$  (3)

**Fig 7 : Patient flow diagram –NNS=23, NNA= 3**



As MCI is a diagnosis made in the memory clinic with a range of assessments 356 case notes were screened to identify patients who are potentially meeting the inclusion criteria. However these patients included the one's in different stages of assessment without a diagnosis, people with established dementia , depression , cognitive impairment due to delirium , alcohol misuse etc . Also information was gathered from the initial assessor regarding the patient's social situation and general physical condition in addition to the information from the case notes before the researchers contacted the patients.

The information included whether the patient has a spouse or partner meeting the inclusion criteria and whether the patient and carer has a serious medical condition or extreme frailty making inclusion in a research project difficult for them . Further to this 126 couples were identified as suitable for the project, however on further telephone contact as well as face to face assessment indicated that 82 of those 126 patients did not meet inclusion criteria including a number of people with lack of interest or lack of psychological motivation to take part in research project. 3 patients were interested in the project because after seeing the information leaflet they believed that a special scan is helpful in making the diagnosis more clear with more understanding about whether they will progress to dementia later. When the researcher explained the nature of the study and the chances of them being randomised to either arm, they informed the researcher that they were only interested in the scan and they were excluded from the study. 2 people dropped out from the therapy because of the changes in their social and physical health. One patient was hospitalised with a suspected stroke and the other patient's husband was hospitalised with serious ill health.

## **4.3 Discussion**

### **4.3.1 Main findings**

This study shows that it is possible to adapt a model of psychotherapy for those with MCI and their carers in a couple form .The study also showed that it is possible to test this complex intervention using an RCT methodology. The study also identified a number of feasibility issues in terms of recruitment, resources as well as use of modern neuro-imaging methods in older people with cognitive impairment. The study also identified the methodological issues in developing and delivering experimental designs in the real life clinical population.

Reasons for a slow accrual were low number of patients with MCI, and any patients not fitting into the inclusion criteria.MCI is a memory clinic only diagnosis and usually no interventions are offered to this patient population from the clinical side with a reassurance that they do not have dementia.

This appeared to be a reason for patients not being interested in taking part in research activities. However the partners generally appeared to be more interested in patients taking part in the research mainly because they had the fear of the patient developing dementia and many partners believed that patients might benefit from psychological interventions as well as a scan to understand better about the nature of their cognitive impairment. Many carers were not interested in the research when they were informed about the possibility of being randomised into a control arm. Although many patients expressed an interest in taking part in the study initially, the time required to complete the study and the commitment required from the patient and the partner , physical health states of the patient and the partner , geographic inaccessibility for the research team , unwillingness to accept without treatment or scan were the main reasons for drop outs later.

All the patients completed the first scan found the procedure lengthy, tedious as well as difficult to complete. Lying down in the scanner for 50 minutes appeared to be too difficult for many who had problems related to arthritis. Also visual problems made it difficult for many to concentrate on the tasks and few patients became particularly very anxious complaining that they may have made too many mistakes when they responded to the tasks. Generally patients reported that the memory task was very difficult to complete. Regarding the sociotropy autonomy task many were unsure whether they were able to picture themselves in the position of the person they have seen in the picture as the people appeared in the picture were young students.

The qualitative data was more derived from the feedback given to the principle investigator in a semi-formal way and there was no standardised approach in the collection of patient and carer feedback.

Although it was not the primary intention to test the efficacy of the treatment intervention the study was useful in gaining insight into main barriers to inclusion in the trial, experience of assessment, challenges in recruitment and retention and reasons for drop out which are discussed in detail below. The qualitative information derived from the study was also very useful. All the outcome measures and psychotherapeutic interventions are well received by the patients with MCI and their partners with good feedback. However the fMRI procedure was not well received by the patient population indicating the necessity to adapt the interventions to suit the population's needs further.

#### **4.3.2 Challenges of conducting this exploratory trial in elderly population with cognitive impairment**

The challenges of conducting this trial are described below in 9 steps detailing the practical aspects as well as learning from this exploratory trial. In each step

few of the general principles outlined above are examined particularly in relationship with this trial.

### **4.3.3 Challenges in developing innovative research methodology**

#### **4.3.3.1 Development of research team and interventions**

Although substantial information is available on how to conduct RCTs in the field of psychotherapy; so far there is no published work detailing how to test a complex health intervention in elderly people with mild cognitive impairment predominantly living in the community. Some early work had reported that in population living in community settings the general dropout rate from psychotherapy is 50-60 % by the fourth session (Klener,1982) with a US national rate of 75% outpatient mental health services. Pruchno (1983) reported 41% of dropout for elderly people who received treatment from an community mental health centre. Similar reports were not available from the UK settings.

The previous work done in the UK indicated the benefits of time limited goal orientated therapy in the elderly. Developing a psychotherapeutic model and adapting it for the elderly population was a challenge. We used practical modelling in the clinical population presenting to the memory clinic and through his approach a more definite treatment intervention was developed. Training process including supervision to standardise the model was developed. Although we had some pilot data from a previous study where a similar model is applied for patients with cognitive impairment, carers were not involved in direct therapy sessions. As psychotherapy is a complex intervention many components including characteristics of the patients and carers, the content of the therapy, the delivery mechanism, the location of the therapy and the characteristics of the therapist etc were important. As Mild Cognitive Impairment is a diagnosis comprising a heterogeneous group of aetiology it was particularly challenging to standardise the therapy model. Here the exploratory

trial is used to consider variants of the intervention and their possible effects on outcomes and an observational method is also used in generating the data.

As the investigators and therapists were full time clinicians this study helped to provide an insight into the training needs and time commitments necessary to conduct a full scale RCT. Also the study helped to provide a theoretical framework for 'modelling' in the future larger scale trials. Moreover this phase has provided an accurate knowledge of resource implications for developing a psychotherapeutic intervention for a challenging population, training resources required to develop a research team as well as need for standardised interventions in pilot RCTs to aid accurate power calculations.

It was also identified that a qualitative research was useful in psychotherapeutic interventions in this patient group to identify which component of therapy was working as the treatment was provided by different therapists with varying experience and observations were made regarding the link between therapist's experience and dropout rates. A qualitative approach was helpful in identifying whether particular characters of patients or subgroups in this heterogeneous population was responding well to the research call, therapeutic intervention or neuro-radiological procedure.

Varying degree of challenges was experienced in developing neuro-imaging methodology. Although there were few small scale neuro-imaging studies in people with Mild Cognitive impairment, so far there were no attempts to study the effects of psychotherapy in MCI population. Developing fMRI as a measure to understand the mechanism of psychotherapy was a novel methodology and in that way this study was a groundbreaking work.

The study provided great deal of information about the suitability of this neuro-imaging intervention for older people; highlighting many practical aspects of applying complex novel interventions in older population. It also gave more

detailed information about feasibility, adaptability and the need for stringent research governance mechanisms in large scale studies. The need for individualisation in certain interventions was also highlighted in the study showing the complexities and pitfalls in a randomised control trial methodology to address some particular clinical research questions. As mentioned before resource issues, expertise for developing fMRI paradigms and analysis methods were also observed as challenging fields providing more insight into the necessity of coordination in interdisciplinary large scale trial where joint expertise is necessary. As this part of the study was designed to investigate the main effect of each task for each group in addition to investigate any statistical differences between the two groups it is used mainly as feasibility study to test whether the methodology is suitable to address the research question.

#### **4.3.3.2 Resource, training and ethical issues**

The study provided factual information about the resource implications and budgeting in large-scale trials. In addition to grants aimed for specific interventions, it was observed that there needed to be budgeting for logistics, staff time and a range of miscellaneous expenses.

There needed to be budgeting for training and development of a research team as well as proper planning was necessary for the staff time. The complex nature of the population necessitated development of methods adaptable for the population including setting of delivery of interventions. Also older population with complex needs were demanding in terms of staff time; and allocation of resources to address this would be key to success in future research projects.

#### **4.3.3. 3 Identification of sample & inclusion and exclusion criteria**

Although identification of patients with MCI has not been challenging according to the literature as well as our previous experience, identification of sample for this study – Patients with MCI and their partners- has been

extremely challenging. As majority of patients presenting with the condition are elderly; many of them have co-morbid health issues associated with frailty. The issues related to sampling indicated the need for a critical evaluation of eligibility criteria specifying the condition MCI and eligible carers. In this heterogeneous population identification of couples meeting specific criteria with less potential for confounding and scope for participation was observed as a major issue affecting the recruitment process. It was identified that data from previous experience of recruiting patients with MCI, resulted in overestimation of potentially eligible candidates –both patients and carers- for a trial with innovative methodology. As suggested by Rinck et al 1997 this exploratory trial is used as a ‘case finding’ strategy, for the investigators to understand how many patients could be recruited to a definitive trial; by testing the methodology in an actual clinical research setting. Contrary to the anticipation it was also identified that a high proportion of this patient and carer population refuse to take part in trials.

Although the development of strict exclusion criteria based on diagnosis and MMSE score helped to define the population, attempt to limit the study to those living with a partner substantially limited the feasibility for recruitment, as there needed to be willingness from both the patient and the partner to take part in the study. Refusal or consent from one participant resulted in couple not taking part in the study on many occasions.

Although the standard contraindications for MRI excluded many potential participants from the study, in the actual setting many potential participants refused to take part after knowing in detail about the time they needed to spend in the MRI as well as tasks they needed to perform. The general physical state of the patients was screened by the researcher and inability to spend long time in the MRI was identified in many patients when the trial progressed, particularly after few initial dropouts as a result of prolonged time in the MRI

scanning. Patients with co-morbid physical problems particularly arthritis found it difficult to tolerate neuro-imaging and to avoid serious adverse events few scans were aborted. Researcher discouraged few participants to take part in neuro-imaging part and on many occasions it was identified that participants had an expectation of having an MRI scan for accurate diagnosis of their condition and understanding about lack of diagnostic and prognostic components in the study resulted in refusals and dropouts. Also high prevalence of sensory deficits in the population excluded many patients from the study.

#### **4.3.3.4 Outcome measures and data collection methods**

Selection of the appropriate primary outcome measure, also correlating with the neuro-radiological tasks has been difficult .The suitability for administration in the cognitively impaired population. CORE was identified as a simple primary outcome measure with good acceptability in this population. However there were no previous studies using CORE in this population. CORE was also not validated in this population and, further studies should aim at validating CORE against Geriatric Depression Scale using the data from first 10 subjects recruited in to the study.

The secondary outcome measures, although were well received by the clinical population individually, the administration of many of them together was not well received by the sample.

#### **4.3.3.5 Screening, consenting and response and establishment of NNS and NNA**

This exploratory trial is designed to provide systematic information about the efficiency of recruitment strategy in this particular population, as well as to identify retention pattern . We proposed a mathematical model similar to a screening taxonomy described by Frobell 2007 to establish the Number Needed to Screen [NNS] and Number Needed to Allocate [NNA]. We also introduced a

newer concept Number Needed to Assess ,which can be significant in populations like elderly with cognitive impairment and physical frailty , which makes the recruitment challenging .

In this model we attempt to use the framework to have consistent definitions of patient groups moving through different stages of evaluation for enrolment into the study.

#### **4.3.3.6 The 15 steps involved in the process are described in detail below**

1. Patient identification: The pool of potential patients included in the study is those patients diagnosed with MCI in the Greater Manchester memory clinics. Each patient came to the attention of the research team through multi-disciplinary meetings as well as case note identification; has undergone a preliminary screening of case notes.
2. Detailed case not review: Each patient identified has undergone a detailed case note review.
3. Telephone contact to determine the interest: The patients appeared to be eligible for the study and their carers were contacted for a discussion over telephone to see whether they are interested to hear about the study and whether a researcher could approach them with more details.
4. Discussion for consent: According to the patient's and carer's suggestions if they are interested in receiving participant information leaflets and consent form ,it was posted to them or presented to them in person by a researcher.
5. Consent Signed: In depth discussions about the process by the researcher and detailed health screening took place in the process of signing the consent form.
6. Formal Entry: Number of patients completed the first part of the outcome measure.

7. Neuro-imaging: Number of patients entered the first part of neuro-imaging.
8. Number of patients completed the first part of neuro-imaging.
9. Number of patients entered in to the psychotherapy / control arm.
10. Number of patients completed the psychotherapy / control arm of the study.
11. Number of patients entered the second part of neuro-imaging.
12. Number of patients completed the second part of neuro-imaging.
13. Number of patients completed the second part of outcome measure.
14. Number of patients completed the study with adequate data.
15. NNs: Number of patients needed to have in the initial screening to get one completed patient.

#### **4.3.3.7 Recruitment efficiency and retention rates.**

The higher NNS in this study indicated a number of challenging issues affecting the recruitment and retention rate. The general health condition of the patient and carer appeared to be an important determinant in the interest in participating in the research as well as a determinant of drop out. Considerable motivation from the patient and carer was needed in the participation for the study.

Generally there was a lack of interest from the patient's side however the carers experiencing stress, appeared to motivate the patient to take part in the procedure. In this group a high expectation of going into the treatment arm resulted in withdrawal of consent after the awareness about the randomisation procedure as well as the possibility of going into the control arm. Many couples although have shown an initial interest, refused to take part in the study after realizing about the time commitments necessary for the study. Also the plan to provide psychotherapy at patient's house resulted in an increase interest, the lengthy neuro-radiological procedure arranged in the hospital setting appeared

to be a determinant for few people's refusal. The standard contraindication for MRI scan appeared to be over-represented in this population and in comparison with standard MRI procedures; the length of stay in MRI as well as the lengthy tasks also resulted in dropouts.

The time taken from the approval of study to the start of recruitment has resulted in many patients identified in the initial pool progressing to the dementia syndrome as well to the exclusion criteria according to the cognitive scores. Many people had co-morbid physical illness resulting in a change in their general health status, hospital admission etc resulting in drop out from the study or refusal in taking part. Many of those couples expressed interest in the MRI part of the study hoping that they get more accurate information about their diagnosis and prognosis were discouraged by the researcher as their general physical state was not suitable for the complex fMRI intervention.

#### **4.3.3.8 Factors to improve acceptability of the study procedure**

This study was also indented to assess factors determining the acceptability of complex research procedures in elderly population with cognitive impairment. The study highlights the importance of minimising the burden to the elderly participant with cognitive impairment participant. In addition to the lengthy duration and commitments from the participant's side the complexity of the trial design with multiple procedures for data collection itself appeared to be the determining factor in lack of participation and difficulties related to the recruitment in the trial. As the complex design necessitated extensive data collection procedures, it highlighted the importance of simplifying the trial design in this patient population.

#### **4.3.3.9 Randomisation, Blinding and issues related to power**

The randomisation was conducted as a part of the educational exercise for the investigator. By this exercise it is observed that a randomised control trail

methodology can be applied to test a psychotherapeutic intervention in a patient group with challenging demographic characteristics.

Although the secondary outcome of this exploratory trial included planning assumptions for a larger study, the treatment effect size calculation was not an aim for this study except for the principal investigator's educational interest.

#### **4.3.3.10 Operational issues**

We conducted this exploratory trial with limited funding. We expect to generate data regarding whether larger study is financially viable in this field. Although the added value of the study is its design similar to a formal trial, conducting this in a setting with limited resources has been challenging. The attempt to conduct this trial in multiple sites highlighted the operational issues like human resources, storage, and data management.

Establishing time scales and keeping up with time scale has also been challenging as there was many unexpected, design related as well as patient related factors delaying the entire process of the study. As it was an innovative methodological design of an exploratory trial, the operational aspects were also carefully studied and we aim to generate sufficient data regarding the financial aspects, training, skill mix as well as strategic of a trial of complex health interventions in elderly population.

#### **4.3.3.11 Summary**

There is critical shortage of large scale clinical trials of psychotherapeutic interventions with robust methodology in the increasing clinical population of older patients with cognitive impairment. There were no studies published, to understand the neuro-biological mechanisms of psychotherapeutic interventions in this population. In spite of the barriers to research identified in this field there is increasing awareness about the necessity to conduct research in this growing

population. We designed this innovative exploratory trial ,in a similar fashion to a full scale RCT as a groundbreaking work in this field particularly to understand the challenges involved in evaluating complex health interventions in older people with cognitive impairment in addition to generate data for a definitive trial in the future .We primarily aim to address the lack of understanding and attention on feasibility of definitive studies in the field of complex health interventions in cognitively impaired people ;which has resulted in many funded trials in this field being unsuccessful. We are also unaware of any publications specifically addressing the challenges in conducting a trial in this population or outlining the steps necessary to design and conduct a formal exploratory trial of a complex health intervention in patients with cognitive impairment and their carers. Through this work we aim to address this issue in a systematic way to guide future research in this field. In the result part we aim to produce a draft framework to support successful completion of high quality research in innovative complex health interventions in clinically and demographically challenging population.

We took a novel approach to the design and conduct of this study, using it as a dynamic learning process, particularly to understand the need to alter the design and as well as to devise recruitment strategies to test complex health intervention in older people. As an added value the design similar to an RCT gave us an opportunity to achieve the researcher's educational goal through a modelling exercise including testing the hypothesis, the methodology as well as understanding the concepts of generating seminal data to aid power calculation. Also we were able to generate more information regarding the adaptability and acceptability of psychotherapeutic as well as neuro- radiological interventions in this population neuro- radiological mechanism of psychotherapy. We were also able to generate important information about psychological needs and response to therapy in this population as well as preliminary findings about the

use of functional neuro-imaging in understanding the biological mechanisms underlying in the treatment response in psychotherapy in people with MCI.

Based on our findings we recommend that modelling studies should be an integral part of any research project involving clinical population particularly when complex interventions are tested. It is also helpful for clinicians new to research to understand the theoretical and practical aspects of conducting bigger studies including RCTs clinical and academic settings. It is also recommended to test staff attitudes towards research and clinicians ability to recruit to the research projects .In any research projects involving older people user and carer involvement in advance would give good sight to researchers about the practical issues they need to be addressing. Staff surveys about the awareness of the importance of research as well as surveys among potential participants about their willingness to take part in the research and structured approach to feedback about trial interventions should be integrated to the methodology of any feasibility studies.

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## **Appendix 1**

### **Psychotherapy in Mild Cognitive Impairment**

#### **Information Sheet [For Patients with Mild Cognitive Impairment]**

Thank you very much for taking the time to read this information sheet.

We would like to invite you and your partner to take part in a research study. Before you decide, you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **What are the purposes of the study?**

We are carrying out a research study into a special type of talking therapy and counselling (psychotherapy) for people with mild memory problems and without dementia at the memory clinic in Wythenshawe Hospital.

The long term aim of the study is to devise specific counselling therapy for people with mild memory problems and their *partners*, which we hope will help to alleviate problems in adjusting to the diagnosis and changes imposed by these mild memory problems on the lives of themselves and their family.

As part of the study you (not your partner) will be invited to take part in an MR scan before and after 3 months of counselling. This is to understand how special counselling changes brain function

#### **Why have I been chosen to participate?**

We are asking you to participate in this study because you have a diagnosis of Mild Cognitive Impairment (mild memory problems reported by you or your family and you don't have dementia)

#### **What will happen if I take part?**

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). In this study a computer generated programme will allocate you either to a group receiving normal care from the memory clinic or to a group receiving normal care from the memory clinic as well as special counselling.

40 couples will take part in this study.

20 of these couples will receive *the normal care from the memory clinic* and 8 sessions of talking therapy and special counselling at weekly intervals with a trained psychiatrist [*your research doctor, another doctor or specialist nurse*] who is specialised in memory problems. The other 20 people will receive their normal care without the special counselling. Most of the counselling sessions will be with the patient and his or her partner.

By taking part in the study you have a 50% chance of getting special counselling in addition to your normal care from memory clinic.

All people taking part in the study, including those not receiving the special counselling, will be asked to complete some questionnaires regarding their mood, daily functioning and memory. You will be seen in a study visit at home by a researcher who will complete the questionnaires. These measures will be completed at the beginning and at the end of the treatment [3 months later] . Those couples receiving the special counselling will be visited at home by the psychiatrist who is doing the therapy, to provide the special counselling for 8 sessions.

As part of the study you (not your partner) will be invited to take part in an MR scan before and after 3 months of counselling.

### **Do I have to take part?**

It is entirely up to you whether or not you wish to take part in the study. If you do, keep this information sheet and sign the consent form. You are free to withdraw from the study at any time. Even if people are not happy to take part in the scan they are allowed to take part in the special counselling. A decision to withdraw at time, or a decision to take part, will not affect the standard of care you receive.

The consent from you and your partner will be required separately before the participation in the study and this consent may be withdrawn at any time during the study. The consent for the special counselling, each session of audio recording and scan will be taken separately.

### **What is involved in the Psychotherapy [Special Counselling]?**

In each session of Psychotherapy [special counselling ] you and your partner discuss your difficulties which are causing or maintaining emotional problems for you or your partner with the research doctor. Then you and your research doctor work together to find practical solutions for these problems.

It is a requirement to do audio recording of the conversation on each special counselling session, so that the supervisors of your research doctor can listen to it and make sure that the therapy is carried out in the correct way.

We appreciate your permission to transcribe the audio-recorded conversation as well as to use direct quotes from the conversation with out revealing your identity, once we publish the research in scientific journals. If you don't want us to transcribe the audio taped conversation, or use the direct quotes from the counselling sessions in the publications you are allowed to withdraw consent for that particular part of the study. After each special counselling session the research doctor will make sure that, you and your partner are happy about us doing transcription as well as using direct quotes. If any of you are not happy about this after the recording, there is an opportunity for you to withdraw the consent for that particular part of the recording to be used. As explained earlier a decision to withdraw at time, or a decision to take part, will not affect the standard of care you receive

### **What is involved in the MR scan?**

MR scanning is considered completely safe and routine and **does not** involve any exposure radiation. You simply lie relaxed and as still as possible on a bed with your head inside the scanner while it builds up pictures of your brain. Pads will cushion your head and you will be given ear plugs, as you will hear knocking noises

while the scanner works but there are no visible or hidden moving parts. Fully trained radiographers and your research doctor will be present at all times.

#### **What do I have to do before and after the scan?**

There are no special requirements prior to the scan. After the scan, we expect you to be able to go about your daily life as usual.

#### **What are the risks of participating in the study?**

There are no identified risks for talking therapies and the scan does not involve any radiation therefore risks will be minimal. Some people may find the inside of the scanner a little bit cramped so it is not advisable to take part in this part of the study if you suffer from claustrophobia (fear of closed spaces). If you begin to feel uncomfortable whilst in the scanner you can stop/suspend the session at any time via the pushing of a special button.

In the unlikely event of you experiencing any discomfort, distress or inconvenience in relation to special counselling or scan your research doctor will provide immediate attention to you. If you wish to get further help, arrangements will be made to refer you to Dr. Lennon, Consultant in Old Age Psychiatry in Wythenshawe hospital.

#### **What are the benefits of participating?**

By participating in this research you may be helping the investigators understand more about how helpful special counselling in people with mild memory problems and their partners is. We cannot promise the study will help you but the information we get from this study will help improve the treatment of people with Mild Cognitive Impairment.

Participation in this research study involves no cost to you and you will not be paid for your participation

This study will be part of a MD qualification for Dr. Arunraj Kaimal [your research doctor] and Prof. Alistair Burns will supervise this.

#### **What if there is a problem or something goes wrong?**

Any complaint about the way you have been dealt with you during the study or any possible harm you might suffer will be addressed.

You should ask to speak with the researchers who will do their best to answer your questions (Dr. Arunraj Kaimal, 07812243439).

If you wish, arrangements will be made for you to discuss this with Prof. Alistair Burns or Dr. Sean Lennon in Wythenshawe hospital.

MR scan is regarded as an entirely safe procedure. However, if you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from the hospital.

*In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Manchester Mental Health and Social Care Trust, but you*

*may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).*

### **What happens when the research study stops?**

Once the research study stops your normal care from memory clinic continues. You will receive verbal feedback or a letter of thanks at the end of the study from your research doctor who is the talking therapist.

### **What will happen to the results of the research study?**

The data gathered from you and all the other participants in the study will be analysed and published in a medical journal and/or presented at medical/academic conferences. The audiotapes will be safely erased after the recommended period they need to be kept.

### **Is the study confidential?**

Your personal information will be kept secure and separate from the data sheets gathered from your answers to the interview questions. This ensures that your personal information will remain confidential. A special study code will be assigned to you and your name will not appear on study forms. If you consent to take part in the research your medical records may be inspected by the regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

It is important for your GP to know that you are participating in a research study. We will ask you whether you are happy for them to be informed of this.

### **Who is supervising and funding the research?**

This study is supervised by Professor Alistair Burns (Wythenshawe Hospital), Professor Else Guthrie (Manchester Royal Infirmary), Dr. Shane McKie & Dr. Rebecca Elliot [Neuroscience and Psychiatry Unit, University of Manchester] and Dr. S. Lennon (Wythenshawe Hospital).

The study is sponsored by Manchester Mental Health & Social Care Trust.

### **Where is the MR scanning done?**

All MR scanning appointments will be arranged at a time of your convenience. Scanning will be done at the 3T scanner located in the Translational Imaging Unit [TIU] located in Hope Hospital, Manchester

### **Where can I get more information?**

The study will be explained in more detail by your research doctor Dr. Arunraj Kaimal, who is a qualified psychiatrist, currently specialising in Old Age Psychiatry and management of memory problems.

Dr. Arunraj B. Kaimal

Specialist Registrar

South Manchester Memory Clinic

Wythenshawe Hospital

Manchester

M23 9LT

TEL: 0161 2916942

Mob: 07812243439

## APPENDIX 2

### **Psychotherapy in Mild Cognitive Impairment**

#### **Information Sheet [for partners of patients with Mild Cognitive impairment]**

Thank you very much for taking the time to read this information sheet.

We would like to invite you and your partner to take part in a research study. Before you decide, you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **What are the purposes of the study?**

We are carrying out a research study into a special type of talking therapy and counselling (psychotherapy) for people with mild memory problems and without dementia at the memory clinic in Wythenshawe Hospital.

The long term aim of the study is to devise specific counselling therapy for people with mild memory problems and their partners, which we hope will help to alleviate problems in adjusting to the diagnosis and changes imposed by these mild memory problems on the lives of themselves and their family.

As part of the study the your partner (**not you**) will be invited to take part in an MR scan before and after 3 months of counselling. This is to understand how special counselling changes brain function

#### **Why have I been chosen to participate?**

We are asking you to participate in this study because your partner has a diagnosis of Mild Cognitive Impairment (mild memory problems reported by the patient or patient's family and the patient does not have dementia).

#### **What will happen if I take part?**

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). In this study a computer generated programme will allocate you either to a group receiving normal care from the memory clinic or to a group receiving normal care from the memory clinic as well as special counselling.

40 couples will take part in this study.

20 of these couples will receive *the* normal care from the memory clinic and 8 sessions of talking therapy and special counselling at weekly intervals with a trained psychiatrist [ your research doctor, another doctor or a specialist nurse] who is specialised in memory problems. The other 20 people will receive their normal care without the special counselling. Most of the counselling sessions will be with the patient and his or her partner. By taking part in the study you have a 50% chance of getting special counselling in addition to your normal care from memory clinic.

All people taking part in the study, including those not receiving the special counselling, will be asked to complete some questionnaires regarding their mood, daily functioning and memory. You will be seen in a study visit at home by a researcher who will complete the questionnaires. These measures will be completed at the beginning and at the end of the treatment [3 months later]. Those couples receiving the special counselling will be visited at home by the psychiatrist who is doing the therapy, to provide the special counselling for 8 sessions.

As part of the study your partner (**not you**) will be invited to take part in an MR scan before and after 3 months of counselling.

#### **Do I have to take part?**

It is entirely up to you whether or not you wish to take part in the study. If you do, keep this information sheet and sign the consent form. You are free to withdraw from the study at any time. Even if people are not happy to take part in the scan they are allowed to take part in the special counselling. A decision to withdraw at time, or a decision to take part, will not affect the standard of care you receive.

The consent from you and your partner will be required *separately* before the participation in the study and this consent may be withdrawn at any time during the study. The consent for the special counselling, *each session of* audio recording and scan will be taken separately.

#### **What is involved in the Psychotherapy [Special Counselling]?**

In each session of Psychotherapy [special counselling ] you and your partner discuss your difficulties which are causing or maintaining emotional problems for you or your partner with the research doctor. Then you and your research doctor work together to find practical solutions for these problems.

It is a requirement to do audio recording of the conversation on each special counselling session, so that the supervisors of your research doctor can listen to it and make sure that the therapy is carried out in the correct way.

We appreciate your permission to transcribe the audio recorded conversation as well as to use direct quotes from the conversation with out revealing your identity , once we publish the research in scientific journals. If you don't want us to transcribe the audio taped conversation , or use the direct quotes from the counselling sessions in the publications you are allowed to withdraw consent for that particular part of the study. After each special counselling session the research doctor will make sure that, you and your partner are happy about us doing transcription as well as using direct quotes. If any of you are not happy about this after the recording, there is an opportunity for you to withdraw the consent for that particular part of the recording to

be used. As explained earlier a decision to withdraw at time, or a decision to take part, will not affect the standard of care you receive

### **What are the benefits of participating?**

By participating in this research you may be helping the investigators understand more about how helpful special counselling in people with mild memory problems and their partners is. We cannot promise the study will help you but the information we get from this study will help improve the treatment of people with Mild Cognitive Impairment.

Participation in this research study involves no cost to you and you will not be paid for your participation

This study will be part of a MD qualification for Dr. Arunraj Kimal [your research doctor] and this will be supervised by Prof. Alistair Burns.

### **What if there is a problem or something goes wrong?**

Any complaint about the way you have been dealt with you during the study or any possible harm you might suffer will be addressed.

You should ask to speak with the researchers who will do their best to answer your questions (Dr. Arunraj Kimal, 01612915909).

If you wish, arrangements will be made for you to discuss this with Prof. Alistair Burns or Dr. Sean Lennon in Wythenshawe hospital.

*In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Manchester Mental Health and Social Care Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).*

### **What happens when the research study stops?**

Once the research study stops your normal care from memory clinic continues. You will receive verbal feedback or a letter of thanks at the end of the study from your research doctor who is the talking therapist.

### **What will happen to the results of the research study?**

The data gathered from you and all the other participants in the study will be analysed and published in a medical journal and/or presented at medical/academic conferences. The audiotapes will be safely erased after the recommended period they need to be kept.

### **Is the study confidential?**

Your personal information will be kept secure and separate from the data sheets gathered from your answers to the interview questions. This ensures that your personal information will remain confidential. A special study code will be assigned to you and your name will not appear on study forms. If you consent to take part in the research your medical records may be inspected by the regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

It is important for your GP to know that you are participating in a research study. We will ask you whether you are happy for them to be informed of this.

**Who is supervising and funding the research?**

This study is supervised by Professor Alistair Burns (Wythenshawe Hospital), Professor Else Guthrie (Manchester Royal Infirmary), Dr. Shane McKie & Dr. Rebecca Elliot [Neuroscience and Psychiatry Unit, University of Manchester] and Dr. S. Lennon (Wythenshawe Hospital).

The study is sponsored by Manchester Mental Health & Social Care Trust.

**Where can I get more information?**

The study will be explained in more detail by your research doctor and Dr. Arunraj Kaimal, who is a qualified psychiatrist, currently specialising in Old Age Psychiatry and management of memory problems.

Dr. Arunraj B. Kaimal

Specialist Registrar

South Manchester Memory Clinic

2<sup>nd</sup> Floor, ERC Building

Wythenshawe Hospital

Manchester

M23 9LT

TEL: 0161 291 6942,

MOB: 07812243439



And reading my medical notes Yes No

(7) I agree to the researcher asking questions to my Husband/Wife Yes No

(8) I agree to the researcher recording the special  
Counselling sessions on Audio tape Yes No

(9) I give permission to the researcher and his team members to  
transcribe the audio recorded conversation Yes No

(10) I give permission to the researcher to use direct quotations  
from the special counselling sessions in scientific publications in  
relation to this research Yes No

(11) I agree to take part in the study Yes No

Name of Participant \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

Name of Researcher \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

**Part B**

I have read and signed the Patient Declaration form regarding participation in the MRI study and confirm to the best of my knowledge that the details are correct.

Name of Participant \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

Name of Researcher \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

I agree to take part in the first MRI scan study

Name of Participant \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

Name of Researcher \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

I agree to take part in the second MRI scan study

Name of Participant \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

Name of Researcher \_\_\_\_\_ Signature \_\_\_\_\_ Date \_\_\_\_\_

## Participant Consent Form

[[For Partners of Patients with Mild Cognitive Impairment]]

**Title of Project: Psychotherapy in Mild Cognitive Impairment**

Researcher: Dr. Arunraj Kaimal, Specialist registrar [memory clinic], Wythenshawe Hospital, Manchester , M23 9LT

Please make sure you have fully read the Participant Information Sheet before completing this form. If you have any questions please do not hesitate to ask.

I .....confirm that

### Part A

- |  |     |    |
|--|-----|----|
| (1) I have read and understood the information sheet   | Yes | No |
| (2) I have had the opportunity to ask questions and discuss the study  | Yes | No |
| (3) I am happy with the answers to my questions  | Yes | No |
| (4) I have received enough information about the study   | Yes | No |
| (5) I understand that if I do not want to take part in the study, it will not affect my regular care and that I can withdraw at any time without giving a reason | Yes | No |
| (6) I agree to the researcher contacting my General Practitioner   |     |    |

