ReMemBrIn Study

Rehabilitation of Memory following Traumatic Brain Injury – a Phase III Randomised Controlled Trial

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This protocol describes the **Rehabilitation of Memory following Traumatic Brain Injury – a Phase III Randomised Controlled Trial** and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.
This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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Glossary of Abbreviations

AE	Adverse event
AP	Assistant Psychologist
CA	Conversation Analysis
CF	Consent Form
CRF	Case Record Form
DMC	Data Monitoring Committee
DMRU	Defence Medical Rehabilitation Unit
HTA	National Institute for Health Research Health Technology Assessment
ICH GCP	International Conference of Harmonisation Good Clinical Practice
MRIS	Medical Research Information Service
NCTU	Nottingham Clinical Trial Unit
NHS	National Health Service
PI	Principal Investigator
PIS	Patient Information Sheet
RA	Research Assistant
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCC	Study Coordinating Centre
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TBI	Traumatic Brain Injury
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Usual care

Keywords

Traumatic Brain Injury, Memory problems, Memory rehabilitation, Cognitive Rehabilitation

Study Summary

TITLE	Rehabilitation of Memory following Traumatic Brain Injury – a Phase III Randomised Controlled Trial
DESIGN	Single blind, multi-centre, Phase-III randomised controlled trial
AIMS	To evaluate the clinical effectiveness and cost-effectiveness of a group-based memory rehabilitation programme for military personnel and civilians who have sustained a traumatic brain injury (TBI).
OUTCOME MEASURES	The primary outcome will be the Everyday Memory Questionnaire-patient version at 6 months after randomisation, a subjective measure of memory failures in daily life, with good ecological validity. Secondary outcomes, assessed at 6 and 12 months include: individual goal attainment, an objective measure of memory (Rivermead Behavioural memory Test RBMT-3), cognitive, emotional and social wellbeing (European Brain Injury Questionnaire EBIQ completed by a relative or friend), mood (General Health Questionnaire 30), health-related quality of life (EQ5D), EMQ-p and EMQ-r (the Everyday Memory Questionnaire completed by a relative or friend). Cost-effectiveness analysis will be determined from an NHS perspective. This cost data will be compared to the Quality Adjusted Life Year scores (QALYs) calculated from the responses from the EQ-5D. This will allow us to calculate an Incremental Cost-Effectiveness Ratio.
POPULATION	Men and women, civilians and military personnel, aged 18 to 69 years, more than 3 months since a traumatic brain injury (TBI). We will recruit 312 patients discharged from NHS hospitals, Defence Medical Rehabilitation Units, Military Trauma Centres (e.g. Birmingham University Hospitals NHS Trust), and through charities (e.g., Headway, Soldiers' Charity, Combat Stress).
ELIGIBILITY	Eligible participants are those who: • Were admitted to hospital with a TBI more than 3 months prior to recruitment. • Report having memory problems as assessed at baseline. • Aged 18 to 69 years of age. • Are able to travel to one of the study centres and attend group sessions. • Give informed consent. Potential participants will be excluded if they: • Are unable or unsuitable to engage in group treatment if allocated • Are involved in other psychological intervention studies. • Have impairment of language, as assessed on the SST (cut-off score <17).
DURATION	Recruitment is for 25 months. The participants are in the study for 12 months.

Reference diagrams

Flowchart 1: Participant flow through the study

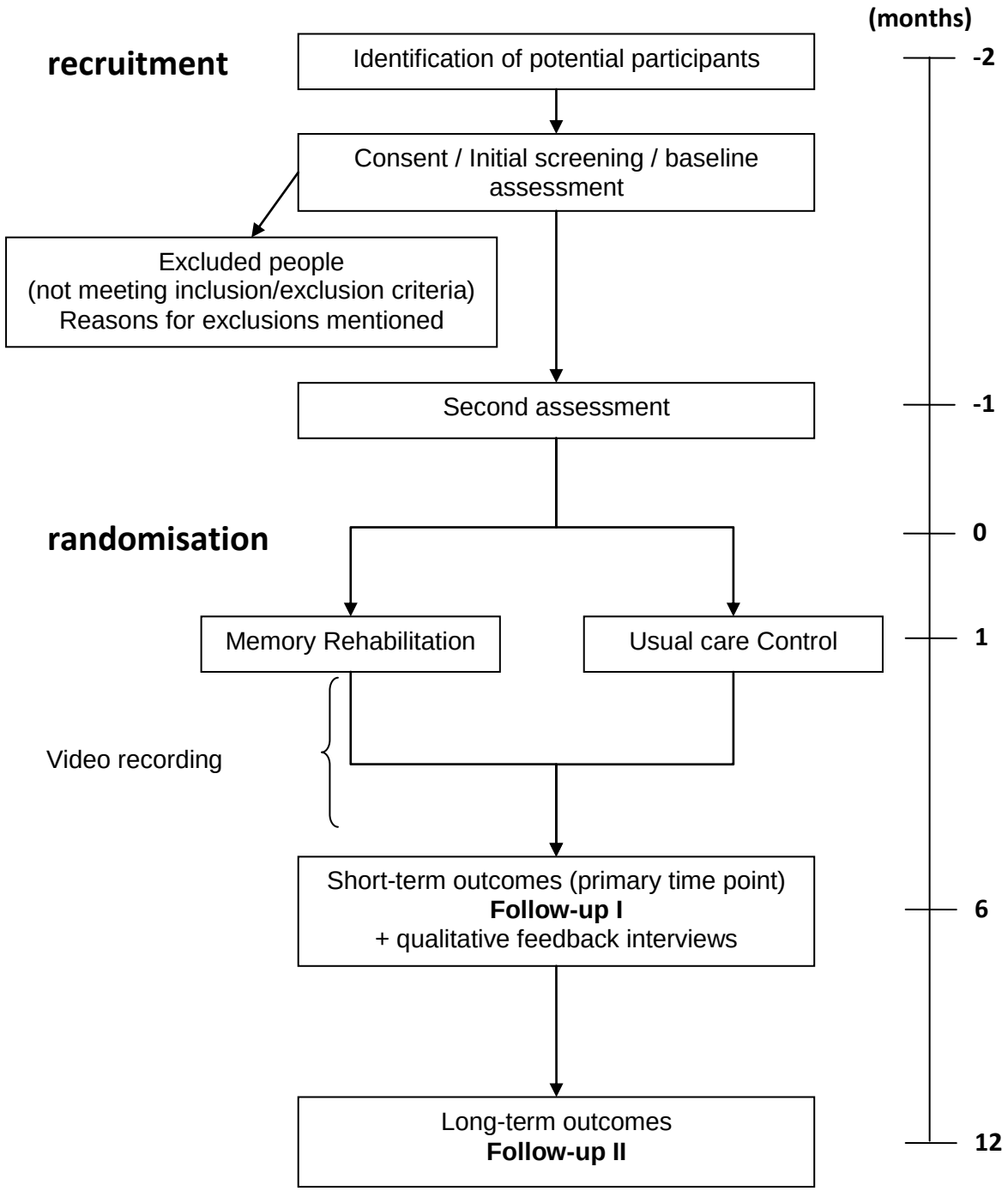

Table 1: Assessments

Assessments	Initial screening assessment*	Second assessment*	RANDOMISATION	Intervention period*:	6 month visit*	12 month visit*
Initial eligibility screening	**X**					
Informed consent	**X**					
Demographic information	**X**					
Everyday Memory Questionnaire – patient version (EMQ-p)	**X**				**X#**	**X#**
Rivermead Behavioural memory Test – Extended version (RBMT-3)	**X**				**X**	**X**
Sheffield Screening Test for Acquired Language Disorders (SST)	**X**					
National Adult Reading Test (NART)	**X**					
General Health Questionnaire (GHQ-30)	**X**				**X#**	**X#**
Setting of short and long term goals		**X**				
EQ5D		**X**			**X#**	**X#**
Service use questionnaire		**X**			**X#**	**X#**
EMQ- relative version (EMQ-r)		**X**			**X#**	**X#**
Check availability for treatment group		**X**				
European Brain Injury Questionnaire – patient version (EBIQ-p)					**X#**	**X#**
European Brain Injury Questionnaire – relative version (EBIQ-r)					**X#**	**X#**
RA opinion on participant's treatment group					**X**	**X**
Assessment of individual goal attainment					**X**	**X**
Feedback interviews+					**X**	
Clinical diagnosis, Severity of injury (Glasgow Coma Scale score), Time since injury, Other medical conditions**					**X**	

Intervention Group receives Memory Rehabilitation (1.5 hour group sessions, once a week for 10 weeks)

Control Group receives usual clinical care.

* Given the participants' memory problems they may be telephoned before an appointment to remind them
\+ With selected participants who will be consented prior to the interview
\# Included in the questionnaire pack
** From medical notes and will be collected before the end of the study, if possible

1 INTRODUCTION

1.1 Background

Impairments of memory are one of the most common cognitive deficits reported by people with traumatic brain injuries (TBIs), affecting 40-60% of patients (Richardson 2000; Goldstein and Levin 2001). These memory problems are not only persistent, but are debilitating and difficult to treat (Williamson, Scott et al. 1996). Memory deficits may also affect the extent to which patients engage with other interventions and rehabilitation. The safety of such patients can also be compromised, making them vulnerable citizens in the home (e.g., forgetting to turn the stove off), community (e.g., forgetting road rules), and work (e.g., forgetting important documents) settings. Memory problems consequently have a devastating effect on the psychological well being of the individuals and others around them (Skeel and Edwards 2001).

Costs of morbidity due to TBI are incurred by the healthcare system and those outside it (in terms of loss of productivity due to short-term sick leave and early retirement), and through non-medical costs (e.g., transformations of house or work environments, etc.). In addition, informal care by family or friends can dominate the costs of care for affected individuals. For TBI, the direct medical costs and indirect costs were estimated at $60 billion in the United States in 2000 (Finkelstein, Corso et al. 2006). The full costs of dealing with memory problems caused by TBI in the UK are not known. Care costs escalate when an intervention is provided on an inpatient basis, but Salazar et al. (Salazar, Warden et al. 2000) demonstrated that the benefits of inpatient and home cognitive rehabilitation programmes for TBI, in terms of return to duty (for military personnel) or employment, were similar.

Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual's memory and other cognitive functions. A narrative review (Cicerone, Dahlberg et al. 2005) reported cognitive rehabilitation to be beneficial for treating cognitive deficits following brain damage. There are recommendations for the provision of cognitive rehabilitation for people with acquired brain injuries (e.g. European Federation of Neurological Societies Guidelines on cognitive rehabilitation (Cappa, Benke et al. 2003); National Service Framework for Long term Conditions (Department of Health 2005)). However recommendations are always qualified by the need for more research, to support the recommendations.

Some randomised controlled trials (RCTs) have demonstrated the effectiveness of cognitive rehabilitation following brain injuries. These have mainly focussed on attention, executive functions, and visual neglect; but memory rehabilitation has not been sufficiently researched (Rohling, Faust et al. 2009). Most evidence for memory rehabilitation comes from single case experimental design studies and controlled clinical trials. The few RCTs in this area have offered some support for the effectiveness of intervention. Wilson et al. (Wilson, Emslie et al. 2005) examined an external memory aid, Neuropage. This enabled participants to achieve more memory related goals than when it was not available. Doornhein and de Haan (Doornhein and de Haan 1998) reported that patients who received a memory training programme performed significantly better than those in a pseudo-treatment control group on trained memory tasks but no differences were observed on subjective ratings of everyday memory functions. Kaschel et al. (Kaschel, Della Sala et al. 2002) reported that imagery mnemonics significantly improved delayed recall of verbal material and reduced observer-rated reports of memory failures. However systematic reviews on memory rehabilitation have not found evidence to support or refute the effectiveness of such programmes (Majid, Lincoln et al. 2002; das Nair 2008). This lack of evidence is partly due to the paucity of well designed trials, and has led a recent meta-analysis to conclude that 'the results for memory rehabilitation are mixed and weak' (Rohling, Faust et al. 2009) (p.33). These authors suggested that 'researchers need to reduce reliance on single-subject and single group designs' (p.34) and recommended more RCT evidence, a view supported by others (Ptak, der Linden et al. 2010). At a recent symposium on disorders of memory, Wilson called for 'better evaluation of memory rehabilitation programmes' (Wilson 2010) (p.e4-5). We have completed systematic reviews of

memory rehabilitation following TBI (das Nair 2008), stroke (das Nair and Lincoln 2007), multiple sclerosis(das Nair, Ferguson et al. 2012), and have updated our searches to cover more recent publications, including the Cochrane Injuries Group register and PsychBITE database (which catalogues studies of cognitive, behavioural and other treatments for psychological problems following acquired brain impairments).

We have recently completed a small scale RCT (n=72) to evaluate a group memory rehabilitation programme (das Nair and Lincoln 2012). Patients with memory problems were randomly allocated to one of three group treatment programmes: compensation strategy training, restitution or a self-help attention placebo control. The results showed that there were no statistically significant differences in outcome, but the study was underpowered to detect differences. However, the trend in the results and the qualitatively analysed participant feedback interviews indicated the interventions seemed worthy of further evaluation. This study has provided feasibility and pilot data for the proposed study.

The proposed study has been designed to assess the effectiveness of a group memory rehabilitation programme, on the basis of recent research suggestions from researchers and clinicians (Ptak, der Linden et al. 2010), our own pilot study (das Nair and Lincoln 2012), and current clinical guidelines and practice in the UK.

1.2 Rationale for current study

Currently, TBI patients with memory problems do not routinely receive follow-up rehabilitation after the early intensive phase, even though their abilities and needs may change once discharged from clinical services. This is mainly due to the current lack of evidence of clinical and cost-effectiveness of the intervention, and resource limitations. This study seeks to address these concerns.

2 STUDY OBJECTIVES AND PURPOSE

What is the clinical and cost-effectiveness of memory rehabilitation for military personnel and civilians with memory problems following traumatic brain injury (TBI)?

2.1 Primary objective

The primary objective is to determine whether attending a group memory rehabilitation programme (the intervention), is associated with improved management of memory in daily life, as measured on the Everyday Memory Questionnaire – patient version (EMQ-p) when compared to a usual care (UC) control.

2.2 Secondary objectives

The secondary objectives are to assess:

- cost-effectiveness of the intervention
- whether the intervention is associated with improvements in participants':
    I. ability to achieve individually set goals
    II. 'objectively' assessed memory abilities
    III. cognitive, emotional, and social wellbeing
    IV. health-related quality of life

3 STUDY DESIGN

3.1 Primary outcomes

The primary outcome, assessed at 6 months after randomisation, will be the EMQ-p, a subjective measure of memory failures in daily life, with good ecological validity.

3.2 Secondary outcomes

Secondary outcomes, assessed at 6 and 12 months after randomisation, include:

- individual goal attainment
- an objective measure of memory (Rivermead Behavioural Memory Test, RBMT-3)
- cognitive, emotional, and social wellbeing (European Brain Injury Questionnaire, EBIQ patient and relative versions)
- mood (General Health Questionnaire, GHQ 30)
- health-related quality of life (EQ5D)
- EMQ-p, completed by the participant (at 12 months)
- Cost-effectiveness analysis will be determined from an NHS perspective, using the service use questionnaire. This cost data will be compared to the Quality Adjusted Life Year scores (QALYs) calculated from the responses from the EQ-5D. This will allow us to calculate an Incremental Cost-Effectiveness Ratio.
- EMQ-r, the EMQ completed by a relative or friend

3.3 Study description

This is a multi-centre, parallel group, randomised controlled trial (RCT). The study is to be single blind for the individual goal attainment performed by the Research Assistant. Blinding participants and therapist is logistically not possible in the study.

Participants will be randomised to receive 10 group memory rehabilitation sessions (1.5 hours long, once a week for 10 weeks) or usual care, and will be followed up for 12 months from randomisation.

The study will be conducted initially in four centres in the UK, but other centres may be included if additional funding becomes available. The enrolment period will last for 25 months.

3.4 Randomisation

Participants will be randomised in clusters of four to six. Once four to six participants have been identified and consented they will be randomly allocated, as a group, to intervention or usual care control (1:1 ratio). The randomisation will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure (SOP) and held on a secure server. The randomisation will be stratified by study site. Access to the sequence will be confined to the NCTU IT Manager. Investigators will access the allocation for each group by means of a remote, internet-based randomisation system developed and maintained by the NCTU. Assistant Psychologists (APs) at each site will enter the basic participant identification data onto the web-based randomisation programme once they have four to six participants who are eligible to take part in the study. The sequence of treatment allocations will be concealed from the study statistician until all interventions have all been assigned and recruitment, data collection, and all other study-related assessments are complete. Participants and staff at the four recruitment sites will not be blinded.

3.5 Minimisation of bias and maximising blinding

The participants and Assistant Psychologists (APs) will not be blind to the allocated treatment. It will be ensured that the Research Associate (RA) is blind to treatment allocation. The memory test (RBMT-3), which requires face-to face contact, will be conducted by the RA, who will not have had any contact with the participants. To prevent unblinding, the RA will request participants not to discuss any aspect of being involved with the study. The RA will also be required to guess the treatment allocation for each participant and this will be compared later to the actual allocation, to determine the degree of unblinding. All of the questionnaire-based outcome data (including the primary outcome) will be completed by the participants, and returned by post to NCTU. Baseline data and questionnaires required prior to randomisation will be entered at site by the AP.

3.6 Study interventions

The intervention (memory rehabilitation) will be compared to a usual care control group.

(i) Memory rehabilitation: The intervention will be offered in a group setting. Each group will be led by an Assistant Psychologist (AP) and consist of 4-6 participants. The APs at the different centres will be trained. Participants will receive 10 group memory rehabilitation sessions (1.5 hours long, once a week for 10 weeks), following a treatment manual which was developed and tested in the pilot study (a detailed description of the manual has been published (das Nair 2008)). The original manual has been revised following extensive consultation and feedback from participants who completed the pilot study. Qualitative research (das Nair 2008) also found that the group format, composition, and duration were acceptable to participants, and delivery of the intervention was feasible. The intervention will include restitution strategies to retrain memory functions, including attention retraining and strategies to improve encoding and retrieval. Compensation strategies will be taught, including internal mnemonics (such as chunking, use of first letter cues, rhymes), use of external devices (such as diaries, mobile phones, calendars) and ways of coping with memory problems. The importance of 'errorless learning' (not making errors while learning new material, and therefore preventing learning the errors (Wilson, Baddeley et al. 1994)) will also be taught. The emphasis will be on identifying the most appropriate strategies to help individuals overcome their memory problems, and in providing participants with a range of memory techniques which they can adapt and use according to their needs. This intervention provides an opportunity for revision of strategies taught during in-patient rehabilitation and discussion of their application in a community setting. Both the APs delivering the treatment and the participants will know to which to group they have been allocated.

(ii) Usual Care (UC): Participants will receive their usual clinical care. This may include the provision of information on memory, and in some centres, participants are offered a few sessions of cognitive rehabilitation. The majority of participants will no longer be receiving any formal rehabilitation. They may be attending self-help groups or Headway services.

All other clinical services will be provided as usual for both groups. This may include referral to employment rehabilitation services, self-help groups or support from specialist charities, such as Headway. Any additional input (including psychological or medical interventions) people receive at the follow-up assessments will be noted from the service use questionnaire.

3.7 Duration of Participant participation

Flowchart 1 shows the expected progress of the study. Participants are in the study for approximately 13 months from the initial screening assessment (12 months from randomisation). Participants will leave the study when they have completed the 12 month follow-up.

The end of the study is defined as the "last participant's last 12 month follow-up appointment".

3.8 Compliance with interventions

To ensure the fidelity of the intervention, the content of treatment will be described and analysed. This will be achieved by video recording 20 intervention sessions. Sessions will be purposively pre-selected for recording in order to include sessions from the start, middle and end of the ten-week course and recordings will be made across the intervention period. Practices for video-recording will draw upon guidance on minimizing intrusiveness of the recording (Jordan and Henderson 1995; Heath 1997). Methods used in previous work will be draw on to analyse the content of training within rehabilitation contexts (Mozzoni and Bailey 1996) (Ducharme and Spencer 2001). Two independent assessors will each separately analyse the video-recordings. They are trained in conversation content analysis and will apply a customized score sheet designed to capture a variety of key elements spanning all aspects of the intervention. Assessors will code these as present or absent over a series of time intervals. This method has previously been used in the pilot study and was able to determine treatment fidelity without disrupting the group sessions.

3.9 Maintenance of randomisation codes and procedures for breaking code

Neither the participants nor the Assistant Psychologists will be blind to which treatment the participants will be receiving. The outcome assessor will be blind to the treatment received but there is no requirement for them to know the treatment allocation at any stage. As a result a procedure for breaking the code is not necessary.

3.10 Source data

The source data are medical notes, questionnaires, case record form (CRF) worksheets, video recordings and interview transcripts. Demographic data, including a minimal amount of information that is required for randomisation, will be collected from each participant. The basic demographics, including NHS number will also be recorded and supplied to the NHS Information Centre to allow mortality checks prior to follow-up.

4 SELECTION AND WITHDRAWAL OF STUDY PARTICIPANTS

4.1 Inclusion criteria

Eligible participants are those who:

- Were admitted to hospital with a TBI more than 3 months prior to recruitment.
- Report having memory problems as assessed at baseline.
- Are 18 to 69 years of age.
- Are able to travel to one of the study centres and attend group sessions.
- Give informed consent.

4.2 Exclusion criteria

Potential participants will be excluded if they:

- Are unable or unsuitable to engage in group treatment if allocated
- Are involved in other psychological intervention studies.
- Have impairment of language, as assessed on the SST (cut-off score <17).

4.3 Participants who withdraw

No withdrawal criteria have been specified, and participants have the right to withdraw from the study at any time. The reasons for leaving the study will be recorded, but participants are not obliged to give reasons. Participants will be assured that withdrawal will not affect the care they receive. They will be informed at the start of the study that data collected up to the point of withdrawal will be retained and may be used in the final analysis. There will be no replacement of participants who withdraw.

All reasonable attempts will be made to contact any participant lost to follow-up during the course of the study in order to complete assessments. A letter may be sent to participants whom the outcome assessor is unable to contact by phone when trying to arrange follow up assessments, so that the participant can contact the outcome assessor to arrange the appointment and/or provide updated contact details.

Participants who are awaiting randomisation at the time their site closes to recruitment, will be sent a letter inform them that the Assistant Psychologist has not been able to recruit enough people to form a group at a time and place that was convenient for that participant and as such their participation in the trial is now at an end.

5 STUDY PROCEDURES

5.1 Study entry and recruitment

Participants may be identified through NHS hospitals and rehabilitation centres by occupational therapists, clinical psychologist, rehabilitation medicine consultants and other healthcare staff. Potential participants who are military personnel will be identified through the Defence Medical Rehabilitation Units (DMRUs) and University Hospitals Birmingham NHS Trust (a military trauma centre for the UK) by their care team.
Local groups organised by brain injury charities, such as Headway, The Soldiers' Charity, Combat Stress, and Soldiers, Sailors, Airmen and Families Association (SSAFA) Forces Help will also aide identification of potential participants.
The study will be advertised to the general public through the study website and on various support groups websites and in their newsletters. Posters will be displayed in clinic areas in the hospitals and other suitable venues.

Depending on the recruitment rate, GP databases may also be used to identify potential participants.

Recruitment will cover a 25 month period. Depending on whether the potential participants are self-referred or referred by others, the first contact with the researchers can vary, as outlined below:

> ***(i) For people referred through the NHS and DMRU services*:** The TBI patient may receive an invitation letter, Patient Information Sheet (PIS) and Consent Form (CF) from their clinician by post or the study may be mentioned by the clinician at a scheduled appointment and the PIS and CF are given to them. Interested patients will have the option of directly contacting their local Assistant Psychologist (AP) by phone, email or complete and post the contact details slip in the stamped addressed return envelope provided. Alternatively, they may provide the clinician with verbal consent for their contact details to be sent to the AP.
> For people that have not responded to the letter, a single phone call by the assistant psychologist or staff on the clinical team to enquire whether they remember receiving the invitation letter, and whether they would like further information about the study will be made, where possible. If they do not wish to have further information, no further contact will be made. If, however, they wish to have more information, the clinical team will request verbal consent to pass on their contact details to the assistant psychologist, who can provide them with more information about the trial. The clinical team will record the date and time when verbal consent was obtained to pass on contact details.
> The AP will explain that the initial screening appointment is to check that the patient meets the study inclusion criteria. Potential participants will be sent an appointment reminder letter and, if they request this, another copy of the PIS and CF, thus providing them with sufficient time and information to understand the study. APs may also telephone patients before the appointment to remind them (given their memory problems).
>
> ***(ii) For people who self-refer and those who are identified through the voluntary sector/charities*:** Potential participants who are outside the NHS and DMRU services can become aware of the study through information via the voluntary sector and/or charities. In these instances interested people can contact the local site or the Study Coordinating Centre (SCC) at the Nottingham Clinical Trials Unit (NCTU) who will pass on their contact details to the local AP.
> The AP will contact them to explain that the initial screening appointment is to check that they meet the study inclusion criteria and will arrange an appointment with the interested patients. Potential participants will be sent the Participant Information Sheet and a copy of the Consent Form along with their appointment letter, providing them with sufficient time and information to understand the study. APs may also telephone patients before the appointment to remind them (given their memory problems). Participants recruited via this route will be made aware that their GP may be contacted to confirm the TBI diagnosis.

Identifying potential participants from multiple sources will enable recruitment of participants representing a cross-section of those seen in clinical practice, and will enable the identification of relevant military personnel. Eligible participants will be filtered through the sites who have agreed to take part, and this will ensure a large and representative military and non-military sample.

Patient Information Sheets and Consent Forms will be based on the documents that were developed for the pilot study and which had been checked for clarity and readability by the service user representative. Potential participants will have the opportunity to read and discuss the study with other clinical staff, family and friends, and the research team before they decide to take part. They will have a minimum of 24 hours to do this. Potential participants will also have the opportunity to go through the Participant Information Sheet and Consent Forms with the AP at their first assessment.

Written informed consent will be obtained by the AP, and participants will be given a copy for their records, the original will be held in the Trial Site File.

5.2 Treatment of participants

5.2.1 Initial screening assessment

At the first appointment, the AP will explain the study and make clear that the initial screening assessments are required to check that the patient meets the inclusion criteria and to obtain baseline data for those who are eligible. The AP will respond to queries, obtain informed consent, and conduct the initial assessments.
Demographic information recorded will include gender, date of birth, ethnicity, years of education, living arrangements and previous/current occupation. The following assessments will be conducted at screening:

- Memory problems in everyday life will be assessed on the Everyday Memory Questionnaire – patient version (EMQ-p; (Sunderland, Harris et al. 1983)), which is a subjective measure of the frequency of memory failures in daily life.
- The Rivermead Behavioural Memory Test- 3rd edition (RBMT-3; (Wilson, Greenfield et al. 2008)) is an ecologically valid measure of memory ability. The RBMT-3 has been used in previous studies and is the version currently used clinically.
- The Sheffield Screening Test for Acquired Language Disorders (SST; (Syder, Body et al. 1993)) will be used to assess language ability.
- Premorbid level of intellectual functioning will be estimated using the National Adult Reading Test (NART; (Nelson and Willison 1991))
- General Health Questionnaire (GHQ-30; (Goldberg and Williams 1988)) is a measure of mood.

The results from the SST, EMQ-p and RBMT-3 will be used to assess the inclusion criteria. The data from NART will be used to describe the population sample. The GHQ-30 is to determine mood.

Those who do not meet the inclusion criteria will be notified by letter to thank them for their interest in the study and a brief report of their test results will be provided if requested. Those who meet the inclusion criteria will be phoned to arrange a second assessment session if they are happy to continue. A letter will be sent confirming the appointment and will also include an information sheet for the carer and the EMQ- relative version. The EMQ-r; (Sunderland, Harris et al. 1983) is identical to the EMQ-p, but is completed by a relative or friend who knows the participant and about their memory problems.

5.2.2 Second assessment

The purpose of this assessment, conducted 2 weeks, +/- 1 week, after the first assessment, is to:

(i) set the short- and long-term goals individual participants would like to achieve by the end of the study
(ii) complete the EQ5D (a health-related quality of life measure, (EuroQol Group 1990))
(iii) complete the service use questionnaire which records current treatment regimens (including psychological therapies)
(iv) check their availability if they were to be assigned to the treatment group
(v) collect the EMQ-r, completed by the carer.

Groups of participants who are able to attend for treatment at the same time and same venue will be created. In the period while waiting for a sufficient number of participants to be included in a group the AP will remain in regular contact with the participants to inform them of any developments. Should recruitment close at a site before all participants awaiting randomisation have been randomised, those awaiting randomisation will be sent a Not Randomised Letter to inform them that their participation in the study is now at an end.

The participants' medical notes may contain information on their clinical diagnosis, severity of injury (Glasgow Coma Scale score), time since injury, and other medical conditions. For the participants whose medical notes can be accessed at the main recruiting centre, every attempt will be made to collect this data.

5.2.3 Intervention period

Participants are randomised to either an intervention group or a control group, in a 1:1 ratio. The participants in the intervention groups will be involved in 10 group-based treatment sessions over 10 weeks. The control groups will receive usual care, which for the majority of participants will mean no further formal rehabilitation.

5.3 Participant follow-up

The NHS number will be supplied to the Medical Research Information Service to allow mortality checks prior to follow-up.

5.3.1 Follow-up at 6 months and 12 months after randomisation

A questionnaire pack, including the relative/friend questionnaires, will be posted to the participant before their 6 or 12 month appointments. They are asked to complete this questionnaire pack at home and return by post to the NCTU as soon as possible.
At the start of the appointment the RA will inform the participants of the importance that the RA should remain blind to group allocation, and will request that participants do not discuss any aspects of their enrolment in the study to minimise chances of the RA becoming unblinded.
At this appointment, the Research Assistant (RA) will conduct the RBMT-3 and record their guess of the participants' allocation in the Case Record Form (CRF). They will then assess goal attainment. At the end of the appointment the RA will record their guess of the group allocation again. This will be used to check for unblinding.

The returned questionnaire packs are checked for completeness and participants may be telephoned if items are missing or need clarification. Checking the questionnaires and seeking clarification will ensure that there is no/little missing data. Participants will also be phoned if their questionnaire packs has not been received.

5.3.2 Feedback interviews

A feedback interview will be conducted within two months of the 6 months appointment, with 32 purposefully selected and willing participants: 16 from each treatment arm. They will be purposefully selected from our participating centres. . The selection strategy will be designed to include participants with varying levels of memory impairments, and with varying social situations. The interviews will be conducted by a second RA (RA2) who was not involved with the participant's

assessment or treatment, thereby reducing social desirability response bias. The RA2 will become aware of the group allocations during the interview so will not be blind to the intervention. The interview will be audio recorded using a digital recorder, transcribed, and analysed using a thematic analysis (following the protocol prescribed by Braun and Clarke (Braun and Clarke 2006). Participant consent for the interviews will be sought separately. The interviews will provide important feedback on the participants' perception of progress over time and for those in the intervention groups, the quality of the interventions provided, and as such will serve as a process measure. Insights from this qualitative data and analysis will serve to inform developments of the intervention programme in the future and to generate user-oriented proposals about areas for further investigations. For those in the control group the interviews will provide confirmation of the nature of usual care received.

6 ADVERSE EVENTS (AE)

The adverse event risks of taking part in the study have been assessed. A part of the baseline assessment is to assess the memory of the participants such that they may become aware of memory problems that they did not know that they had. As a result, the main risk associated with this intervention is distress caused by the realisation that their memory is not as good as they had thought. However, firstly, distress caused in this way is considered very unlikely; and, secondly, any distress caused is likely to be mild. In addition, for the intervention group, this is also dealt with during the course of the intervention and the group therapy will address this on a participant by participant basis. So overall the risk has been assessed as negligible.

As a result no adverse events (or serious adverse events) will be recorded or reported for this study.

In order to provide some formal reassurance that the study is indeed of extremely low-risk, the DMC will be provided with a report detailing hospital and GP visits (either related to TBI or otherwise, as recorded from participant reported service use questionnaires) for all participants, plus a record of any deaths (as retrieved from the Medical Research Information Service (MRIS)).

6.1 Recording procedures

6.1.1 Non serious adverse events

N/A

6.1.2 Serious adverse events

N/A

6.2 Reporting procedures

6.2.1 Non-serious adverse events

No formal reporting of adverse events to the REC will occur, except number of deaths.

6.2.2 Serious adverse events

No formal reporting of serious adverse events to the REC will occur, except number of deaths.

7 STATISTICS AND DATA ANALYSIS

7.1 Sample size

The sample size calculation is based on the primary outcome measure (EMQ-p) at six months post-randomisation. The main study aim is to detect a minimum clinically relevant difference in mean EMQ-p score of 12 between the memory intervention group and the usual care group. A 12-point difference on this measure was deemed to be a clinically significant change based on our pilot data (das Nair 2008) and clinical interviews. A common standard deviation of 21.9 from the pilot gives an effect size of 0.55. An alpha value of 0.05 and power of 90% were used for the calculation. A fixed effects model at the level of the 4 centres is assumed, with 10% of the total variation due to between-centre variation. The patients are cluster randomised into groups of 6 at the second level and a random effects model will be used with a small intracluster correlation coefficient (ICC=0.1). This ICC is likely to be small because within each centre the therapist, intervention, and delivery location do not vary. Using the 'Optimal Design' software with these parameters, the calculation gives 10 groups of each intervention, per centre. Data from the pilot study and taking account that the control group only receives usual care suggests a possible dropout rate of 20%, so 26 groups of each intervention will be required or 312 patients in total. Based on our pilot study, we will need to screen 400 participants to recruit the required 312. Clinicians at the four centres have indicated that this is an achievable target in the timeframe proposed.

7.2 Outcomes assessment

Outcomes will be assessed at six and twelve months after randomisation to assess immediate and long-term effects of the intervention. The primary time point of interest is six months after randomisation. This time point has been chosen to allow time for completing 10 group sessions, whilst allowing for one group session to be rescheduled if it has to be cancelled through illness or other unforeseen circumstances. The 12 month assessment is to determine whether any treatment gains have been maintained over time.

The primary outcome measure: will be the Everyday Memory Questionnaire – patient version (EMQ-p), a subjective measure of memory failures in daily life. This is a patient-centred outcome with good ecological and face validity, and has been previously used in cognitive rehabilitation studies. In neuropsychological rehabilitation there is debate about the most appropriate outcome measures (Lincoln and das Nair 2008). We feel that a subjective report should be the end point of significance because it assesses the effect of memory problem in everyday life and provides a patient-centred outcome rather than the views of healthcare professionals. It is also suitable for independent completion and return by post, which will ensure blind assessment of outcome. Other studies have considered goal attainment as a primary outcome. While we consider this as a valid measure, we felt that it would be more suited as a secondary outcome measure because the goals set are strongly influenced by the expectation of the treatment and the goals are likely to change over the course of the year when follow-up assessments are conducted. Previous studies (Wilson, Emslie et al. 2001) using goal attainment as a primary outcome have had to modify their randomisation protocol to accommodate patient-relevant goals, thereby potentially biasing the study.

Secondary outcome measures: The following measures will be completed by participants and returned by post:

i. The European Brain Injury Questionnaire (EBIQ): is a 66-item self-report and relative-report measure of the subjective experience of cognitive, emotional and social difficulties experienced by people with brain injury. It is now used in several rehabilitation centres as an outcome measure. The EBIQ is a clinically reliable measure to determine the subjective well-being of people with brain injury and to assess change of subjective concerns over time (Teasdale, Christensen et al. 1997; Sopena, Dewar et al. 2007).

ii. The EQ-5D (EuroQol Group 1990): is a validated, generalised health profile questionnaire used to determine health-related quality of life, and is routinely used in health-economic analysis.

iii. The EMQ-r: is a parallel version of the EMQ-p, which offers an independent rating by a significant other of the memory problems a patient experiences. This has been used in previous studies, and also assesses the level of insight a patient has regarding their memory problems. This has been included to identify any effect of treatment on daily life problems as observed by another person. This will provide information on benefits of the intervention which may not be immediately apparent to the participants themselves.

iv. GHQ30: is a 30-item questionnaire that is commonly used to assess mood. It compares the patient's current state from his or her usual mood state. Short, popular, easy to administer, understand, and score, the GHQ30 has been frequently used in neurological literature. It has good psychometric properties and has been used in previous TBI and rehabilitation studies.

v. Cost-effectiveness will also be assessed as an outcome and is described in detail in the Health Economic Evaluation section (below).

Additional outcomes will be assessed during a face-to-face assessment by the RA:

vi. RBMT-3: is a standardised objective measure of memory, with adequate psychometric properties. This has been chosen as an objective measure which closely reflects daily life memory ability, and has been used as an outcome measure in other studies of memory rehabilitation.

vii. Individual goal attainment: Goals set at baseline will be evaluated in terms d the degree to which each goal has been met (scaled in terms of not met to fully met on a 5-point Likert scale) at follow-up. Goal attainment scaling has been used in memory rehabilitation studies, and has been recommended as an outcome measure of choice for cognitive rehabilitation (Bouwens, van Heugten et al. 2009).

All the measures have been selected on the basis of their clinical utility, psychometric properties, ease of use for participants, and relevance to the clinical condition. Furthermore, the measures reflect the three levels of the International Classification of Function (World Health Organisation 2001) domains: impairment, activity limitations, and participation restrictions, thereby embracing the aims and spirit of cognitive rehabilitation (see (Wilson 2002; Wade 2005)).

7.3 Statistical analysis

Database lock will take place once all data entries have been checked and sufficient verification processes have been completed (e.g., checking of valid entry values, random checks against conditional random fields). Analysis will be completed with the latest version of SPSS. The baseline characteristics of both groups will be described using appropriate summary statistics, for the salient variables, to ensure that the randomisation process has resulted in even distribution of factors. To maintain the integrity of the randomisation, Intention to Treat (ITT) analysis will be used.
The psychometric properties of a range of the instruments used will be evaluated when sufficient baseline data have been collected.

7.3.1 Analysing primary outcomes

Inspection of the pilot EMQ-p data for the target population shows that the scores are well centred in the scale with no ceiling or floor effects evident and no significant evidence of non-normality; similar checks will be done on the study data. A mixed model regression analysis of the EMQ-p outcome at six months follow-up will be used with fixed effects at the centre level and random

effects at the group level to assess the treatment effect. The dependent variable in the model will be the EMQ-p at six months with the baseline EMQ-p included as a covariate.

7.3.2 Analysing secondary outcomes

The secondary outcomes of EBIQ, GHQ30 and EQ-5D at six months follow-up will be analysed using the same techniques as for the primary outcome. Analysis of the pilot data for the RBMT outcomes within the target population shows possible ceiling effects and so it may be necessary to apply a suitable transformation to the data prior to analysis or to use non-parametric data analysis techniques. The decision on the suitable method will be taken following an examination of the distribution of the scores in the study data.

The analyses for all the outcomes will be repeated with the 12 month follow-up data following similar initial distribution checks and using the same techniques.

All secondary variables will the presented using appropriate descriptive statistics and analysed on the basis of the level of measures and the distribution of scores (where appropriate). In addition to the calculated values, confidence intervals and odds-ratios will be presented when appropriate. All clinical information including all adverse events will be presented in full. All secondary analyses will be interpreted with caution as the sample size calculation is based on the primary outcomes only. However, the level of power associated with secondary results will be investigated.

7.3.3 Health economic evaluation

The cost-effectiveness will be assessed from the perspective of the UK NHS and personal social services. The costs associated with the intervention will be determined by calculating the cost of staff time, materials, etc. used in providing the intervention. These will be compared with changes in the number of visits to GPs, hospital, prescribed medication and social services contacts in the intervention and control groups during the investigation. The costs will be compared with the outcomes generated and a series of incremental cost-effectiveness ratios computed, including a cost/QALY analysis – based on changes in EQ-5D. A series of one-way sensitivity analyses will be undertaken to determine the extent to which baseline findings will change in light of parameter variation. Given the limited time duration of the study and follow-up, a decision analytic model will be constructed to determine the cost-effectiveness of the intervention from a lifetime perspective, a series of scenarios will be constructed to reflect the extent to which differential outcomes can be predicted to continue over longer-time periods, using expert opinion and information available in the literature. A probabilistic sensitivity analysis will be carried out to determine the extent to which the intervention can be regarded as representing value for money.

7.4 Criteria for terminating the study

The study maybe stopped as a whole because of a change in opinion of the REC or safety concerns or issues with study conduct at the discretion of the sponsor.

7.5 Procedures for accounting for missing, unused and spurious data

The data entered into the database will be validated prior to analysis to correct spurious and missing data, if possible, by referring to the original data source.

In the case of missing outcome data, we will inspect the pattern of the missing data and use appropriate multiple imputation such as mixed models for repeated measurements (accounting for dropout bias using mixed-effects models (Mallinckrodt, Clark et al. 2001)). If there is evidence for the data being Missing Not at Random, such as significant difference in drop-out rate between arms, then a sensitivity analysis will be performed.

8 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and regulatory authorities to permit trail-related monitoring, audits and inspections.

9 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICG GCP, relevant regulations and standard operating procedures.

9.1 Monitoring

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the Trial Manager or where required, a nominated designee of the Sponsor, will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol GCP and the applicable regulatory requirements.

9.2 Audits

The study may be subject to inspection and audit by Nottingham University Hospitals NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9.3 Archiving

When the study has been completed and all the data has been analysed, participants who requested a copy of the report will be sent a lay summary of the study. All documents will be stored securely for ten years from the date of completion of the study, in accordance with the NHS Trust policy on data storage, and will be securely destroyed thereafter.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.
The trial master file and study documents held by the chief investigator on behalf of the sponsor shall be finally archived at secure archive facilities at Nottingham University Hospitals NHS Trust. This archive shall include all study databases and associated meta-data encryption codes.

10 STUDY MANAGEMENT

Prior to the commencement of the study, the research team (applicants) will meet with all study collaborators from each site (PI) to discuss implementation and training issues to ensure that all members are familiar with all aspects of the study. The APs will also have direct contact with the NCTU Trial Manager, who will keep track of recruitment and data collection.

10.1 Trial Management Group

A Trial Management Group (TMG) will be convened and meet regularly. This group will be in charge of the everyday running of the trial.

10.2 Trial Steering Committee

The Trial Steering Committee (TSC) will oversee the conduct of the study and will have an independent Chair. A service user representative and a member from one of the military charities will also be invited to join this group. It will advise on recruitment strategies, monitor progress with recruitment, and check adherence to the study protocol. Observers from the NIHR HTA programme (the funder) will be invited to TSC meetings.

10.3 Data Monitoring Committee

The Data Monitoring Committee (DMC) will be an independent group, the members of which have no other involvement with the study. Members of this committee will include rehabilitation professionals. An experienced study statistician will also be involved.

It will safeguard the interests of trial participants, with particular reference to safety and the efficacy of the intervention, monitor the overall progress and conduct of the trial and assist and advise the Investigators so as to protect the validity and credibility of the trial.

The TSC and the DMC will meet independently of each other.

10.4 Service User Involvement

One service user has had experience of rehabilitation in NHS services and has taken part in the pilot study underlying this study. Their advice was on recruitment and dissemination options, and has contributed to the development of the intervention manual, and the lay summary of the project. This service user will sit on the TSC. Other service user representatives will be recruited to the TSC and DMC from relevant charities (e.g. Headway and The Soldiers' Charity). Service user involvement will contribute to: team meetings and project management decisions, project approval through IRAS, recruitment and consent (contribute to the development of participant information sheets), data gathering (through developing patient information leaflets explaining the survey tools where appropriate), interpretation of findings (through the development of recommendations for practice and patient information leaflets about therapy), and dissemination of the findings through existing networks. All service user involvement has been resourced appropriately. In addition we will enlist the support of Trent CLRN for training and supporting patients for involvement in clinical studies.

10.5 Definition of a protocol deviation

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of a study inconsistent with the protocol, consent document or other study procedures. All protocol deviations shall be recorded on the electronic CRF(eCRF) by local investigator staff.

Protocol violations are deviations that affect eligibility or outcome measures. Protocol violations of eligibility criteria will be discussed by the TMG and may lead to withdrawal of those participants. These and other deviations from protocol will be assessed by TMG and discussed with the TSC during study evaluation before data lock and unblinding.

11 ETHICS

11.1 Approvals

The Chief Investigator will obtain approval from a NRES Research Ethics Committee and will be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the SSA approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions, the NHS Research Governance Framework for Health and Social Care (2nd edition) and the principles of the ICH Guidelines for Good Clinical Practice.

Ethical approval will also be sought from the Ministry of Defence Research Ethics Committee and their equivalent of Trust approval.

The study will be registered on the ISRCTN website (http://isrctn.org/).

All subsequent amendments to the protocol and associated documents will be submitted for approval prior to their implementation. The chief Investigator will provide reports to the ethics committee at the intervals stipulated in the ethics committee guidelines.

11.2 Records

Each participant will be assigned a study identification number, allocated at enrolment for use on CRFs, other study documents and the study database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mmm/yyyy).
CRFs will be treated as confidential documents and held securely in accordance with regulations. The local investigator or their designee will make a separate confidential record of the participant's name, date of birth, local hospitals number or NHS number and participant study number, to permit identification of all participants enrolled in the study, in case additional follow-up is required.
CRFs shall be restricted to those personnel approved by the chief or local principal investigator and recorded on a delegation log.

All paper forms shall be filled in using black/blue ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

Source documents shall be filed at the local site and may include but are not limited to consent forms, current medical records and CRFs. Only study staff as listed on the delegation log shall have access to the study documentation other than the regulatory requirements listed above.

Data transfer and storage will meet with the requirements of the Data Protection Act (1998). Patient data will be identified by initial and study code only. Standard Operating Procedures will be used to guide the study at all sites to ensure standard practices are used.

11.3 Participant confidentiality

Participant identifiable data will only be accessed by the participant's member of the clinical care team and with the consent of the participant by the research team. Participants have the right to revoke their consent for the use of personal information.
Study data will be anonymised by use of unique participant study numbers. The Chief Investigator, Dr das Nair, is the custodian of the data. Participants will not be identified in any future publication.

12 DATA HANDLING AND RECORD KEEPING

All study outcome data will be entered on a study specific database. Participants will be anonymised and only identified by unique study number, DOB and initials. The name and any other identifying details will NOT be included in any study outcome data.

Data quality and compliance with the protocol will be assessed throughout the study by site visits and verification of study data against clinical records, and by data checking for accuracy and internal consistency.

Data will be entered into a specifically developed database and stored at the study coordinating centre, access to the database will be restricted and secure. All data will be anonymous.

13 INDEMNITY AND FINANCING

National Institute for Health Research Health Technology Assessment (HTA) are funding this study. Nottingham University hospitals NHS Trust will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.
Standard NHS Indemnity applies.
Participant visits in their own home or at community centres will be done in accordance to the sponsor's lone working policy.
Participants' reasonable travel expenses to the hospital for assessments and intervention sessions will be reimbursed.

14 PUBLICATION POLICY

The study has been designed and will be reported according to the CONSORT guidelines.

The findings from this study will provide robust evidence for clinicians working in memory rehabilitation. Findings will be published in peer-reviewed scientific journals and will also be made available through publications of charities, such as Combat Stress, The Soldiers' Charity, and Headway. We will also present the results at national and international conferences, such as the World Federation of Neuropsychological Rehabilitation, and the Headway conference. The results will be appropriate for inclusion in meta-analytic studies, such as those completed by the Cochrane Collaboration, and inclusion in the PsycBITE database (a specialised brain injury database). Our applicants have been involved in memory rehabilitation (and other) reviews commissioned by Cochrane.
Participants who requested a copy of the report will be sent a lay summary of the study.

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Appendix 1. Principal Investigator Declaration

Principal Investigator Declaration

I confirm I have read and understood this protocol and I agree to conduct the study in accordance with the protocol.

Principal Investigator: (name) _____

Centre name: _____

Signature: _____

Date: _____