

Cognitive Rehabilitation for Attention and Memory for people with Multiple Sclerosis (CRAMMS): A pragmatic randomised controlled trial

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TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Ms Angela Shone
Head of Research Grants and Contracts
Research and Graduate Services
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Chief investigator:

Professor Nadina Lincoln
Professor of Clinical Psychology
Division of Rehabilitation and Ageing
School of Medicine
B127a Medical School
Queens Medical Centre
Nottingham NG7 2UH
Phone: 0115 951 5315
Email: nadina.lincoln@nottingham.ac.uk

Co-investigators:

Dr Roshan das Nair
Division of Rehabilitation and Aging
University of Nottingham
Queens Medical Centre
Nottingham NG7 2UH
Roshan.nair@nottingham.ac.uk

Professor Avril Drummond
Professor of Healthcare Research
University of Nottingham
Queens Medical Centre
Nottingham NG7 2UH
Avril.drummond@nottingham.ac.uk

Professor Cris Constantinescu
University of Nottingham
Queens Medical Centre
Nottingham NG7 2UH
Cris.constantinescu@nottingham.ac.uk

Professor Ceri Phillips
Head of Research and Professor of Health Economics
Swansea Centre for Health Economics
Swansea University
Singleton Park
Swansea SA2 8PP
C.J.Phillips@swansea.ac.uk

Professor Alan Montgomery
Professor of Medical Statistics and Clinical Trials
Nottingham Clinical Trials Unit
University of Nottingham
Queens Medical Centre
Nottingham NG7 2UH
Phone: +44 (115) 884 4953
Email: alan.montgomery@nottingham.ac.uk

Ms Miriam Morgan
Service User Representative

Professor Marion Walker
University of Nottingham
Queens Medical Centre
Nottingham NG7 2UH
Marion.walker@nottingham.ac.uk

Trial Statistician:

Professor Alan Montgomery
Nottingham Clinical Trials Unit
Phone: +44 (115) 884 4953
Fax: 0115 748 4092
Email: alan.montgomery@nottingham.ac.uk

Trial Coordinating Centre:

Nottingham Clinical Trials Unit
University of Nottingham
Nottingham Health Science Partners
Nottingham University Hospitals NHS Trust Queen's
Medical Centre
Nottingham NG7 2UH
Tel: 0115 8844919
Fax.: 0115 748 4092
Email: CRAMMS@nottingham.ac.uk

SYNOPSIS

Title	Cognitive Rehabilitation for Attention and Memory for people with Multiple Sclerosis (CRAMMS): A pragmatic randomised controlled trial
Acronym	CRAMMS
Short title	Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis
Chief Investigator	Professor Nadina Lincoln
Objectives	The overall aim is to assess the clinical and cost-effectiveness of cognitive rehabilitation for attention and memory problems in people with multiple sclerosis (MS)
Trial Configuration	Parallel group randomised controlled trial.
Setting	Secondary care and community care.
Sample size estimate	Based on a two sample test, 143 participants per arm are required for analysis in order to detect a difference of 3 points on the Multiple Sclerosis Impact Scale – Psychological Subscale (MSIS-Psy), assuming a standard deviation of 9, with 80% power, and 5% two-sided alpha. However, a clustering effect may be expected to occur in the intervention arm due to the intervention being delivered in groups. Based on an average cluster size of 5 evaluable participants (those providing primary outcome data at 12 months after randomisation), and an ICC of 0.1 in the intervention arm and an optimal allocation ratio of 6:5 in favour of the intervention group, a total of 336 evaluable patients would provide 80% power to detect such a difference (182 to intervention and 154 for usual care). A total of 400 participants will be randomised (216 to intervention and 184 to usual care) to allow for non-collection of primary outcome data in 15% of participants.
Number of participants	Four hundred adults aged 18 or over and under 70 years
Eligibility criteria	<p>The target population is English-speaking men and women, aged 18 or over and under 70 years, who have MS, and report having cognitive problems in daily life.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Are 18 or over and under 70 years of age. The lower age limit is because MS is usually diagnosed in adulthood and treatment strategies tend to be different for children. People over 69 may start to encounter age-related cognitive problems, which may confound the effects of cognitive problem due to MS. Also, most tests are standardised on this adult age group. • Have relapsing or progressive MS, diagnosed by a neurologist at least 3 months prior to recruitment, to allow for adjustment to diagnosis. • Report having cognitive problems as determined by a cut-off score of >27 on the patient version of the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ). This cut-off is based on previous research and is two standard deviations below the mean for healthy participants.

	<ul style="list-style-type: none"> • Have cognitive deficits, defined as performance more than one standard deviation below the mean of healthy controls corrected for age and education on any test of the <i>Brief Repeatable Battery of Neuropsychological Tests</i> (BRBN). • Are able to travel to one of the centres and attend group sessions. • Are able to speak English sufficiently to complete the cognitive assessments and take part in group sessions. • Give informed consent. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Vision or hearing problems, such that they are unable to complete the cognitive assessments, judged by assessor. • Have concurrent severe medical or psychiatric conditions which would prevent participants from engaging in treatment, if allocated. • Are involved in other psychological intervention trials.
Description of interventions	The intervention is <u>Cognitive rehabilitation</u> , offered in addition to usual clinical care. The rehabilitation is delivered to groups of 4-6 participants for 10 weekly sessions. The programme will be tailored to each patient's cognitive status while maintaining a systematic approach to attention and memory by following a treatment manual. The control group participants will receive their usual clinical care, which may include information on cognitive problems but not cognitive rehabilitation.
Duration of study	The overall duration of the study is 48 months. Participants will on average participate in the study for 16 months, from consent to final follow-up.
Randomisation and blinding	Participants will be individually randomised (6:5) to allow for clustering in intervention arm to intervention or control, stratified by recruitment site and minimised by MS-type (relapsing-remitting or progressive) and gender. The randomisation will take place once there are 9-11 individuals who have consented and who are able to attend the same therapy group (location, day of the week and time of day) should they be randomised to receive it. The allocation algorithm will be created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure and held on a secure server. Neither the participants nor the Assistant Psychologists will be blind to which treatment the participants are receiving. The outcome assessor will be blind to the treatment received as there is no requirement for them to know the treatment allocation at any stage.
Outcome measures	Outcomes will be assessed at 6 and 12 months after randomisation to assess immediate and long-term effects of the intervention. The primary follow up is at 12 months after randomisation. The primary outcome is the <i>psychological impact of MS on everyday life, as a reflection of health related quality of life. It is measured using the Psychological Subscale of an MS specific quality of life scale the Multiple Sclerosis Impact Scale – (MSIS-Psy).</i> Secondary outcomes are:

	<ul style="list-style-type: none"> • <i>Memory problems in everyday life</i> as measured using the Everyday Memory Questionnaire patient and relative versions • Mood as measured using the General Health Questionnaire-30 • Fatigue as measured using the Fatigue Severity Scale • <i>Carer</i> strain as measured using the Modified Carer Strain Index • <i>Quality of Life</i> as measured using the EQ-5D-5L • <i>Attention and memory abilities</i> measured by a cognitive test battery <ul style="list-style-type: none"> ○ <i>Brief Repeatable Battery of Neuropsychological Tests</i> (BRBN). ○ <i>Doors and People</i> ○ <i>Trail Making Test</i> • <i>Physical impact of MS</i> on quality of life as measured using the Multiple Sclerosis Impact Scale – Physical Subscale (MSIS-Phy) • <i>Cost-effectiveness</i> as measured by the Use of Health and Social Service Questionnaire • and EQ-5D-5L • <i>Employment status</i> as measured as part of the Use of Health and Social Service Questionnaire • <i>Number of reported relapses in the previous six months</i> • <i>Disability</i> as measured by The Guys Neurological Disability Scale.
Statistical methods	<p>The main analyses will be intention-to-treat. Between-group estimates of effectiveness will be derived from appropriate multivariable regression models adjusting for stratification variables, baseline values of outcomes and taking appropriate account of clustering in the intervention group. Between group estimates will be presented with 95% confidence intervals and exact p-values. Sensitivity analyses will investigate the effects of missing outcome data and non-adherence.</p>

ABBREVIATIONS

BRBN	Brief Repeatable Battery of Neuropsychological Tests
CA	Conversation Analysis
eCRF	electronic Case Report Form
DMC	Data Monitoring Committee
EMQ-p	Everyday Memory Questionnaire patient version
EMQ-r	Everyday Memory Questionnaire relative version
GCP	Good Clinical Practice
HSCIC	Health and Social Care Information Centre
CF	Consent Form
MS	Multiple Sclerosis
MSIS-Phy	Multiple Sclerosis Impact Scale – Physical Subscale
MSIS-Psy	Multiple Sclerosis Impact Scale – Psychological Subscale
MSNQ	Multiple Sclerosis Neuropsychological Screening Questionnaire
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
PIS	Participant Information Sheet
RA	Research Assistant
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SCC	Study Coordinating Centre
TMG	Trial Management Group
TSC	Trial Steering Committee

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STUDY BACKGROUND INFORMATION AND RATIONALE

BACKGROUND AND RATIONALE

Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual's memory and other cognitive functions. A narrative review ([Cicerone 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 multiple sclerosis (e.g. European Federation of Neurological Societies Guidelines on cognitive rehabilitation ([Cappa 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.

Two pilot small scale randomised controlled trials (RCTs) have used similar rehabilitation programmes. The ReMIND trial ([das Nair and Lincoln 2012](#)) (n=72) evaluated the effectiveness of group memory rehabilitation programmes in patients with memory problems, most of whom had MS (n=39). Participants were randomly allocated to one of three programmes: compensation strategy training, restitution, or a self-help control. As a pilot trial, the study was not powered to detect clinically important between-group differences in outcome. However, both quantitative and qualitative data from the study ([das Nair and Lincoln 2012](#); [Das Nair and Lincoln 2013](#)) indicated the interventions were worthy of further evaluation. Our ReMIND-MS trial ([Carr et al. 2014](#)) was a modified version of the cognitive rehabilitation group intervention, combining restitution and compensation strategies, compared with usual care control with people with MS (n=48). Again the data suggested the intervention to be potentially useful, and importantly, these two pilot RCTs demonstrated the feasibility of conducting such trials, and have informed the sample size calculations and assessment and treatment methods for this trial.

EVIDENCE WHY THIS RESEARCH IS NEEDED NOW

Some Randomised Controlled Trials (RCTs) have demonstrated the effectiveness of cognitive rehabilitation in people with MS ([Solari et al. 2004](#); [Tesar et al. 2005](#); [Hildebrandt et al. 2007](#); [Stuifbergen et al. 2012](#)), but most evidence comes from single case experimental design studies, non-RCTs, and small pilot RCTs. Systematic reviews on memory rehabilitation have not found evidence to support or refute the effectiveness of such programmes ([O'Brien et al. 2008](#); [Brissart et al. 2011](#); [das Nair et al. 2012](#)). 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 et al. 2009](#))(p33). 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 et al. 2010](#)). At a recent symposium on disorders of memory, Wilson called for 'better evaluation of memory rehabilitation programmes' ([Wilson 2010](#)).

Previous research has mainly focussed on computerised retraining activities designed to improve memory and attention skills ([Solari et al. 2004](#); [Tesar et al. 2005](#); [Hildebrandt et al. 2007](#); [Stuifbergen et al. 2012](#)). The focus is therefore on improving the underlying cognitive deficit and few studies have assessed functional outcomes. In contrast, our research ([das Nair and Lincoln 2012](#); [Carr et al. 2014](#)) has focussed on teaching people strategies to cope with cognitive problems in everyday life, with an emphasis on addressing the disability rather than the impairment.

This trial has been designed to assess the clinical and cost-effectiveness of a group cognitive rehabilitation programme, on the basis of recent research suggestions ([Ptak et al. 2010](#)) and Cochrane Reviews ([Thomas et al. 2006](#); [das Nair et al. 2012](#)), our own pilot studies ([das Nair](#)

[and Lincoln 2012](#); [Carr et al. 2014](#)) and the treatment manuals developed, and current clinical guidelines and practice in the UK.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The overall aim is to assess the clinical and cost-effectiveness of cognitive rehabilitation for attention and memory problems in people with multiple sclerosis (MS).

PRIMARY OBJECTIVE

The primary objective is to determine whether attending group cognitive rehabilitation programmes (the intervention) in addition to usual care, is associated with reduced impact of multiple sclerosis on quality of life, as measured on the MS Impact Scale (MSIS) when compared to usual care alone (control).

SECONDARY OBJECTIVES

The secondary objectives are to assess cost-effectiveness of the intervention, and whether the intervention is associated with improvements in participants' attention and memory abilities, self-reported attention and memory problems in daily life, mood, fatigue, employment status, and carer strain.

STUDY DESIGN

STUDY CONFIGURATION

The study is a multi-centre involving secondary care and community care. Four hundred adults with multiple sclerosis (MS) who have problems with attention or memory will be randomised into a parallel group randomised controlled trial.

Participants will be randomised to receive cognitive rehabilitation plus usual care or usual care alone. The cognitive rehabilitation intervention in this study is delivered to groups of four to six participants for 10 weekly sessions. Cognitive rehabilitation is a structured set of therapeutic activities designed to improve cognitive function and to reduce the impact of cognitive impairment on daily life.

The emphasis of the intervention will be on identifying the most appropriate strategies to help individuals overcome their cognitive problems (and associated difficulties), and in providing participants with a range of techniques, which they can adapt and use according to their needs.

Each rehabilitation group will be led by an assistant psychologist, under the supervision of a clinical psychologist using a systematic approach to working on attention and memory functions.

In the standard NHS care pathway, people with cognitive problems may get advice from MS nurses and occupational therapists on how to manage any cognitive difficulties. There are information sheets available on web pages of MS charities which include suggestions for coping. However, usual care does not normally include any specific intervention for cognitive problems or cognitive rehabilitation.

OUTCOMES

Outcomes will be assessed at 6 and 12 months after randomisation to assess immediate and long-term effects of the intervention. The primary follow up is at 12 months after randomisation.

Primary outcome

The primary outcome, is the *psychological impact of MS on everyday life, as a reflection of health related quality of life*. It is measured using the Psychological Subscale of an MS specific quality of life scale the Multiple Sclerosis Impact Scale –(MSIS-Psy).

Secondary outcomes

Secondary outcomes are:

- *Memory problems* in everyday life as measured using the Everyday Memory Questionnaire patient and relative versions
- *Mood* as measured using the General Health Questionnaire-30
- *Fatigue* as measured using the Fatigue Severity Scale
- *Carer strain* as measured using the Modified Carer Strain Index
- *Quality of Life* as measured using the EQ-5D-5L
- *Attention and memory abilities* measured by a cognitive test battery
 - *Brief Repeatable Battery of Neuropsychological Tests* (BRBN).
 - *Doors and People*
 - *Trail Making Test*
- *Physical impact of MS* on quality of life as measured using the Multiple Sclerosis Impact Scale – Physical Subscale (MSIS-Phy)
- *Cost-effectiveness* as measured by the Use of Health and Social Service Questionnaire and EQ-5D-5L
- *Employment status* as measures as part of the Use of Health and Social Service Questionnaire
- *Number of reported relapses in the previous six months*
- *Disability* as measured by The Guys Neurological Disability Scale.

Description of outcome measures

Multiple Sclerosis Impact Scale (MSIS) ([Hobart et al. 2001](#)) is a self-report measure developed for people with MS to assess quality of life. It has two subscales, physical and psychological.

Everyday Memory Questionnaire patient (EMQ-p) and relative versions (EMQ-r ([Sunderland et al. 1983](#))) measures participants' attention and memory problems in daily life

General Health Questionnaire-30 ([Goldberg and Williams 1988](#)): to assess mood

Fatigue Severity Scale ([Krupp et al. 1989](#)) to document the severity of fatigue using the 5-item Rasch analysed version ([Mills et al. 2009](#)).

Modified Carer Strain Index ([Thornton and Travis 2003](#)) to detect strain levels among informal caregivers.

EQ5D-5L is a generic health-related quality of life measure, and used for health economic evaluations ([EuroQol Group 1990](#)).

Brief Repeatable Battery of Neuropsychological Tests (BRBN) ([Rao 1990](#)) is short screening battery designed to detect cognitive problems in people with MS.

Doors and People ([Baddeley et al. 1994](#)) is a measure of memory function with separate scores for verbal, visual, immediate and delayed domains.

Trail Making Test (from the Delis-Kaplan Executive Function System) ([Delis et al. 2001](#)) to assess attention and executive abilities.

Use of Health and Social Service Questionnaire: provides a record of the frequency with which participant's access NHS services, such as visits to general practitioners and other healthcare professionals, and access services provided by charities, such as MS Society groups. Current medication and medications over the previous three months will be recorded as well as employment status.

Guy's Neurological Disability Scale ([Sharrack and Hughes 1999](#)) is a self-report measure to document the symptoms of MS. This will be used to ascertain any changes in disability due to MS.

The number of *relapses* in the previous six months, as reported by participants, will also be recorded.

Safety outcomes

A significant increase in score on the GHQ 30, defined as an increase of 30 points or more, between baseline and 6 month assessments.

Stopping rules and discontinuation

The study has an internal pilot phase of one year from the date the first participant is randomised. During the first year it is expected that 100 participants will be recruited. The Trial Management Group and the Trial Steering Committee will review recruitment targets and attendance at group sessions. Strategies to increase recruitment and adherence will be implemented if required. After the first year the TSC will formally review recruitment and provide recommendations.

The sponsor and Funder reserve the right to discontinue this study at any time for failure to meet expected recruitment goals, for safety or any other administrative reason. The Sponsor and Funder shall take advice from the Trial Steering Committee as appropriate in making this decision.

All participation may be stopped if the study sponsor or REC terminates the study prior to the planned end date.

RANDOMISATION AND BLINDING

Participants will be individually randomised to intervention or control on a 6:5 ratio to allow for clustering in the intervention arm. Allocation will be stratified by recruitment site, and minimised by MS-type (relapsing-remitting or progressive) and gender. Randomisation will take place once there are 9-11 individuals who have consented and who are able to attend the same therapy group (location, day of the week and time of day) should they be randomised to receive it. The allocation algorithm will be created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure and held on a secure server.

Assistant Psychologists at each site will use the remote, internet-based randomisation system to obtain allocations for each participant.

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 recruitment sites will not be blinded.

Maintenance of randomisation codes and procedures for breaking code

Access to the randomisation sequence will be confined to the NCTU IT Manager. Only appropriate members of the trial team and the NCTU IT Manager will be aware of the allocation to intervention or control group. Since the intervention is rehabilitation therapy, no special arrangements are necessary for breaking the randomisation code.

Neither the participants nor the Assistant Psychologists will be blind to which treatment the participants are receiving. The outcome assessor will be blind to the treatment received as 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.

TRIAL MANAGEMENT

The trial is funded by NIHR Health Technology Assessment Programme. It is sponsored by the University of Nottingham and will be managed and co-ordinated from the Nottingham Clinical Trials Unit.

The Trial Steering Committee (TSC) will provide independent oversight of the study. They will meet (in person or by telephone conference) prior to commencement of the study, at the end of the internal pilot phase and have at least one other meeting. The TSC will comment on the protocol, advise on recruitment strategies, monitor progress with recruitment, and check adherence to the study protocol.

A separate and independent Data Monitoring Committee (DMC) will be convened. It is anticipated that the members will meet once to agree terms of reference and at a schedule to be agreed with the TSC. This Committee will be independent of the study organisers and the TSC. 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.

The Trial Management Group (TMG) is responsible for the day-to-day management of the trial and will meet frequently. The TMG will review recruitment, retention, adherence with the treatment allocation and data quality to ensure efficient study conduct according to the research timelines. They will report to the TSC at their meetings.

The Chief Investigator has overall responsibility for the study and will oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

The overall duration of the study is 48 months. It is planned that recruitment will take 24 months. Participants will be followed-up for 12 months. The target recruitment for the pilot phase of the trial is 100 participants randomised in the 12 months from the first randomised participant.

Participants will on average participate in the study for 16 months, from consent to final follow-up.

End of the Trial

The end of the study is defined as the “last participant’s last 12 month follow-up”.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Participants will be resident in community settings. They will be identified through the following routes: NHS trusts, self-referral and the study will be advertised to the general public through the study website, social media and on other websites, in newsletters and in appropriate media.

NHS trusts

Postal invitation

In each NHS trust, the hospital neurology services have regular contact with all people with MS in the community. The clinical staff will identify potential participants from hospital records. Invitation letters will be posted by a member of the clinical care team. This invitation letter will include study information and local research team details. Patients who are interested will contact the local team to arrange a screening visit.

For people that have not responded to the letter, a single phone call by 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 that verbal consent was obtained to pass on contact details.

The Assistant Psychologists will explain that the 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 Participant Information Sheet (PIS) and Consent Form (CF), thus providing them with sufficient time and information to understand the study. The appointment will be on a date and time and place that is suitable to the potential participant. Assistant Psychologists may also telephone patients before the appointment to remind them (given their memory problems).

Face to face invitation

In addition to the invitation letter, potential participants who attend clinic visits can be introduced to the study by their neurologist, MS nurses or members of the community rehabilitation team and given the PIS. People who do not contact the local research team will have a single phone call by the clinical team to enquire whether they remember receiving the PIS, and whether they would like further information about the study, where possible. If they do not wish to have further information, no further contact will be made by the researchers. 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.

Posters will be displayed in areas where patients visit to advertise the study.

Self-referral

Potential participants who are not identified through the NHS can become aware of the study through information via the UK MS Research Register hosted by the University of Swansea

and MS charities. In these instances interested people can contact the Study Coordinating Centre (SCC) at the Nottingham Clinical Trials Unit (NCTU) who will pass on their contact details to the local Assistant Psychologist.

The Assistant Psychologist will contact them to explain that the 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. The appointment will be on a date and time and place that is suitable to the potential participant. Assistant Psychologists may also telephone patients before the appointment to remind them (given their memory problems).

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

- Are 18 or over and under 70 years of age. The lower age limit is because MS is usually diagnosed in adulthood and treatment strategies tend to be different for children. People aged 70 and over may start to encounter age-related cognitive problems, which may confound the effects of cognitive problem due to MS. Also, most tests are standardised on this adult age group.
- Have relapsing or progressive MS, diagnosed at least 3 months prior to the baseline assessment contact with the study team, to allow for adjustment to diagnosis. Report having cognitive problems as determined by a cut-off score of >27 on the patient version of the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ ([Benedict et al. 2003](#))). This cut-off is based on previous research ([Benedict et al. 2003](#)) and is two standard deviations below the mean for healthy participants.
- Have cognitive deficits, defined as performance more than one standard deviation below the mean of healthy controls corrected for age and education on any test of the *Brief Repeatable Battery of Neuropsychological Tests* (BRBN ([Rao 1990](#))).
- Are able to travel to one of the centres and attend group sessions.
- Are able to speak English sufficiently to complete the cognitive assessments and take part in group sessions.
- Give informed consent.

Exclusion criteria

- Vision or hearing problems, such that they are unable to complete the cognitive assessments, judged by assessor.
- Have concurrent severe medical or psychiatric conditions which would prevent participants from engaging in treatment, if allocated.
- Are involved in other psychological intervention trials.

Expected duration of participant participation

Participants will on average participate in the study for 16 months, from consent to final follow-up.

Withdrawal from intervention or from the trial

Participants in the intervention group may withdraw from study treatment at any time. They may choose to remain in the study in order to undertake follow up assessment, or they may withdraw entirely from the study. Likewise, participants in the control group may withdraw from the study at any time. The reasons for leaving the intervention or 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 (via the information sheet and consent form) that data collected up to the point of withdrawal cannot be erased 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. For those unable to be contacted a record of any deaths will be retrieved from the Health and Social Care Information Centre (HSCIC).

Informed consent

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 Assistant Psychologist at their first assessment.

Any questions that the participant may have concerning study participation will be answered. All participants will give written informed consent. The Consent Form will be signed and dated by the participant before they undergo any interventions (including cognitive assessment and history taking) related to the study. Participants will be given a copy for their records; the original will be kept by the Investigator in the site file.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

STUDY TREATMENT AND REGIMEN

INTERVENTIONS

Cognitive rehabilitation.

The cognitive rehabilitation programme is based on that used in previous studies ([das Nair and Lincoln 2012](#); [Carr et al. 2014](#)). A manual has been developed and the ability of therapists to deliver the intervention according to the manual has been checked ([Smale et al. 2014](#)).

Cognitive rehabilitation will be offered to groups of four to six participants for 10 weekly sessions. The intervention will include:

- (i) *Restitution strategies* to retrain attention and memory functions, including strategies to improve encoding and retrieval.
- (ii) *Compensation strategies*, including internal mnemonics (such as first letter cues and rhymes), use of external devices (such as diaries, mobile phones and calendars) and ways of coping with attention and memory problems.

The emphasis will be on identifying the most appropriate strategies to help individuals overcome their cognitive problems and in providing participants with a range of techniques,

which they can adapt and use according to their needs. Each group will be led by an Assistant Psychologist, under the supervision of a clinical psychologist. The programme will be tailored to each patient's cognitive status depending on the impairments identified during the baseline assessment while maintaining a systematic approach to working on attention and memory functions. Participants will receive 10 weekly sessions, each lasting 1.5 hours, following a treatment manual that was developed and tested in our pilot studies, and modified based on participant-feedback.

Both the assistant psychologists delivering the treatment and the participants will know to which group they have been allocated. The assistant psychologists will record attendance. The frequency of any catch up sessions will also be recorded.

Usual Care.

This trial will use a usual clinical care control group. All participants will receive their usual clinical care. Usual care may include the provision of information on cognitive problems but they are unlikely to be offered cognitive rehabilitation. They may be attending MS Society meetings. Most people with MS with cognitive problems do not get any treatment for these difficulties following diagnosis. Other clinical services may include referral to employment rehabilitation services, self-help groups or support from specialist charities, such as the MS Society. The study will record the content of usual care on the economic evaluation service use questionnaire at the follow-up assessments.

Figure 1. Participant Flow Chart

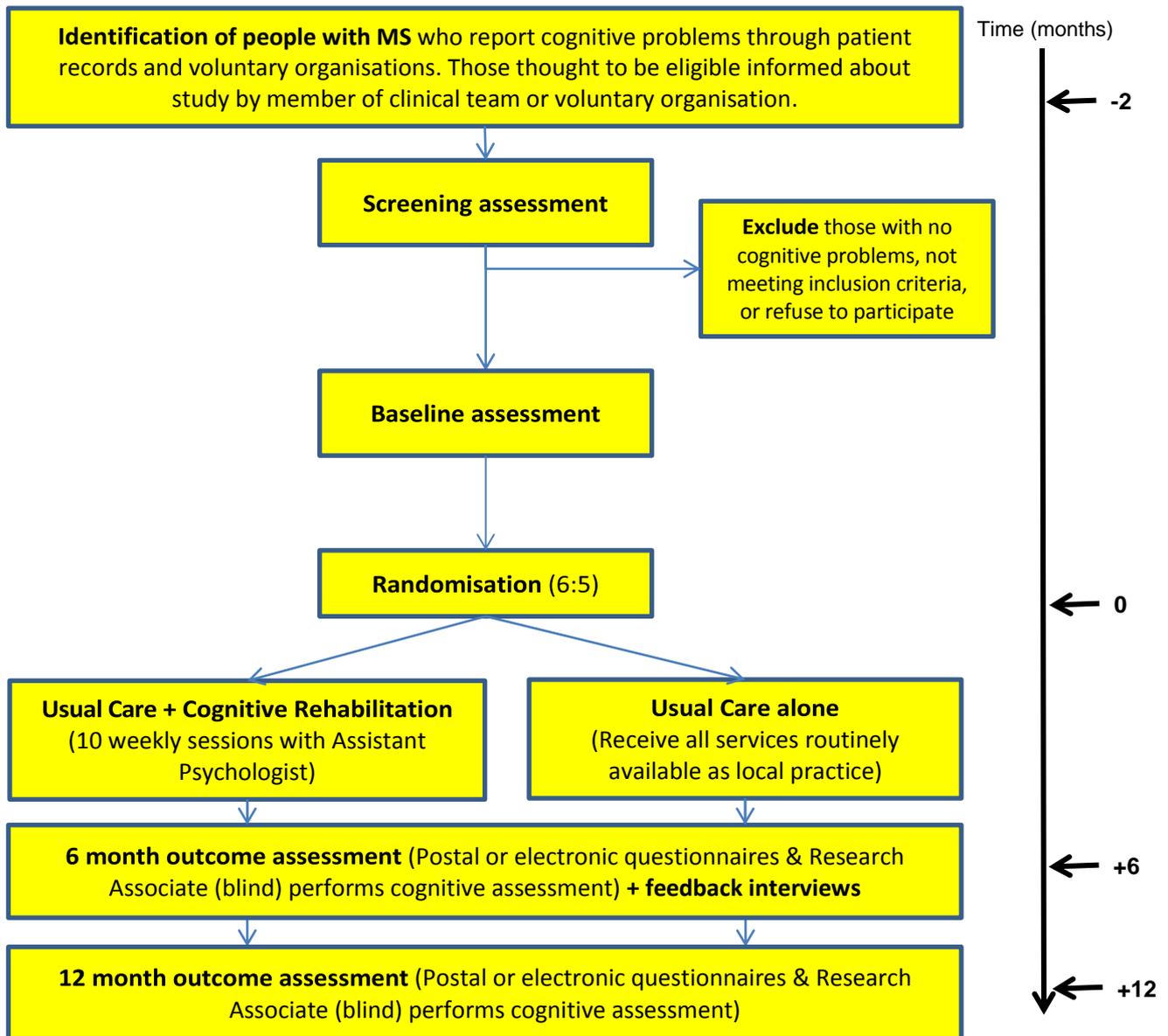


Table 1 – Study assessments

Assessments	Screening assessment*	Baseline assessment*		RANDOMISATION	Intervention period*	6 and 12month visit*	
		Postal	Face to face			Postal or electronic	Face to face
Initial eligibility screening	X				Intervention Group Memory Rehabilitation (weekly group sessions for 10 weeks) plus usual clinical care		
Informed consent	X						
Demographic information	X						
Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ)	X						
Brief Repeatable Battery of Neuropsychological Tests (BRBN)	X						X
Guy's Neurological Disability Scale	X						X
MS Impact Scale		X					X
Everyday Memory Questionnaire – patient version (EMQ-p)		X					X
Fatigue Severity Scale		X					X
General Health Questionnaire-30		X					X
Doors and People			X				X
Trail Making Test			X				X
EQ-5D-5L			X				X
Service Use Questionnaire			X				X
Check availability for treatment group			X				
EMQ- relative version – relative version (EMQ-r)		X					X
Modified Carer Strain Index							X
Feedback interviews							

* 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. The interview will be within three months of the 6 month follow-up appointment

DATA COLLECTION METHODS

Screening assessment

At the first appointment, the assistant psychologist 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 some baseline data for those who are eligible. The Assistant Psychologist 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 marital status.

The following assessments will be conducted at screening:

- *Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ)*
- *The Brief Repeatable Battery of Neuropsychological Tests (BRBN)*
- *Guy's Neurological Disability Scale*

The results from the MSNQ and BRBN will be used to assess the inclusion criteria. Following screening, participants will be informed whether they meet the inclusion criteria.

Those who do not meet the inclusion criteria will be notified 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 willing to continue. They will be sent questionnaires to complete in their own time, to be collected at the baseline assessment visit:

- *MS Impact scale*
- *Everyday Memory Questionnaire patient (EMQ-p)*
- *Fatigue Severity Scale*
- *General Health Questionnaire-30*

While arranging the baseline appointment with the eligible participant the Assistant Psychologist will explain that the study is also interested in the view of the participant's attention and memory problems from a relative or friend's perspective. Participants will be sent an information sheet for the relative/friend and the EMQ- relative version (EMQ-r) to pass on.

Baseline assessment

At the baseline visit the following assessments will be conducted by the Assistant Psychologist:

- *Doors and People*
- *Trail Making Test (from the Delis-Kaplan Executive Function System)*
- *EQ-5D-5L*
- *Use of Health and Social Service Questionnaire*

The Assistant Psychologist will check availability to attend groups on certain days. Participants will only be randomised if they can attend on the days that groups are scheduled. Those unable to attend on scheduled days will be held in reserve until such time that a new group, matching their availability, is scheduled. In the period while waiting for a sufficient number of participants to be included in a group the Assistant Psychologist will remain in regular contact with the participants to inform them of any developments.

Intervention period

Participants will be assigned to either an intervention group or a control group in a 6:5 ratio. The intervention group will be involved in 10 group-based treatment sessions over about 10 weeks.

The content of treatment will be video recorded and analysed. All sessions may be recorded, unless participants do not give their consent, in order to avoid participants changing their behaviour in response to the recording. From these recordings, a sample of at least 80 sessions from two treatment groups per site will be analysed, in order to include sessions from the start, middle and end of the 10- week course. Further sessions may be purposefully selected on basis of information obtained from initial analyses and further analyses will take place until saturation has been reached.

Practices for video recording will draw upon guidance on minimizing intrusiveness of the recording ([Jordan and Henderson 1995](#); [Heath 1997](#)). This includes setting up the video camera for several group sessions, even when recording is not planned, so as to enable habituation to the camera's presence. The methods used in previous work will be drawn on to analyse the content of training within rehabilitation contexts ([Mozzoni and Bailey 1996](#); [Ducharme and Spencer 2001](#)). The assessor analysing the videos will be trained in conversation analysis (CA) and will apply a customized score sheet designed to capture a variety of key elements spanning all aspects of the intervention. The assessors will code these as present or absent over a series of time intervals. In addition, CA may be used to identify and describe some of the specific clinical communication patterns involved in cognitive rehabilitation. Consent will be sought for the use of the video data as a separate item on the Consent Form. Participants will not be excluded from the study if they do not want to be video recorded and the cameras will be set up to ensure those who do not wish to be videoed are not visible to the camera.

Any participants who fail to attend for treatment will remain in the trial and receive outcome assessments.

The control group participants will receive usual care information before they end their visit. However, for the majority of participants this will mean no further formal rehabilitation.

6 month and 12 month follow-up visit.

Participants will receive the follow-up questionnaires before their 6 or 12 month appointments. These are either posted to them or a link is provided by email to complete these electronically according to their preferred method as recorded at the baseline visit.

Participants whose relative/friend completed the baseline EMQ-r will be posted the relative/friend follow-up questionnaire to pass on.

The postal questionnaires will be collected by the research assistant (RA) at the follow-up appointment. The RA will check that they have been completed and if they have not will ask the participant to complete them during the visit.

The questionnaires to be completed are:

- *Guy's Neurological Disability Scale*
- *MS Impact scale*
- *Everyday Memory Questionnaire (patient and relative)*
- *Fatigue Severity Scale*
- *General Health Questionnaire-30*

- *Modified Carer Strain Index*

At 6 and 12 months follow-up appointment the participants will be assessed face-to-face by a Research Assistant who is not aware of the group allocation. The assessments are

- *Doors and People*
- *Trail Making Test (from the Delis-Kaplan Executive Function System)*
- *EQ5D-5L*
- *Use of Health and Social Service Brief Repeatable Battery of Neuropsychological Tests (BRBN)*

Feedback interviews

Qualitative feedback interviews will be conducted within three months of the 6 months appointment, with at least 32 purposefully selected and willing participants: minimum 4 intervention and minimum 4 control participants, from each participating centre. The selection strategy will be designed to include participants with varying levels of memory impairments, and with varying social situations using a maximum variation sampling strategy.

The interviews will take place at a time and place that is convenient for the participant. Some interviews will be conducted by a researcher (supervised by a qualified qualitative researcher), the remaining will be completed by one of our service user partners, who will be trained. Feedback interviews may be conducted in person or by telephone.

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 at the initial assessment. The interviews will provide important feedback on the participants' perception of changes of memory problems over time and for those in the intervention groups, the quality of the interventions provided, and as such will serve as a process measure. For those in the control group the interviews will provide confirmation of the nature of usual care received.

Compliance

The fidelity of the intervention is assessed from the video recording of the treatment sessions.

Data quality and compliance with the protocol will be assessed throughout using central monitoring techniques. This will be achieved through routine review of submitted data to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systematic or significant errors in data collection and reporting at a site.

The Trial Manager, Statistical colleagues and IT staff will by means of various database reports and statistically programmed oversight reports, define the critical/essential data to maintain trial oversight and also define events that will lead to a triggered requirement for an in-person site monitoring visit.

Criteria for terminating trial

This trial involves group rehabilitation and as such is very low risk.

The study maybe stopped as a whole because of a change in opinion of the Research Ethics Committee (REC) or TSC concerns or issues with study conduct at the discretion of the sponsor.

Should the trial be terminated, the research data will not be destroyed.

STATISTICS

Methods

The analysis and presentation of the trial will be in accordance with CONSORT guidelines ([Schulz et al. 2010](#)), with the primary comparative analyses being conducted on an intention-to-treat basis and due emphasis placed on confidence intervals for the between-arm comparisons. A full analysis plan will be developed prior to completion of data collection and discussed and agreed with the Trial Steering Committee and Data Monitoring Committee.

Descriptive statistics of demographic and clinical measures at baseline will be used to examine balance between those randomised to intervention and control. The primary analysis will employ a mixed effects linear regression model of the MSIS-Psy outcome at 12 months adjusted for baseline value and stratification variables, and taking appropriate account of clustering by therapy group. Distributions of raw outcome scores and regression model residuals will be examined and the data suitably transformed or a non-parametric analysis employed if necessary. For a parametric analysis, the comparison will be presented as an adjusted difference in mean MSIS-Psy score along with 95% confidence intervals and exact p-value. We will investigate whether further adjustment for any variables exhibiting marked imbalance at baseline influences the primary findings.

Earlier effects on the primary outcome will be investigated in a secondary analysis by comparing the arms at 6 months after randomisation. Similar analyses using appropriate regression models depending on outcome type will be conducted for secondary outcomes. Additional, secondary analyses of the primary outcome will take three general forms. First, the influence of missing data will be investigated using sensitivity analyses that make different assumptions, such as “best” and “worst” case scenarios depending on outcome type, as well as using multiple imputation methods. Second, the effect of adherence with treatment will be investigated using allocation respecting methods such as complier averaged causal effects (CACE) modelling using instrumental variable regression. Third, appropriate interaction terms will be entered into the primary regression analyses for MSIS-Psy in order to conduct pre-specified subgroup analyses according to MS-type, baseline MSNQ, and baseline Doors and People test. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, the results of these exploratory analyses will be presented using confidence intervals and interpreted with due caution.

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 and social services contacts, and prescribed medication use in the intervention and control groups during the investigation. This method has been used in a previous evaluation of psychological interventions for people with MS ([Humphreys et al. 2013](#)) and in a current cognitive rehabilitation study for memory problems in people with brain injuries. 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 EQ5D. 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 trial 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. These analyses will be conducted by a research assistant, under the supervision of a health economist.

Minimizing risk of bias

The following steps will be undertaken to reduce the risk of bias in this trial: (1) allocation will be randomly assigned and concealed using an automated web-based operated by NCTU; (2) the allocation algorithm will employ a computer-generated random number sequence; (3) there will be a single primary outcome (MSIS-Psy) and all outcomes specified in the protocol will be analysed and reported; (4) while the primary outcome is self-reported and therefore not blinded, some secondary outcomes will be assessed by a researcher who will be blinded to treatment allocation; (5) collection of outcome data will be attempted from every randomised participant not known to have died at the time of follow up and who has not withdrawn consent, regardless of adherence with allocated treatment; and (6) it is anticipated that there will be some non-collection of primary outcome data, and while the primary intention-to-treat analyses will be without imputation of missing data, sensitivity analyses will investigate various assumptions about the missing data

The participants and Assistant Psychologists will not be blind to the allocated treatment. It will be ensured that the Research Associate (RA) is blind to treatment allocation. The cognitive tests, which require 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 collected by the research assistant or completed online. Baseline data and questionnaires required prior to randomisation will be entered at site by the Assistant Psychologist.

Sample size and justification

The number of people with MS at each of four sites that have so far agreed to participate is approximately 1500 on active follow-up with approximately 60 patients seen in MS clinics per site per week (Sharrack, 2013, personal communication). Of these 40% are likely to report memory problems in daily life ([Grafman et al. 1990](#)). Of these 50% are likely to give consent, which gives 300 potential participants in each site. Our sample size estimate is based on analysis of the MSIS-Psy at 12 months post-randomisation. A clinically meaningful effect using this outcome is probably in the range 3-3.5 (using version 1 of the MSIS-Psy scored 9 to 45). In the pilot study, the 95% confidence interval for the difference between intervention and usual care was -1 to +8, indicating that the intervention has the potential to have an effect that is regarded as clinically worthwhile. The common standard deviation in the pilot study was 7.5. However we expect the standard deviation will be higher in our proposed study as the sample for the pilot study were all recruited from an out-patient rehabilitation unit, whereas the proposed sample will include people who have not.

Based on a two sample test, 143 participants per arm are required for analysis in order to detect a difference of 3 points on the MSIS-Psy, Version 1, assuming a standard deviation of 9, with 80% power, and 5% two-sided alpha (effect size 0.33). However, a clustering effect may be expected to occur in the intervention arm due to the intervention being delivered in groups. We estimate this clustering effect to be 0.1 ([das Nair and Lincoln 2012](#)). Design and analysis issues in partially clustered clinical trials have been reported ([Roberts and Roberts 2005](#)). Based on an average cluster size of 5 evaluable participants (those providing primary outcome data at 12 months after randomisation), and an ICC of 0.1 in the intervention arm, a total of 336 evaluable patients would provide 80% power to detect such a difference (184 to intervention and 154 to usual care). Additionally, the optimal allocation ratio depends on the

cluster size and the ICC. In this case, we will allocate participants in a ratio of 6:5 in favour of the intervention arm.

Data from the pilot study suggested non-collection of primary outcome data among 8% of participants. However because of the wider recruitment strategy and on the evidence of recruitment to other related studies ([Lincoln et al. 2002](#); [Lincoln et al. 2011](#)), we estimate it will be 15%. We will therefore aim to randomise a total of 400 participants (216 to intervention and 184 to usual care).

Version 2 of the MSIS-Psy will be used in this study with scores ranging between 9 and 36. The standard deviation of the MSIS-Psy version 2 in the UK South West Impact of Multiple Sclerosis cohort was 6.4 ([Hawton et al. 2012](#)). If the standard deviation in this study is between 6 and 9, differences of between 2 and 3 points on version 2 of the MSIS-Psy will be detectable based on the effect size specified above, with assumed similar clinical importance as for version 1.

Procedures for missing data

Missing outcome data occurs for two reasons: participants miss off items in multi-item questionnaires or do not answer a specific question; and participants are lost to follow-up. To minimise missing data a multi-domain preventive strategy has been introduced in the trial design and during the implementation of the trial by having detailed study documentation in the form of a study operation manual, training of all study personnel, and having monitoring records ([Wisniewski et al. 2006](#)). The number of questionnaires has been kept to a minimum and all are patient-friendly in format and style. When the questionnaires are collected by the research assistant (RA), they will be checked for any missing data items. The RA will prompt the participant to complete any missing data. .

ADVERSE EVENTS

The adverse event risks of taking part in the study have been assessed to be low. There are, however, non-specific risks involved in travelling to the research sites.

Participants may experience some distress if they find they are not performing as well as they think they should on cognitive assessments. However, firstly, distress caused in this way is considered very unlikely; and, secondly, any distress caused is likely to be mild. This distress will be managed by the psychologists who will be qualified to deal with such situations in an empathic manner, and make necessary referrals (to the participant's GP) if needed. 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 reported for this study.

When home visits are carried out to complete assessments, the psychologists will comply with their employing Trust's lone working policy. All researchers will also comply with the standard health and safety procedures of their employing Trust and the University. This will minimise the risk to researchers.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms, and one will be held in the Trial Master File at site.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number, allocated after consent has been obtained, for use on worksheets, other trial documents and the electronic 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).

All trial paperwork and the eCRF will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, and Participant Trial Number (the Trial Recruitment

Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

All trial paperwork and the eCRF shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

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

The Chief or local Principal Investigator will sign a declaration ensuring accuracy of data recorded in the eCRF.

Source documents

Source documents will be filed at the investigator's site and may include but are not limited to consent forms, current medical records and records. Worksheets may also completely serve as source data. Only trial staff as listed on the Delegation Log will have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes will made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); accountability of trial materials and equipment calibration logs.

TRIAL DATA

Monitoring of trial data will include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Team, or where required, a nominated designee of the Sponsor, will carry out monitoring of trial data as an ongoing activity.

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial team, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity using various database reports and statistically programmed oversight reports.

In-person site monitoring visits will be triggered by pre-defined requirements. During such an inspection a sample of entries on the eCRF will be verified against the source data. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive will include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the Chief Investigator and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The study has been designed and will be reported according to the CONSORT guidelines. Dissemination of the research findings will aim to cover as many potential avenues as possible to ensure that patients, carers, and clinicians are informed.

People with MS will be informed through the MS Society and MS Trust newsletters. Findings will be published in peer-reviewed scientific journals, such as *Multiple Sclerosis Journal*, and in journals read by practicing clinicians in rehabilitation services, such as *Clinical Rehabilitation*. This will ensure dissemination to both academics and those responsible for service delivery in the NHS. We will present the results at national and international conferences, such as the *World Federation of Neuropsychological Rehabilitation* and the *MS Frontiers* conference, and conferences for service users. 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 neuropsychology database).

If the intervention is found to be effective, the treatment manual will be made available through the MS Society website and extracts from video recordings may be used for the purpose of training therapists to deliver the intervention.

USER AND PUBLIC INVOLVEMENT

One service user is a co-applicant who has had experience of NHS services and has received cognitive rehabilitation in our pilot study. She has advised us on recruitment and dissemination options, and has helped us modify our intervention manual, and the lay summary of the project. Together with another service user, nominated by the MS Society, they will also be involved in conducting some of the feedback interviews and offer a patient-perspective on the analysis of qualitative data. A service user will sit on the TMG. We will also include service users to sit on the TSC and DMC. A Service User Advisory Group will be set up via email to further support the project. Members of this group will be invited to join through the MS Society, and from participating centres through their existing involvement mechanisms. Service user involvement will contribute to: project management decisions, recruitment, 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 will be resourced appropriately. In addition, we will enlist the support of the PPI Manager at Nottingham University Hospitals NHS Trust for training and supporting patients for involvement in clinical trials.

When the trial 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.

STUDY FINANCES

Funding source

This study is funded by NIHR Health Technology Assessment - 12/190/05

Participant stipends and payments

Participants' reasonable travel expenses to the hospital for assessments and intervention sessions will be reimbursed.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) _____

Signature: _____

Date: _____

Trial Statistician: (name) _____

Signature: _____

Date: _____

REFERENCES

- Baddeley, A., H. C. Emslie, et al. (1994). Doors and people: a test of visual and verbal recall and recognition. Bury St Edmunds, England, Thames Valley Test Co.
- Benedict, R. H., F. Munschauer, et al. (2003). "Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire." Mult Scler **9**(1): 95-101.
- Braun, V. and V. Clarke (2006). "Using thematic analysis in psychology." Qualitative Research in Psychology **3**(2): 77-101.
- Brissart, H., F. Daniel, et al. (2011). "[Cognitive rehabilitation in multiple sclerosis: a review of the literature]." Rev Neurol (Paris) **167**(4): 280-290.
- Cappa, S. F., T. Benke, et al. (2003). "EFNS guidelines on cognitive rehabilitation: report of an EFNS task force." Eur J Neurol **10**(1): 11-23.
- Carr, S. E., R. das Nair, et al. (2014). "Group memory rehabilitation for people with multiple sclerosis: a feasibility randomized controlled trial." Clin Rehabil **28**(6): 552-561.
- Cicerone, K. D., C. Dahlberg, et al. (2005). "Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002." Arch Phys Med Rehabil **86**(8): 1681-1692.
- das Nair, R., H. Ferguson, et al. (2012). "Memory Rehabilitation for people with multiple sclerosis." Cochrane Database Syst Rev **3**: CD008754.
- das Nair, R. and N. B. Lincoln (2012). "Evaluation of rehabilitation of memory in neurological disabilities (ReMiND): a randomized controlled trial." Clin Rehabil **26**(10): 894-903.
- Das Nair, R. and N. B. Lincoln (2013). "The effectiveness of memory rehabilitation following brain damage; A qualitative inquiry of patient perspectives." Neuropsych Rehabil.
- Delis, D., E. Kaplan, et al. (2001). Delis Kaplan Executive Function System (D-KEFS). San Antonio, TX, The Psychological Corporation.
- Department of Health (2005). The national service framework for long-term conditions. London, Great Britain, Department of Health.
- Ducharme, J. M. and T. F. Spencer (2001). "Training brain injury rehabilitation therapists to use generalized teaching and interaction skills." Brain Inj **15**(4): 333-347.
- EuroQol Group (1990). "EuroQol: a new facility for the measurement of health-related quality of life." Health Policy **3**: 199-208.
- Goldberg, R. J. and P. A. Williams (1988). User's guide to the General Health Questionnaire. Windsor, NFER-Nelson.
- Grafman, J., S. Rao, et al. (1990). Disorders of memory. neurobehavioural aspects of multiple sclerosis. S. Rao. New York, Oxford University Press: 102-117.
- Hawton, A., C. Green, et al. (2012). "Using the Multiple Sclerosis Impact Scale to estimate health state utility values: mapping from the MSIS-29, version 2, to the EQ-5D and the SF-6D." Value Health **15**(8): 1084-1091.
- Heath, C. (1997). Analysing work activities in face to face interaction using video. Qualitative Methods. S. D. London, Sage: 183-200.
- Hildebrandt, H., M. Lanz, et al. (2007). "Cognitive training in MS: effects and relation to brain atrophy." Restor Neurol Neurosci **25**(1): 33-43.
- Hobart, J., D. Lamping, et al. (2001). "The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure." Brain **124**(Pt 5): 962-973.
- Humphreys, I., A. E. Drummond, et al. (2013). "Cost-effectiveness of an adjustment group for people with multiple sclerosis and low mood: a randomized trial." Clin Rehabil **27**(11): 963-971.
- Jordan, B. and A. Henderson. (1995). "Interaction analysis: foundations and practice." Retrieved 18.04.11, from <http://irs.ed.uiuc.edu/students/c-merkel/document4.HTM>.
- Krupp, L. B., N. G. LaRocca, et al. (1989). "The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus." Arch Neurol **46**(10): 1121-1123.

- Lincoln, N. B., A. Dent, et al. (2002). "Evaluation of cognitive assessment and cognitive intervention for people with multiple sclerosis." Journal of Neurology, Neurosurgery & Psychiatry **72**(1): 93-98.
- Lincoln, N. B., F. Yuill, et al. (2011). "Evaluation of an adjustment group for people with multiple sclerosis and low mood: a randomized controlled trial." Multiple Sclerosis Journal **17**(10): 1250-1257.
- Mills, R., C. Young, et al. (2009). "Rasch analysis of the Fatigue Severity Scale in multiple sclerosis." Mult Scler **15**(1): 81-87.
- Mozzoni, M. P. and J. S. Bailey (1996). "Improving training methods in brain injury rehabilitation." Journal of Head Trauma Rehabilitation **11**(1): 1-17.
- O'Brien, A. R., N. Chiaravalloti, et al. (2008). "Evidenced-based cognitive rehabilitation for persons with multiple sclerosis: a review of the literature." Arch Phys Med Rehabil **89**(4): 761-769.
- Ptak, R., M. V. der Linden, et al. (2010). "Cognitive rehabilitation of episodic memory disorders: from theory to practice." Front Hum Neurosci **4**.
- Rao, S. (1990). A Manual for the Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis. Milwaukee, Medical College of Wisconsin.
- Roberts, C. and S. A. Roberts (2005). "Design and analysis of clinical trials with clustering effects due to treatment." Clinical Trials **2**(2): 152-162.
- Rohling, M. L., M. E. Faust, et al. (2009). "Effectiveness of cognitive rehabilitation following acquired brain injury: a meta-analytic re-examination of Cicerone et al.'s (2000, 2005) systematic reviews." Neuropsychology **23**(1): 20-39.
- Schulz, K. F., D. G. Altman, et al. (2010). "CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials." Trials **11**: 32.
- Sharrack, B. and R. A. Hughes (1999). "The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis." Mult Scler **5**(4): 223-233.
- Smale, K. J., S. E. Carr, et al. (2014). "An evaluation of treatment integrity in a randomised controlled trial of memory rehabilitation for people with multiple sclerosis." Clin Rehabil.
- Solari, A., A. Motta, et al. (2004). "Computer-aided retraining of memory and attention in people with multiple sclerosis: a randomized, double-blind controlled trial." J Neurol Sci **222**(1-2): 99-104.
- Stuifbergen, A. K., H. Becker, et al. (2012). "A randomized controlled trial of a cognitive rehabilitation intervention for persons with multiple sclerosis." Clin Rehabil **26**(10): 882-893.
- Sunderland, A., J. E. Harris, et al. (1983). "Do Laboratory Tests Predict Everyday Memory - a Neuropsychological Study." Journal of Verbal Learning and Verbal Behavior **22**(3): 341-357.
- Tesar, N., K. Bandion, et al. (2005). "Efficacy of a neuropsychological training programme for patients with multiple sclerosis -- a randomised controlled trial." Wien Klin Wochenschr **117**(21-22): 747-754.
- Thomas, P. W., S. Thomas, et al. (2006). "Psychological interventions for multiple sclerosis." Cochrane Database Syst Rev(1): CD004431.
- Thornton, M. and S. S. Travis (2003). "Analysis of the reliability of the modified caregiver strain index." J Gerontol B Psychol Sci Soc Sci **58**(2): S127-132.
- Wilson, B. (2010). "Rehabilitation of Memory Disorders." Journal of Neurology Neurosurgery and Psychiatry **81**(10): E4-E5.
- Wilson, B. A., A. Baddeley, et al. (1994). "Errorless Learning in the Rehabilitation of Memory-Impaired People." Neuropsychol Rehabil **4**(3): 307-326.
- Wisniewski, S. R., A. C. Leon, et al. (2006). "Prevention of missing data in clinical research studies." Biol Psychiatry **59**(11): 997-1000.