Neuropsychological Evaluation and Rehabilitation in Multiple Sclerosis (NEuRoMS): Refining the screening and management pathway in routine clinical practice (Phase 1: Work Package 2ii Qualitative Study)

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Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

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Position:

.....Head of Research and Evidence.....

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Contents

1 Abbreviations 5
2 Study Summary ..... 6~~7~~
3 Background 8
4 Rationale 9
5 Study Objectives ..... 10~~11~~
6 Study Design 11
6.1 Study Setting 11
6.2 Study Outline 11
6.3 Participant Identification and Involvement ..... 12~~13~~
6.4 Participant Recruitment 14
7 Participation Eligibility Requirements 15
7.1 Inclusion Criterion 15
7.2 Exclusion Criteria 16
7.3 Expected Participant Duration 16
7.4 Informed Consent ..... 16~~17~~
7.5 Participant Withdrawal 18
8 Research Data 18
8.1 Data Analysis 18
8.2 Participant Sample Size 19
9 Adverse Events 19
10 Regulatory Aspects 20
10.1 Ethical and other NHS Approvals 20
10.2 Deception 20
10.3 Consent 21
10.4 Right to Withdraw 21
10.5 Confidentiality and Data Protection 22
10.6 Vulnerable Groups 22
10.7 Confidentiality 23
10.8 Indemnity 23
10.9 Sponsor 23
11 Funding 23
12 Payment 23
13 Patient and Public Involvement 24

14 Dissemination 24
15 Appendices 2524
16 References 31

1 Abbreviations

CI	Chief Investigator
CRF	Case Report Form
DMT	Disease Modifying Therapy
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
MS	Multiple Sclerosis
NEuRoMS	Neuropsychological Evaluation and Rehabilitation in Multiple Sclerosis
NHCT	Nottinghamshire Healthcare NHS Trust
NHS	National Health Service
NRES	National Research Ethics Service
OT	Occupational therapist
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PMG	Programme Management Group
PPI	Patient and Public Involvement
R&D	NHS Trust R&D Department
RCT	Randomised controlled trial
REC	Research Ethics Committee
SDMT	Symbol Digit Modalities Test
SOP	Standard Operating Procedure
WP	Work Package

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Neurologists, MS nurses, administrative staff, physiotherapists, occupational therapists, Clinical Research Network (CRN).

Assistant Psychologists and Research Nurses: Employed by participating NHS Trust or University of Nottingham, undertaking research and/or clinical activities specifically for NEuRoMS (including providing the NEuRoMS intervention).

2 Study Summary

Full Study Title	Neuropsychological Evaluation and Rehabilitation in Multiple Sclerosis (NEuRoMS): Refining the screen and management pathway in routine clinical practice (Phase 1: Work Package 2ii)
Short Study Title	Refining the neuropsychological screening and management pathway in routine clinical practice - Qualitative Study
IRAS ID	276903

Study Design	▪ 10 case studies of people with multiple sclerosis (MS) who received the screening and NEuRoMS intervention, using routinely collected clinical notes and interviews with people with MS, staff who deliver the intervention/pathway, and carers or family members who support people with MS.
Study Participants	People with multiple sclerosis, carers or family members, and clinicians delivering the screen and management pathway.
Study Sample Size	Qualitative study: People with MS: n=10 Carers/ family members: n=10 Clinicians: n=12 (4 clinicians from each site) Intervention providers: n=3 (One Assistant Psychologist or Research Nurse from each site)
Study Locations	Three MS clinics who delivered the screening and management pathway: ▪ Nottingham University Hospitals NHS Trust ▪ Cardiff and Vale University Health Board ▪ Blizard Institute, Barts Health NHS Trust
Participant Inclusion Criteria	People with MS: ▪ Diagnosis of MS ▪ Received NEuRoMS screening and mild cognitive problems identified (in WP2i IRAS ID: 276570) Related informants: ▪ Relative/ carer of a person with MS Clinicians: ▪ Health professionals (i.e., neurologists, MS nurse specialists, psychologists, occupational therapists) delivering the NEuRoMS screening and management pathway to people with MS. Intervention providers: ▪ Assistant Psychologists/Research Nurses delivering the intervention to people with MS identified above in 1.) All participants: Aged 18 years or above, able and willing to give informed consent and able to communicate in English.
Primary Research Questions	▪ To improve understanding of how the NEuRoMS screening and management pathway is integrated within routine clinical practice. ▪ To improve understanding of how the NEuRoMs intervention programme is experienced by those who deliver and receive it.
Secondary Research Question/s	▪ Refine intervention resource book and staff training package. ▪ Develop fidelity tools for the definitive trial.

Interventions	The NEuRoMS intervention (referred to as NEuRoMS cognitive management programme in patient-facing documents): A therapist-led, manualised psycho-education programme to teach people with MS about cognitive problems and how to deal with them. Up-to 6 sessions, these can be delivered completely remotely over telephone or video conferencing. Hybrid models will also be available (dependent on government and NHS advice) with approximately 1-2 sessions delivered face-to-face in clinic and 3-6 delivered over telephone or video conferencing.

3 Background

The UK has over 127,000 people with Multiple Sclerosis (Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2014), with approximately 100 diagnosed weekly (MS Trust, 2016b), and increasing rates of diagnosis (Multiple Sclerosis International Federation [MSIF], 2013a). MS is an incurable, frequently progressive disease, often diagnosed in young adulthood or early middle age and is a leading cause of neurological disability in young adults (Multiple Sclerosis International Federation [MSIF], 2013a). Up to 70% of people with MS experience cognitive problems (Fischer et al., 2014), half having mild-moderate levels (Multiple Sclerosis International Federation [MSIF], 2013b) (often subtle and difficult to identify until severe), which can impact adversely on quality of life, daily activities and employment (Chiaravalloti & DeLuca, 2008; Cutajar et al., 2000; Langdon & Thompson, 1996; Rao et al., 1991). Cognitive deficits manifest as an inability to pay attention (e.g., getting easily distracted), forgetting in daily life (e.g., leaving the stove on after cooking), and problem-solving difficulties (e.g., getting confused when completing a multi-stage task like cooking). Natural history studies of cognitive dysfunction in MS indicate that once the deficits develop, they are unlikely to improve, with deterioration seen in many (Bagert, Camplair, & Bourdette, 2002). Cognitive problems are associated with high costs for people with MS, their families, and society (Multiple Sclerosis International Federation [MSIF], 2010). A national survey found cognitive problems were the most debilitating and distressing symptoms for people with MS (Dorning, Luck, & Holloway, 2013), so addressing cognitive problems, unsurprisingly, is a James Lind Alliance/MS Society 'top 10' research priority for people with MS (MS Society & James Lind Alliance, 2013).

In people with MS, neuropsychological management (e.g., psychoeducation, internal and external compensatory strategies) can ameliorate effects of cognitive problems (e.g., loss of independence), low mood, and improve work life, quality of life and activities of daily living (Chiaravalloti & DeLuca, 2008). Clinicians' and patients' knowledge of neuropsychological screening results may facilitate and improve shared decision-making regarding dose or choice of MS disease modifying therapies (DMTs), and neuropsychological rehabilitation can improve DMT adherence (Devonshire et al., 2011), which is often low (systematic reviews show MS DMT adherence rates of 41-88%) (Menzin et al., 2013). Nationally, almost 45% of MS specialists report that existing neuropsychological services are

insufficient, with people with MS often referred too late to benefit (Croft, Mynors, Roberts, Doncaster, & Bowen, 2016; MS Trust, 2015, 2016a; Mynors, Bowen, & Doncaster, 2016; Roberts, Mynors, & Bowen, 2016). Given costs, it is unlikely that more neuropsychological services will be commissioned soon, therefore, we need to use existing services more efficiently, with minimal extra costs. MS services need to (i) identify and triage people with MS for timely cognitive assessment; (ii) develop and deliver appropriate, resource-efficient interventions, making full use of technological advances; and (iii) help clinic staff find new ways of working.

4 Rationale

Currently, staff at NHS MS clinics do not routinely screen and provide sufficient support for all patients with MS who present with cognitive problems (Croft et al., 2016; MS Trust, 2015; Mynors et al., 2016; Roberts et al., 2016). By not intervening early, disability accrues, and people with MS are less likely to benefit from rehabilitation (Giovannoni et al., 2016), and costs for the people with MS, their families, the NHS and society are likely to escalate.

We are currently conducting an NIHR Programme Grant for Applied Research on Neuropsychological Evaluation and Rehabilitation in Multiple Sclerosis (NEuRoMS) which addresses the important gap identified above by developing a pathway for routine screening, and developing and evaluating a brief cognitive rehabilitation (NEuRoMS) intervention programme for mild cognitive problems, providing appropriate and timely support. The programme contains many work packages. In Work Package (WP) 1, we developed a blueprint of the screening and rehabilitation based on extant literature and stakeholder consultation, and designed a programme theory and logic model. This ethics application focuses on WP2.

In Work Package (WP) 2, the theoretical framework (see Appendices for logic model) needs to be further refined to move incrementally towards a stronger screening and management pathway founded on explicit application to real-world clinical settings. Three NHS MS clinics have agreed to be early adopters of the screening and management pathway, and all patients will be screened as part of usual care. Patients typically attend these clinics annually, and they will be informed through their usual clinical appointment letters of the newly introduced screening and management pathway. They will be provided with a weblink to complete the screening at home, or in the clinic with assistance if required (dependent on Government and NHS advice).

As part of the proposed pathway, screened participants with no cognitive problems identified will be informed of this and retested at their next appointment as part of their routine clinic follow-up. Those with moderate-severe cognitive problems will be referred to Occupational Therapy (OT) or psychology/neuropsychology services (as per routine care) and those with moderate-severe mood problems will be referred to psychology or psychotherapy for further assessment and intervention (as per routine care). Those with mild cognitive problems will be offered a manualized NEuRoMS intervention led by an Assistant Psychologist/Research Nurse. The intervention will be tailored to

screening profile and individual needs, but will focus on: psychoeducation, internal and external compensatory strategies; environmental modifications; and the importance of dealing with low mood and fatigue. Ten people with mild cognitive problems (3-4 from each site) will receive the NEuRoMS intervention and later take part in a semi-structured interview as part of 10 case studies. Qualitative analysis of the case studies will be reported to understand participants' experiences and identify any barriers/ facilitators to delivery of the screening and management pathway. The others will receive the NEuRoMS intervention following their next clinic appointment, when the intervention will be more established at each site.

We are interested in those with 'mild' cognitive problems in study, because the feedback we received from participants who took part in our previous cognitive rehabilitation trial (CRAMMS (Lincoln et al., 2019)) was that they had too severe cognitive problems to actually benefit from the rehabilitation. Participants felt that had they received the rehabilitation earlier, when their cognitive problems were milder, they may have been able to benefit more.

Research focus
The present study will investigate what potential benefits and issues people with MS who undergo neuropsychological screening encounter, and tries to identify any barriers/ facilitators to delivery of the screening and management pathway. Ten patients who experienced the neuropsychological screening (IRAS ID: 276570) and were identified as having mild cognitive problems, will be offered a manualized NEuRoMS intervention led by an Assistant Psychologist or Research Nurse. After completing the intervention, semi-structured interviews will be conducted with participants and related informants (family or carers) and clinicians to understand their experiences of the screening and management pathway. These qualitative case studies will help refine the pathway and facilitate its implementation.

5 Study Objectives

Primary Objectives and Outcomes

- To improve understanding of how the NEuRoMS screening and management pathway is integrated within routine clinical practice.
- To improve understanding of how the NEuRoMs intervention programme is experienced by those who deliver and receive it.

Secondary Objectives

- Refine intervention resource book and staff training package.
- Develop fidelity tools for the definitive trial.
- The primary endpoints of the qualitative interviews are based on:

Study Outcomes

- Improved understanding of how the NEuRoMS screening and management pathway is integrated within routine clinical practice (e.g. contextual factors which influence its delivery, those mechanism which influence its affect and those outcomes which are described by interviewees).
- Improved understanding of how the NEuRoMs intervention programme is experienced by those who deliver and receive it (e.g. behavioural elements of the intervention, essential resources needed for, and barriers to screening and intervention delivery).

6 Study Design

6.1 Study Setting

This is a multicentre study conducted across three NHS sites with MS outpatient clinics. A list of participating sites can be found in section 1 Study Summary.

6.2 Study Outline

This qualitative study (WP2ii) involves interviews with 10 patients (and related informants, clinicians and intervention providers) who experienced the screening and management pathway and are completing the NEuRoMS intervention.

A self-administered, brief online neuropsychological screening (completed at home prior to clinic visit) or tablet-based version (completed in clinic prior to routine appointment -dependent on Government and NHS advice) that can be administered with minimal support from clinical staff will be introduced as part of usual care at three NHS sites. The screen will capture cognitive function (memory, information processing and executive function), mood and fatigue. The screen will be used to facilitate discussions about managing cognitive problems between patients and clinicians.

The current study will recruit ten people with MS who received the screen and were identified as having mild cognitive problems. These participants will be offered the NEuRoMS intervention during a discussion of their screening results with a member of their clinical team (MS nurse, neurologist, OT, psychologist or physiotherapist). Patients will be selected using a maximum variation sampling technique (varied according to demographic and illness characteristics).

The newly designed NEuRoMS intervention is multi-faceted, involving various components (i.e., information provision, goal setting), and a range of strategies and techniques (e.g., psychoeducation, compensatory strategies, boosting cognitive reserve), delivered by a trained Research Nurse or Assistant Psychologist (under the supervision of a clinical psychologist). Sessions will predominately be delivered remotely via videoconferencing and telephone sessions, however those who prefer to undertake intervention sessions face-to-face can opt to do so for the first two sessions (dependent on Government and NHS advice). The Research Nurse or Assistant Psychologist will receive monthly supervision (60 minutes) via telephone/videoconference or face-to-face (depending on current government and NHS COVID guidelines) with a clinical psychologist.

They will also receive additional monthly group supervision, peer supervision and research supervision from the research team members. The intervention was designed by the research team who have considerable expertise around designing complex cognitive rehabilitation interventions and was informed by evidence gathered from systematic reviews (Goverover, Chiaravalloti, O'Brien, & DeLuca, 2018), interviews and focus groups with relevant stakeholders (e.g., people with MS, neuropsychologists and OTs), PPI input and clinical experiences. The intervention is person-centred, tailored to the needs and lifestyle of each participant, and aims to help people with MS cope with and manage cognitive problems by establishing strategies that can be maintained once the intervention sessions are finished. Please see enclosed 'NEuRoMS Resource Book' (Please note: The layout/design/formatting of the Resource book may change, but the content will stay the same). To facilitate remote delivery of the intervention, people with MS will also be able to access digital intervention content (i.e., brief videos) that will complement the Resource Book. The videos showcase PPI members providing an overview of the intervention content (e.g., what to expect, tips on how best to utilise the intervention resources). The digital content will be hosted on the NEuRoMS project website (www.neuroms.org), and will only be accessible to participants using a generic login. A PDF copy of the Resource Book will also be available on this platform.

Upon completion of the NEuRoMS intervention, a member of the research team will conduct semi-structured interviews (remotely) with people with MS, their related informants (family members, carers), clinicians and intervention providers. Data will be analysed to inform: (i) understanding of people with MS' experiences of receiving the intervention, (ii) the iterative refinement of the screening and management pathway (iii) the revision of programme theory. Interviews will be conducted remotely over the phone/videoconferencing. Please see Appendices for semi-structured interview guides which were developed with our PPI co-investigators.

Monthly teleconferences between a member of the research team and Clinicians at the three MS clinics will also be recorded and used as a data source. These conversations will explore any problems with implementation, possible solutions, what is working well and why. This will include consideration of participation rates with different screening modalities (online at home or tablet) and telephone support. Intervention sessions will also be audio-recorded for fidelity checks and supervision evaluations. Intervention providers will also complete intervention case notes and intervention record forms (detailing the content of therapeutic interactions), which will be used for fidelity checks.

Data collection will be completed in September 2022. We believe this is achievable given the average clinic throughput of 150 patients per month per clinic (Evangelou, personal communication, 2019), assuming a 20% attrition rate and allowing for some delays due to the COVID-19 pandemic which may slow recruitment and increase withdrawal rate.

6.3 Participant Identification and Involvement

All participants will provide informed consent before they enter the study (see Figure 1). Details of the study will be explained via a Participant Information Sheet (specific to the participant group, for example, people with MS, related informant, clinicians), ensuring that the patient has sufficient time

to consider participating or not. Participants will be given at least 24 hours to decide whether they wish to participate and be told that participation is voluntary. Please see the enclosed Participant Information Sheets.

1. Patients

A member of the clinical team will approach eligible participants who have undergone neuropsychological screening in WP2i (IRAS ID: 276570). For this study, we will only be recruiting people with MS with mild cognitive problems, so the clinician will discuss the results of the screening with the patient (as part of their routine clinical care) and inform them of this research study which includes a brief NEuRoMS intervention and an interview to gather feedback on the screening and management pathway. The clinician will also explain that we want to gather feedback from related informants such as family members and carers with insights into how the pathway is experienced by those living alongside or supporting someone with MS (e.g., have attended appointments with patient, have assisted patient to use online technology, have seen the intervention resource booklet and the digital intervention resources). By explaining the importance of related informant feedback and providing advance notice of these interviews we hope to avoid delays or gaps in the recruitment of related informants.

A member of the clinical team will answer any immediate questions that the patient has concerning study participation during their routine appointment and will refer them to the research team/ Assistant Psychologist or Research Nurse for telephone or email support if any questions later arise. Participants will be interviewed within approximately two weeks of completing the NEuRoMS intervention by the research team.

2. Related informants

Patients who consent to the study will be provided with Participant Information sheets along with a cover letter to pass onto related informants who they feel may have an insight into the pathway (patients will be reminded of this during their intervention appointments). Contact details will be provided for the research team/ Assistant Psychologist or Research Nurse so that related informants can approach the team to express interest and/or ask any questions about the study via email or telephone. Participants will be interviewed by the research team within approximately two weeks of the person with MS they support completing the NEuRoMS intervention.

3. Clinicians

Qualitative case studies will be introduced during the Site Activation Visits, where a member of the research team will explain the purpose of the interviews (process evaluation of the screening and management pathway; problems with implementation, possible solutions, what is working well and why) and answer any questions that the clinicians have. The PI for the site will identify relevant clinicians and invite them to the Site Activation Visit. Relevant clinicians will be provided with a Participant Information Sheet and a Consent Form. Those who consent will be interviewed by the research team after experiencing the different elements of the pathway (i.e. screening, triaging, and intervention).

4. Intervention providers
Assistant Psychologists and Research Nurses from each site who are being employed to deliver the intervention will also be interviewed and have their intervention sessions audio-recorded. A member of the research team will explain the purpose of the interviews (process evaluation of the screening and management pathway and involvement with patient case study) and answer any questions that they have during the Site Activation Visit. They will also be provided with a Participant Information Sheet and a Consent Form. Those who consent will be interviewed by the research team after experiencing the different elements of the pathway (i.e. screening, triaging, and intervention delivery).

The duration of the intervention will be up to 4hours spread across up to 6sessions (patient participants). We anticipate these sessions to occur over a 2month period, based on patient availability. Interviews will take up to 60minutes (all participants- patient, related informant, clinicians, and intervention providers). Recruitment will begin July 2021, with interviews taking place until the end of September 2022.

6.4 Participant Recruitment

This study will collect qualitative data from ten patients. Related informants, clinicians and intervention providers will also be invited to take part in a semi-structured interview. The study will be set across three NHS sites, with interview data collected over the phone/videoconferencing.

Ten people with MS who were identified as having mild cognitive problems following neuropsychological screening, will be invited to receive the NEuRoMS intervention and take part in a semi-structured interview, by a member of the clinical team during their discussion about the screening results (see Figure 1). The clinician will confirm the patient's contact details, and with the patient's consent, pass these onto the Research Nurse or Assistant Psychologist (intervention providers) who will contact the patient to provide them with a Participant Information Sheet and Consent Form which they will sign ahead of their first NEuRoMS intervention session. Patients will be selected using a maximum variation sampling technique (varied according to demographic and illness characteristics).

Consenting patients will also be provided with a cover letter, Participant Information Sheet and Consent Form to give to related informants (e.g. carers, family members) during their intervention sessions with the Research Nurse or Assistant Psychologist. These will provide details of a researcher the informant can contact to discuss the study, answer questions and arrange an appointment. Clinicians and intervention providers will be invited to take part in the interviews during the Site Activation Visit. Participant Information Sheets and Consent Forms will be provided during the visit with researcher contact details provided for further questions.

We will explain to the potential participants that entry into the study is entirely voluntary and that they can withdraw at any time (see section 7.5 Participant Withdrawal for more information).

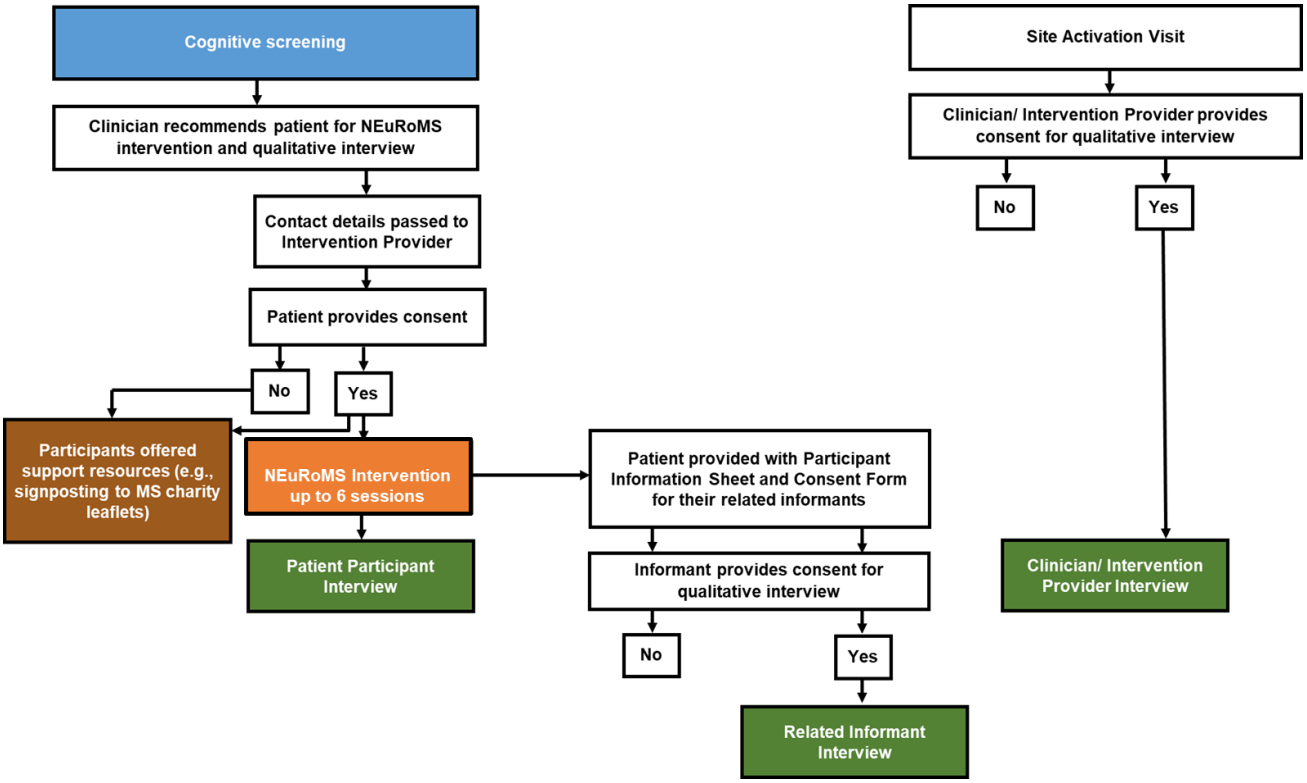


Figure 1. Consenting flowchart for participants in Qualitative study

7 Participation Eligibility Requirements

7.1 Inclusion Criterion

1.) People with MS:

- Diagnosis of MS
- Received neuropsychological screening and mild cognitive problems identified (in WP2i IRAS ID: 276570)

2.) Related informants:

- Relative, friend or carer supporting a person with MS

3.) Clinicians:

- Health professionals (e.g., neurologists, MS nurse specialists, psychologists, occupational therapists) delivering the NEuRoMS screening and management pathway to people with MS.

4.) Intervention providers:

- Assistant psychologists or Research Nurses delivering the intervention to people with MS identified above in 1.)

All individuals: Aged 18 years or above, able and willing to give informed consent and able to communicate in English.

7.2 Exclusion Criteria

•Do not have mental capacity to consent to take part in the study
•Are unable to communicate in English (standardised materials are to be used which have not yet been developed for other groups)

7.3 Expected Participant Duration

NEuRoMS intervention = up to 4hours across up-to 6 sessions, these can be delivered completely remotely over telephone or video conferencing. Hybrid models will also be available (dependent on government and NHS advice) with approximately 1-2 sessions delivered face-to-face in clinic and 3-6 delivered over telephone or video conferencing (see Figure 2).

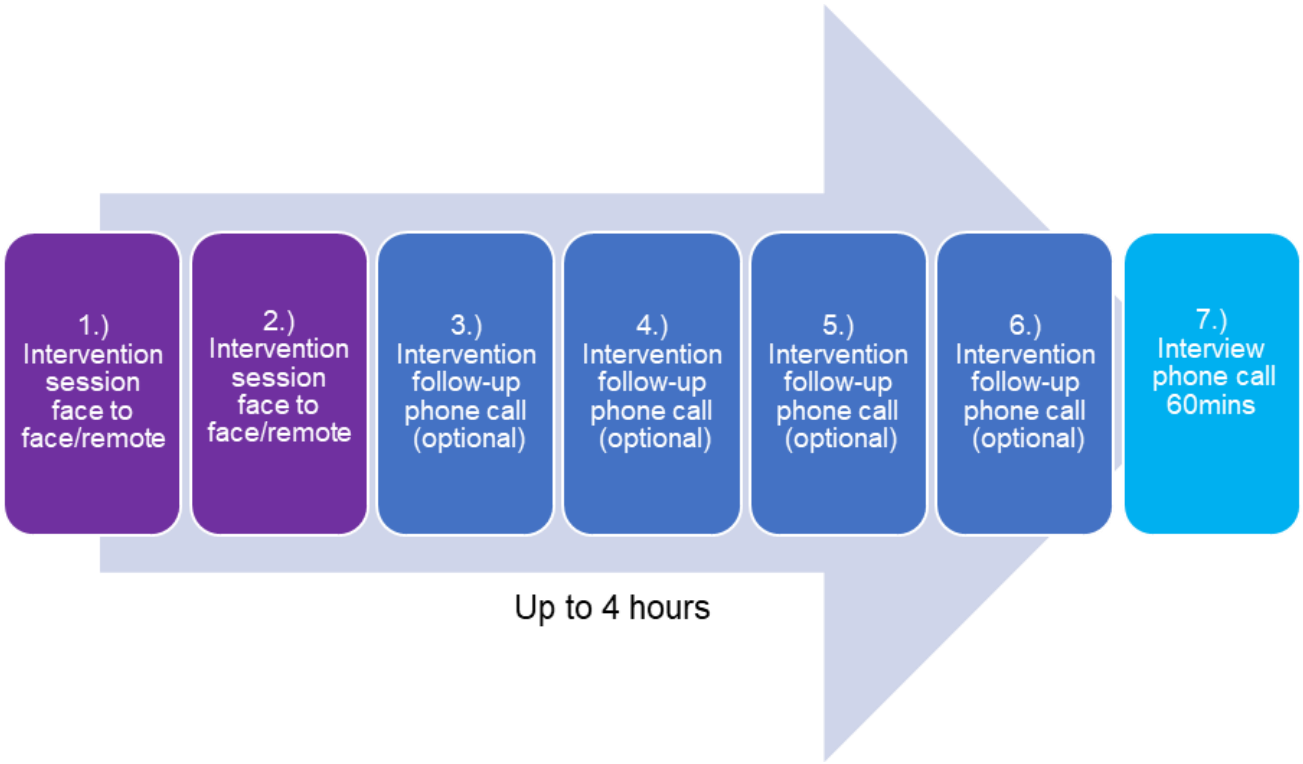


Figure 2. Qualitative study schedule for patient participants

7.4 Informed Consent

All participants will provide informed consent before they enter the study. Details of the study will be provided in a Participant Information Sheet, ensuring that the individual has sufficient time to consider participating or not (at least 24 hours).

Ten patients with mild cognitive problems will be invited to take part in a case study where they will receive the NEuRoMS intervention and complete a digitally-recorded interview (along with related informants, clinicians and intervention providers). A member of the clinical team will explain the study to the participant and confirm their contact details. With the patient's consent, these will be passed onto the intervention provider who will contact patients with Participant Information Sheet and Consent Forms. After allowing at least 24hours, the intervention provider will contact patients again to check if they wish to participate and will arrange their initial appointment. Patient participants will be asked to provide consent via Phone/Videoconferencing, Online via email or using a secure web application, or Post (see below) ahead of their initial NEuRoMS intervention session, or can bring their signed copies of their Consent Form along to the session (if meeting face-to-face – dependent on current Government and NHS COVID guidelines). During this session participants will also be provided with a cover letter, Participant Information Sheet and Consent Form for their related informants. Patients will be reminded to pass the study documents on to their related informants during the intervention sessions.

We will not inform GPs of patients' involvement in the study, as the care for the patients is provided by the MS Services once they are diagnosed with MS. A record of the patient's involvement in this study will be held in their medical notes at the MS clinic.

Clinicians and intervention providers will be informed of the study during the Site Activation Visit and provided with a Participant Information Sheet and Consent Form from a member of the research team. For more information see Section 6.4 on Participant Recruitment.

Telephone and email contact details for the research team will be provided for related informants, intervention providers and clinicians to ask questions and arrange an interview appointment where consent will be taken. To facilitate the consent process, informed consent will be obtained through the following routes, based on participant preference.

1. Phone or Videoconferencing: Participants will be offered the opportunity to provide their consent orally, over the telephone or videoconferencing. With the participant's approval, the consent process will be digitally recorded using an audio recorder. We will also record the date and time when oral consent was obtained using a researcher record of oral consent document to obtained participant consent. Participants will receive a hard copy of the researcher record of oral consent document for their own records, we will send this later by post.

2. Post: Participants can sign the Consent Forms and return these to us using a pre-paid envelope provided.

3. Online: Participants can sign the Consent Forms electronically via email or using a secure web application. An electronic copy of the signed Consent Form can be downloaded from the webpage.

Should there be any subsequent amendment to the final protocol, which might affect participation in the study, continuing consent will be obtained using an amended Consent Form which will be signed by the participant. If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

Participants will not be excluded from the study if they do not want to be audio recorded. A researcher record of oral consent and notes from the interview can be taken instead of an audio-recording should the participant prefer.

7.5 Participant Withdrawal

Participants may be withdrawn from the study either at their own request or at the discretion of the Chief Investigator or treating clinician (in the case of patient participants). Patient participants will be informed that this will not affect their future medical care. Participants will be made aware (via the information sheet and Consent Form) that should they withdraw all personal data will be destroyed but other data collected up to the point of withdrawal may still be used in the final analysis. All participants will be informed that if they withdraw their legal rights will not be affected.

If consent is withdrawn, the participants will be discontinued from the study. Due to the characteristics of the some members of the sample (i.e. having multiple sclerosis or being an informal carer), should any participant become tired or demonstrate that the interview session is causing them any discomfort or distress, we will check with them whether they wish to continue, and proceed only with their permission. Breaks will be provided where this is needed or requested.

8 Research Data

8.1 Data Analysis

Research data will consist of audio recordings of (i) interviews and (ii) NEuRoMS intervention sessions. Interviews will be audio-recorded and transcribed verbatim, with field notes made to capture contextual information, and analysed (on NVivo) using framework analysis. This is a hierarchical, matrix-based method developed for applied qualitative research (Pope, Ziebland, & Mays, 2000) (Ritchie & Lewis, 2003). Taking this type of analytical approach is appropriate for the purposes of the research, as framework analysis is particularly suited to research where the objectives of the study are clearly defined at the onset (i.e., to further develop and refine initial programme theory). The interview data will be mapped to thematic matrices (see Appendices for Logic Model) which reflect resources required for NEuRoMS to be delivered, contextual factors which influence its delivery, those mechanism which influence its affect and those outcomes which are described by interviewees. This will enhance our understanding of the key issues for people with MS and other stakeholders in relation to screening and intervention. It will allow us to explore the behavioural elements of the intervention, essential resources needed for, and barriers to screening and intervention delivery. If required, the framework will be revised to include new concepts or themes introduced during the interviews. Once all the data are mapped onto the framework, tables will be used to summarise each main theme. Each

theme will be interpreted to inform the development of the proposed screening and management pathway for subsequent elements of the wider NEuRoMS programme grant.

The intervention audio-recordings and intervention record forms will be mapped onto the intervention manual to determine 'how much' of the manual was covered in each session, what was left out, what the patients found difficult to follow, etc. This will give us some indication of how the intervention should be refined.

The audio-recordings of the interviews, monthly teleconferences and intervention sessions and intervention record forms will be treated as confidential documents and held securely in accordance with regulations. Each participant will be assigned a unique participant identity code number by the research team, for use on study documents and the electronic database (see section 10.5 for Confidentiality and Data Protection).

8.2 Participant Sample Size

Sample sizes for the interviews are based on our previous experience and extant literature, which suggest these numbers will achieve 'theoretical sufficiency' to answer specific questions (Dey, 1999) and inform the ongoing development of NEuRoMS. Purposive sampling will be used for the interviews. We intend to complete ten detailed qualitative case studies conducted with people with MS, and their related informants (n=10, one per participant, representing all three sites). We will interview all the intervention providers (Research Nurses/ Assistant Psychologists) (one per site; n=3), and four clinicians from each of the three screened sites (n=12).

9 Adverse Events

The occurrence of an adverse event as a result of participation within this study is not expected, since the trial involves a NEuRoMS intervention and qualitative interview only. However, it is possible that talking about cognitive difficulties may sometimes create distress for people with MS or their related informants during the study. This distress will be dealt with during the course of the intervention and the intervention sessions will address this on a participant by participant basis. The intervention will be delivered by a trained Assistant Psychologist or Research Nurse who will receive monthly supervision. 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.

In the event of discomfort/distress during interviews, the following protocol will be in place:

1. Ensure sufficient time to be given for debriefing after the meeting.
2. Facilitators/interviewers to be actively looking for cues of distress/discomfort and check with participants whether they wish to continue, and proceed only with their permission.
3. If the participant no longer wish to continue and consent is withdrawn, one of the researchers (who is a health professional) will accompany the participant out of the room to allow debrief and to provide support, as needed.

4. Contact information on appropriate referral sources will be provided should participants feel they need further information/support on cognitive problems.
5. If needed, participants to be advised to approach their GPs.
6. Contact details of the research team will be provided in case of any enquiry about the research or to discuss the feelings of the distress caused by the interview/discussions later on.

10 Regulatory Aspects

10.1 Ethical and other NHS Approvals

Approvals for this study will be sought from NHS Research Ethics Committee, Health Research Authority (HRA) and NHS R&D prior to commencement. The study will not be initiated before the protocol, Consent Forms and Participant Information Sheets have received approval/ favourable opinion from the REC. 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/ favourable opinion from the REC. 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. Planned deviations from the protocol will not be permitted, any accidental deviations will be documented (to avoid recurrences) and reported to the Chief Investigator and sponsor immediately. All correspondence with the REC will be retained in the Study Master File.

The study will be conducted in accordance with the ethical principles based on the UK Policy Framework for Health and Social Care (Health Research Authority, 2017), Good Clinical Practice and the Declaration of Helsinki 1996 (Organization, 1996).

The sponsor and funder reserve the right to discontinue the 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 Programme Steering Committee as appropriate in making the decision. There are no formal statistical criteria for stopping the study early.

10.2 Deception

Participants will be informed of all research activities prior to participating in the study thus there are no risks of deception.

During the interviews some topics of conversation around experiencing cognitive issues and accessing support services to help people with MS manage these cognitive problems may cause some discomfort or distress to the people with MS. Enough time will be given for debrief after the meeting. The interviewers will be actively looking for cues of distress or discomfort and they will check

with participants whether they wish to continue, and proceed only with their permission. If the participants no longer wish to continue and consent is withdrawn, one member of the research team will take them out of the room to allow debrief and to provide support, as needed.

Contact information on appropriate referral sources will also be provided for participants who feel they need further information/support with respect to cognitive problems in MS. If needed, people with MS will also be advised to approach their General Practitioner (GP). Also, the participants will receive the contact details of the research team in case of any enquiry about the research.

10.3 Consent

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.

Ten participants identified as having mild cognitive problems will be invited to take part in an additional case study where they will receive the NEuRoMS intervention and will later be interviewed. A member of the clinical team will explain the case study to the participant at their routine clinical appointment. With the patients' permission, the Assistant Psychologist or Research Nurse will then contact them with a Participant Information Sheet and Consent Form. Participants will be asked to provide consent via Phone/Videoconferencing, online, or Post (see Section 7.4 for Informed Consent), or can bring signed copies of their Consent Form along to the session (if meeting face-to-face –dependent on Government and NHS advice). Patients and intervention providers will also be asked to provide their consent for the intervention sessions to be recorded for fidelity and supervision purposes.

Other stakeholders will either give consent for the interviews orally over the phone/videoconferencing, online, or complete hardcopies if preferred. Participants will receive a copy of the signed and dated Consent Form and the original will be retained in the Study records. A copy of the patient's Consent Form will also be retained in their medical notes.

The decision regarding participation in the study is entirely voluntary and participants will be encouraged to take their time making this decision. The Participant Information Sheet will emphasize that consent regarding study participation may be withdrawn at any time without penalty. The Information Sheet will also provide contact details should the participant want to ask any questions about the study. No study-specific interventions will be done before informed consent has been obtained.

10.4 Right to Withdraw

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.

Participants will not be withdrawn from the study if they do not want to be audio recorded. A researcher record of oral consent and notes from the interview can be taken instead of an audio-recording should the participant prefer.

10.5 Confidentiality and Data Protection

The only identifiable information will be the names and contact details of the participants, which will be stored separately to the interview data. Each participant will be assigned a Participant ID Number by a member of the research team, for use on the interview transcripts and the electronic database. The research team will make a separate confidential record of the participant's name and Participant ID Number stored at the University of Nottingham, to permit identification of all participants enrolled in the study, in case additional follow-up is required.

The interviews will be audio-recorded using an encrypted, Trust approved, digital recorder and transcribed. A Trust approved external company or a University approved secure, web-based automated interface will be used for transcribing the interviews. A confidentiality agreement will be in place before transferring the interview data to the external company. The audio-recordings of intervention sessions and interviews will be treated as confidential documents and held securely in accordance with regulations at the University of Nottingham. Participants will be informed in the Participant Information Sheet that this agreement may be breached to report an incident to the appropriate persons if they reveal something of concern that may put themselves or anyone else at risk. Source documents shall be restricted to those personnel approved by the Chief Investigator and recorded as such in the study records. Source documents shall be filed at the investigator's site and may include but are not limited to, Consent Forms, interview transcriptions, audio-recordings and records. Only study staff shall have access to study documentation other than the regulatory requirements listed below. All source documents shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. We will only collect the minimum required information for the purposes of the study. This will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data 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).

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

10.6 Vulnerable Groups

The only group which will be participating in the research can be considered vulnerable adults are the patient participants. We will be clear about the voluntary nature of their participation, and we will provide them with sufficient time to consider participation and to discuss with others before they

participate. They are free to withdraw at any time, without such withdrawal affecting their rights or future care. Since we will only include those who can communicate in English, we will not need to amend any of the study documentation for other groups (e.g., those with language difficulties, e.g., aphasia). The initial contact will be made by a member of the clinical team.

10.7 Confidentiality

Each participant will be assigned a unique Participant ID Number, for use on the interview transcripts and the electronic database (see section 10.5 for confidentiality and data protection).

The audio-recordings of intervention sessions and interviews, and intervention record forms will be treated as confidential documents. Source documents shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records (see section 10.5 for confidentiality and data protection).

10.8 Indemnity

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

10.9 Sponsor

Nottinghamshire Healthcare NHS Trust will act as the main Sponsor for this study. The Sponsor's Standard Operating Procedures (SOPs) will be used to govern the conduct of all aspects of the study. The Sponsor will ensure the study is run in accordance with their SOPs and auditing and monitoring plan will be developed in partnership with the sponsor. A self-audit checklist will be developed and completed regularly by each site to ensure adherence to the protocol and accurate and complete data collection. The study will be managed and co-ordinated from the Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham.

11 Funding

This study is funded by the NIHR Programme Grants for Applied research (ref no. RP-PG-0218-20002) and was peer-review by an anonymous panel of experts.

12 Payment

An inconvenience voucher worth £20 will be offered to each patient and family member/carer who participated in the interviews as a thank you for their time.

Patients taking part in the NEuRoMS intervention sessions will also have their travel expenses covered for face-to-face sessions (dependent on Government and NHS advice).

13 Patient and Public Involvement

Our research team has excellent networks with people with MS and we have an extensive track record of conducting research studies in MS. We have developed this proposal in conjunction with an MS-PPI group.

Our PPI co-investigators (Clare Bale and James Turton, who have MS) have been involved with every key stage of the research process and offered guidance for the project. Work Package 1 gathered the views of people with MS, carers and family, charity volunteers and clinicians on the proposed programme of NEuRoMS research via interviews and focus groups, which helped shape our pathway and logic model. We have also organized and held two PPI engagement events to discuss the NEuRoMS screening and management pathway and present our findings to date.

We have received some very useful and positive verbal feedback from people with MS which has helped shape our research strategy and design. We aim to work closely with the people with MS and their families/carers through our MS PPI group to ensure we produce useful findings that can facilitate the transferability of the screening and management pathway into practice a range of healthcare settings. Our patient partners (Bale and Turton) and our PPI group will continue to be involved with every key stage of the research process providing us with the real life experiences of living with MS, and what they feel is needed.

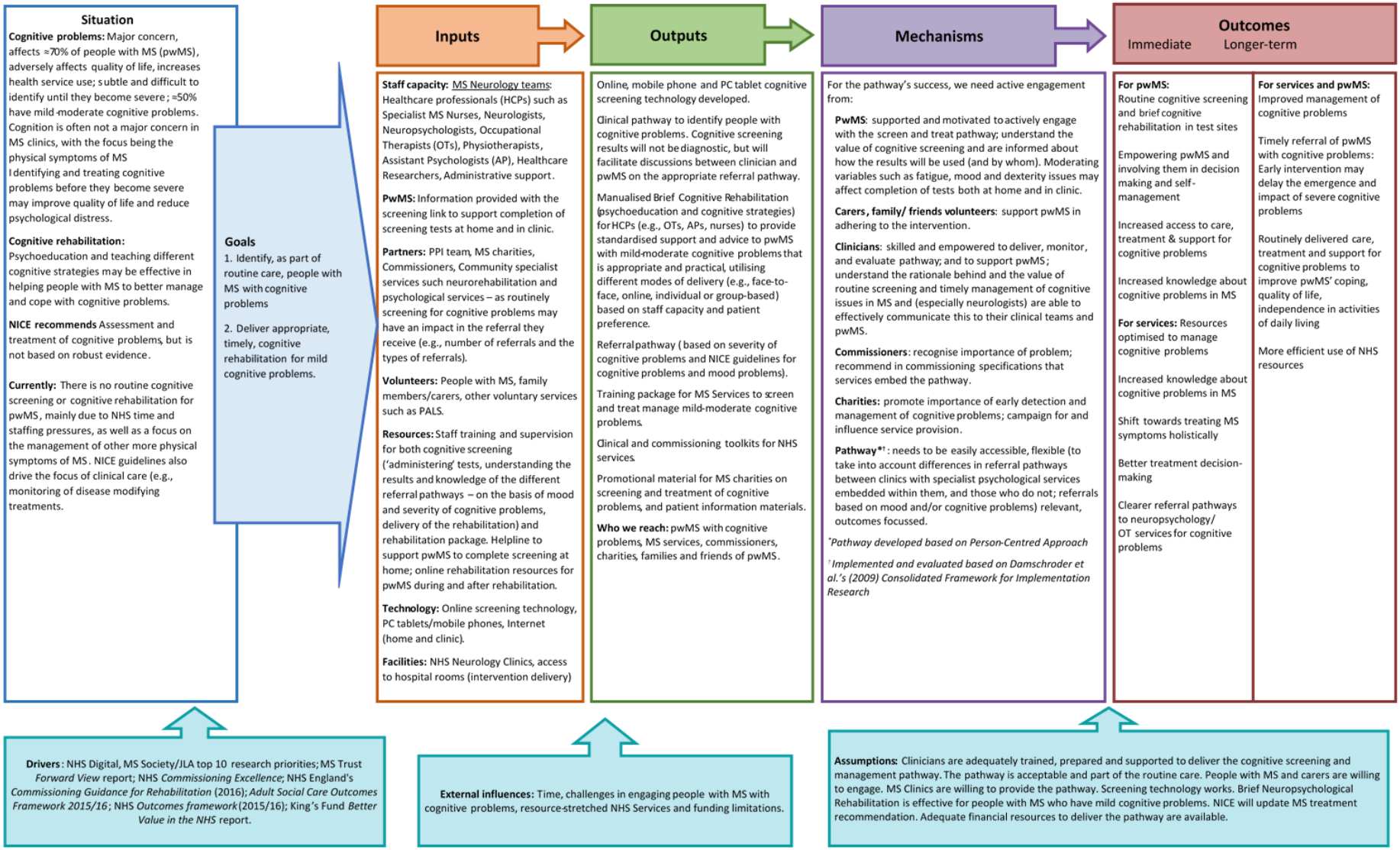
14 Dissemination

Findings will be published in scientific journals and disseminated to scientific audiences, people with MS (e.g., MS Life Conference), policy makers, healthcare networks, relevant organisations and stakeholders. A summary of the study findings will be made available through the NEuRoMS web page and newsletters.

15 Appendices

Final Version 7.0 05.07.2022

Cognitive Screening and Management Pathway in MS –logic model v4 23.10.2019



Final Version 7.0 05.07.2022

NEuRoMS WP2ii Qualitative Study: Patient-Participant Semi-structured interview Guide

Final Version 2.0, 29.06.2021

[Note: As per the methodology, the semi-structured interview is only a guide, and is necessarily an iterative process (i.e., it gets modified slightly after each interview, based on the information that participants provide).]

Screening

- Can you give me your general impressions of using the screening tool(s)?
- Was there anything you particularly liked?
- Was there anything you particularly disliked or found difficult?

Screening and management pathway

- What do you see as the main challenges to delivering our approach to monitoring and supporting your cognitive problems?
    - What can be done to address these challenges?

NEuRoMS cognitive management programme

- How did you find the NEuRoMS programme sessions?
    - What did you find helpful/unhelpful about the programme sessions?

- How did you find the NEuRoMS resource book?
    - What did you find helpful/unhelpful about the resource book?

- How did you find the NEuRoMS online video resources?
    - What did you find helpful/unhelpful about the online resources?

- What do you think about where the sessions were held?
- What do you think about the person who delivered the sessions?
    - Knowledgeable?
    - Clear and understandable?
    - Empathetic? Helpful?

- How do you think we could improve the cognitive management programme in the future?

- Have you experienced any changes since taking part in this study?
    - What are these changes?
    - How do you make sense of these changes?

- Is there anything else you would like to tell me about?

NEuRoMS WP2ii Qualitative Study: Clinician/ Intervention Provider-Participant Semi-structured interview Guide

Final Version 1.0: 16.01.2020

[Note: As per the methodology, the semi-structured interview is only a guide, and is necessarily an iterative process (i.e., it gets modified slightly after each interview, based on the information that participants provide).]

Demographics

- Gather demographic information about the participant and their job role.

Screening and management pathway

- How did the screening and management pathway work in your service?
- How well did the screening and management pathway work with your systems?
- What were the main facilitators to integrating the screening and management pathway within your service?
- What were the main barriers to integrating the screening and management pathway within your service?
    - What can be done about the barriers?

NEuRoMS cognitive management programme (only for intervention providers)

- Please can you tell me about your experiences of delivering NEuRoMS cognitive management programme?
    - What went well?
    - What were the difficulties and how did you overcome them?
    - How did you find the training that you received?
    - How did you find using the manual?
    - How did you find the clinical supervision at site/ by the trial therapists?
    - How did you find the monitoring of your practice during the research study?

- How did participants find the NEuRoMS cognitive management programme?
    - Were there any particular aspects which were good or bad?
    - Did participants experience any changes/benefits from the cognitive management programme?

- How do you think the cognitive management programme could be improved in the future?

NEuRoMS WP2ii Qualitative Study: Family Member/ Carer -Participant Semi-structured interview Guide

Final Version 1.0: 16.01.2020

[Note: As per the methodology, the semi-structured interview is only a guide, and is necessarily an iterative process (i.e., it gets modified slightly after each interview, based on the information that participants provide).]

Demographics

- Gather demographic information about the participant and their relationship to the person they support.

Screening

- Can you give me your general impressions of how your family member/friend found using the screening tool(s)?
- Was there anything you think they particularly liked?
- Was there anything you think they particularly disliked or found difficult?
- Did you provide your family member/friend with any support to complete the screening tasks?
- Were you surprised to hear that your family member/friend might have cognitive problems?

Screening and management pathway

- What do you see as the main challenges to delivering our approach to monitoring and supporting cognitive problems in MS?
    - What can be done to address these challenges?

NEuRoMS cognitive management programme

- How do you think your family member/ friend found the NEuRoMS programme sessions?
    - What do you think they found helpful/unhelpful about the programme sessions?

- What do you think about where the sessions were held?

- What do you think about the person who delivered the sessions?
    - Knowledgeable?
    - Clear and understandable?
    - Empathetic? Helpful?

- How do you think we could improve the NEuRoMS cognitive management programme in the future?

- Has your family member/friend experienced any changes since taking part in this study?
    - What are these changes?
    - How do you make sense of these changes?

- Is there anything else you would like to tell me about?

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