

Neuropsychological evaluation and rehabilitation in multiple sclerosis (NEuRoMS): A mixed-methods, multi-centre feasibility randomised controlled trial

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Abstract

Background: Cognitive difficulties are common in people with multiple sclerosis (pwMS), yet access to neuropsychological rehabilitation is often limited or only provided to those with more severe impairments. The NEuRoMS intervention provides brief, tailored neuropsychological rehabilitation for pwMS with mild-to-moderate cognitive difficulties.

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Objectives: To evaluate feasibility and acceptability of the intervention and test procedures for a definitive trial.

Methods: A mixed-methods, multi-centre feasibility randomised controlled trial (RCT) was conducted. Feasibility outcomes were recruitment, retention, outcome completion, randomisation, intervention delivery and fidelity. Quantitative data were collected at baseline, 3- and 6-months, supplemented by interviews with pwMS and healthcare providers.

Results: Seventy-nine participants were randomised (mean age = 54.5 ($SD = 11.5$); 70% women) from three UK MS clinics. Most feasibility criteria were met: retention (>80%) and outcome-measure completion (81%–89%) were high, and trial procedures were acceptable. Intervention delivery was feasible and delivered as intended, but staffing-related recruitment challenges need addressing in future trials. Preliminary signal of efficacy was observed, with 3.42-point difference (effect size = 0.48) in the planned primary outcome (MS psychological impact) favouring the intervention, supported by qualitative evidence of sustained behaviour change.

Conclusion: The NEuRoMS intervention and trial procedures were feasible and acceptable, with early indication of efficacy. A definitive RCT is underway.

Trial registration: ISRCTN11203922; <https://doi.org/10.1186/ISRCTN11203922>

Keywords

Multiple sclerosis, cognition, rehabilitation, RCT, feasibility trial

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Introduction

Up to 70% of people with multiple sclerosis (pwMS) experience cognitive difficulties,¹ with around half experiencing at least mild-to-moderate impairment.² Information processing speed, memory, attention and executive functions are commonly affected.^{1,3} Although often under-identified until more severe, these difficulties can substantially disrupt daily functioning, quality of life, social participation and employment,³ contributing to social and economic burden.⁴

Neuropsychological rehabilitation aims to mitigate difficulties by enhancing insight into deficits and providing structured training in internal and external compensatory strategies.⁵ Systematic reviews report evidence of modest but meaningful improvements in cognitive functioning and related outcomes such as mood and quality of life,^{6,7} though findings remain inconclusive due to poor methodological quality (e.g., heterogeneous samples, lack of pre-specified primary outcome). Robust, multi-centre randomised controlled trials (RCTs) using valid health and economic outcomes are needed.

Emerging evidence suggests neuropsychological rehabilitation has greater benefits among pwMS with mild-to-moderate cognitive difficulties,⁸ highlighting value in early interventions. Thus, Neuropsychological Evaluation and Rehabilitation in Multiple Sclerosis (NEuRoMS) was co-developed with pwMS and stakeholders^{9,10} as a brief, manualised intervention tailored for pwMS with mild-to-moderate cognitive difficulties.

To inform a definitive RCT evaluating the clinical and cost-effectiveness of the NEuRoMS intervention, guided by established principles for developing and evaluating complex interventions,¹¹ we assessed feasibility

parameters. Objectives were to: (1) evaluate feasibility and acceptability of trial procedures and assessment measures; (2) assess intervention delivery and fidelity; (3) characterise intervention context and usual care; (4) develop a cost-effectiveness analysis framework; and (5) gather stakeholder feedback to refine study procedures, intervention delivery and training.

Methods

The trial protocol was prospectively registered (ISRCTN11203922; 09/08/2021) and published.⁹ Ethical approval was granted by the Health Research Authority North West Greater Manchester West Research Ethics Committee (20/NW/0454, 13/01/2021). Reporting follows CONSORT for pilot and feasibility trials.¹²

Design

This multi-centre, mixed-methods, parallel-group feasibility RCT compared NEuRoMS plus usual care (intervention group) with usual care alone (control group) in pwMS with mild-to-moderate cognitive difficulties, with nested fidelity evaluation and feedback interviews.

Participants

Adults (≥ 18 years) from three UK National Health Service (NHS) sites with a neurologist-confirmed multiple sclerosis (MS) diagnosis, able to communicate in English and provide informed consent, were eligible. All sites invited pwMS to complete online cognitive screening as part of their routine MS clinic appointments. Mild-to-moderate

cognitive difficulties were defined as scores 1.5 to 3 standard deviations (SDs) below the mean on the Symbol Substitution Task (SST), a web-based variant of the Symbol Digit Modalities Test.¹³ SST scores were interpreted using raw thresholds because demographic-adjusted norms were not available when this trial began. We excluded individuals outside this range and those receiving neuropsychological intervention for cognition at recruitment.

Eligible pwMS were approached by their clinical team and, if interested, contacted by the research team to provide study information. Participants provided consent before baseline assessments.

Sample size

Consistent with feasibility trial guidelines,¹⁴ we aimed to recruit 60 to 80 participants to assess feasibility and estimate parameters for the definitive trial, providing a 95% confidence interval (CI) of $\pm 8.8\%$ – 10.1% around the proposed 80% retention rate.

Randomisation and blinding

After consent and baseline, participants were individually randomised (1:1), stratified by site, using an online dynamic adaptive algorithm.¹⁵ Blinding of participants and intervention providers (Assistant Psychologists [APs]) was not possible; however, researchers collecting and analysing outcome data were blind to group allocation.

Intervention and usual care

NEuRoMS is a person-centred rehabilitation programme combining information provision, goal-setting, psychoeducation and compensatory strategies, tailored to individual needs. It supports pwMS to manage cognitive difficulties by teaching them evidence-based cognitive strategies. Intervention, provided by APs (who are psychologists pre-specialisation) under Clinical Psychologist and/or Neuropsychologist supervision, lasted up to 4 hours (across up to six sessions) over approximately 2 months. Sessions were delivered one-to-one over videoconferencing, face-to-face, or phone. Intervention recipients received a workbook and access to brief Patient and Public Involvement (PPI)-led videos introducing the intervention. While core components were standardised across all intervention participants, optional components specified in the manual and the number and duration of sessions were intentionally tailored to individual goals and cognitive needs within the manualised framework.

To support consistency across facilitators, the feasibility study incorporated standardised training, use of a structured facilitator manual, session checklists and regular supervision. To minimise contamination, only NEuRoMS-trained APs (who did not provide usual care) delivered the

intervention, and access to materials was restricted via a password-protected website.

Usual care primarily involved signposting to charity resources or referrals for MS-related symptoms (e.g., fatigue, mood).

Outcomes

Outcomes focused on feasibility of proceeding to a definitive trial (Table 1).

Participants completed self-report questionnaires across MS impact, cognitive, psychosocial, functional and work-related domains. Service use, health-related quality-of-life, MS-specific health-state and capability-based wellbeing measures were collected for future health economic evaluation. See Table 2 and Supplemental Material 1 for details of these measures. Measures were selected based on PPI endorsement, psychometric robustness and brevity.

Data collection methods

Self-reported questionnaires were completed online, by phone or on paper at baseline and 3- and 6-months post-randomisation. For phone completions, an independent researcher administered measures. Any unblinding events were recorded.

Intervention fidelity

Fidelity assessment was guided by the Conceptual Framework for Implementation Fidelity (CFIF).¹⁶ With consent, sessions were audio/video-recorded, and APs completed session record forms. We undertook time-sampling of all available recorded sessions for a random sample of participants. Sessions were coded in 1-minute intervals using an iteratively developed deductive-inductive coding framework capturing intervention-specific components and non-specific content. Two researchers compared these data with the intervention manual to assess delivery of key intervention components (content, dose, frequency, duration) and to identify omissions, participant difficulties, facilitation strategies, delivery quality and participant responsiveness. Frequencies and percentages of components delivered as intended were recorded. Clinical competencies were assessed using an adapted rehabilitation competency checklist¹⁷ (0 = not observed to 3 = done well), covering facilitation, communication skills, interpersonal style and session structure.

Interviews

Semi-structured interviews were conducted online with 39 stakeholders: 25 pwMS from both trial arms, eight clinicians and six APs. PwMS were purposively sampled for maximum variation and interviewed at two timepoints (after

Table 1. Feasibility outcome domains and assessment methods.

Feasibility outcome domain	Assessment procedures	Assessment timepoints
Recruitment feasibility	1. Response and recruitment rates: number of eligible pwMS who consent and decline to participate (including reasons for non-participation) 2. Appropriateness of eligibility criteria: number of participants referred or interested who meet the eligibility criteria 3. Appropriateness of eligibility screening and recruitment procedures: interviews 4. PwMS willingness to be recruited: interviews	Throughout recruitment period and interviews
Retention feasibility	Retention rates: number of participants who consent and remain in the trial by 3- and 6-month follow-ups	Throughout data collection period (baseline, 3-month and 6-month follow-up)
Feasibility of self-report clinical outcome measures	1. Completion rates: number of fully completed measures, partially completed measures, and lost to follow-up 2. Missingness: number of missing data 3. Suitability and appropriateness: interviews 4. Acceptability: interviews	Throughout data collection period (baseline, 3-month and 6-month follow-up) and interviews
Randomisation feasibility	1. Randomisation rate: number randomised. 2. Randomisation process and pwMS willingness: interviews	Point of randomisation and interviews
Feasibility of NEuRoMS intervention	1. Feasibility of delivery: number of fully completed and partially completed interventions and interviews 2. Acceptability: interviews 3. Intervention fidelity: fidelity checklist, intervention record forms, audio/video recordings and case notes of intervention sessions	Point of intervention and interviews
Feasibility of conducting a health economic evaluation	Feasibility of collecting economic outcome measures: completion and return rates	Throughout data collection period (baseline, 3-month and 6-month follow-up) and interviews
Exploration of efficacy	Signal of efficacy	3-month and 6-month follow-up and interviews

Note: pwMS = people with MS.

completing 3- and 6-month follow-ups). Clinicians and APs were interviewed once after gaining experience with the NEuRoMS pathway (~12 months of delivery). Interview schedules were developed iteratively with PPI input. Interviews were audio-recorded and transcribed verbatim.

Analyses

Quantitative data were analysed in Stata 16 and R 4.0.2. Feasibility outcomes for recruitment, retention and completeness were assessed using Red (stop)/Amber (review)/Green (go) (RAG) criteria.¹⁸ Recruitment was evaluated by monthly averages (Go: ≥ 12 /month, Review: 6–11/month; Stop: ≤ 5 /month), retention by 3- and 6-month follow-up completion (Go: $\geq 80\%$, Review: 50%–79%; Stop: $\leq 49\%$)

and outcome measure suitability by completion rates using the same thresholds, focused on the proposed primary outcome for the definitive trial (Multiple Sclerosis Impact Scale-Psychological Subscale [MSIS-Psych]).¹⁹

Descriptive statistics were reported as means and SDs (or medians and interquartile ranges for non-normal data) and categorical variables as counts and percentages. Effect sizes for the definitive RCT were estimated using adjusted mean differences from multilevel mixed-effects models under intention-to-treat principles. No imputation was performed, as missing data were feasibility outcomes. Continuous outcomes were analysed using multilevel mixed-effects linear models and categorical outcomes using multilevel mixed-effects logistic regression. Models included covariates (age, time since diagnosis) and factors (allocated group,

Table 2. Self-reported clinical and economic outcome measures.

Domain	Questionnaires
Psychological and physical impact	Multiple Sclerosis Impact Scale (MSIS-29) ^{*a}
Perceived cognitive impairment	Perceived Deficits Questionnaire (PDQ-20) ^b
Mood	Patient Health Questionnaire-9 (PHQ-9) ^c ; Generalised Anxiety Disorder-7 (GAD-7) ^d ; Whooley Questions for depression screening ^e
Functional ability	Nottingham Extended Activities of Daily Living Scale (NEADL) ^f
Self-efficacy	Multiple Sclerosis Self-Efficacy Scale (MSSE) ^g
Work-related issues	Multiple Sclerosis Work Difficulties Questionnaire Short Form (MSWDQ-23) ^h
Impact of cognitive difficulties on work/education and medication adherence	Two single bespoke questions
Use of health and social care services	Bespoke service use questionnaire (SUQ)
Quality of life and capability-based wellbeing for health economics evaluation	EQ-5D-5L ⁱ ; ICEpop CAPability measure for Adults (ICECAP-A) ^j

*The MSIS-Psychological Sub-Scale was identified as the candidate primary clinical outcome for a future definitive trial, informing the sample size calculation.

Note: Markers a–j are reference letters indicating the citations for the validated questionnaires, which are listed in Supplementary Materials 1.

assessment timepoint, cognitive impairment, gender, education, MS subtype), with group*timepoint interactions tested and site included as a random effect. Normality and linearity assumptions were checked, with transformations applied where required.

For health economics, feasibility was assessed descriptively, including completion rates, missing data and potential ceiling effects.

Fidelity analyses summarised the proportion of coded time in content categories and the distribution of intervention components.

Interview data were analysed using framework analysis,²⁰ mapped to thematic matrices informed by the NEuRoMS programme theory and logic model.¹⁰

Results

Seventy-nine participants were randomised over 9 months (Figure 1). Demographic and clinical characteristics (Table 3) were broadly comparable between groups, and representative of the UK MS population.²¹

Feasibility outcomes are summarised using RAG progression criteria (Table 4), with illustrative quotations in Supplemental Material 2.

Recruitment feasibility

Eligibility, screening and recruitment procedures were rated Green/Go. Of 125 individuals screened, 79 consented (63%). Forty-six (37%) did not proceed, mostly due to non-response ($n = 18$, 39%) or declining participation ($n = 13$, 28%). The average monthly recruitment rate was 8.8 participants (Amber/Review). We recruited to target. Interviews indicated that pwMS found processes and study information clear and appropriate. APs suggested that offering more information about rehabilitation at recruitment could help clarify the trial's focus on cognitive difficulties. PwMS valued this focus and were motivated by the opportunity to receive cognitive rehabilitation and contribute to research benefiting others.

Retention feasibility

Retention was high. Seventy participants completed the 3-month follow-up (89%) and 64 at 6 months (81%), with 63 (80%) completing both (all Green/Go).

Withdrawal rate was 10% ($n = 3$ at baseline, $n = 2$ at 3 months, $n = 3$ at 6 months), due to ill-health ($n = 3$), loss of interest ($n = 2$), or personal commitments ($n = 1$); two provided no reason. Most follow-ups were completed within the intended time-window (75% at 3 months; 80% at 6 months), with the remainder completed within 2 months and all within the allowable window for analysis. Approximately half of participants required reminders ($n = 42$, 55% at both timepoints), mostly via system-generated emails.

Feasibility of self-reported clinical outcome measures

Outcome completion was high, with 70 (89%) completing at 3 months and 64 (81%) at 6 months. Completion of the planned primary outcome (MSIS-Psych) was 92% at 3 months and 87% at 6 months (Green/Go). Missingness was minimal, with only one partially completed MSIS-Psych at 6 months. Most participants (>95%) completed questionnaires online.

PwMS interviews indicated that questionnaires were clear, acceptable and relevant. While many found the number of questionnaires manageable, some however, found them lengthy. Suggested improvements included reducing

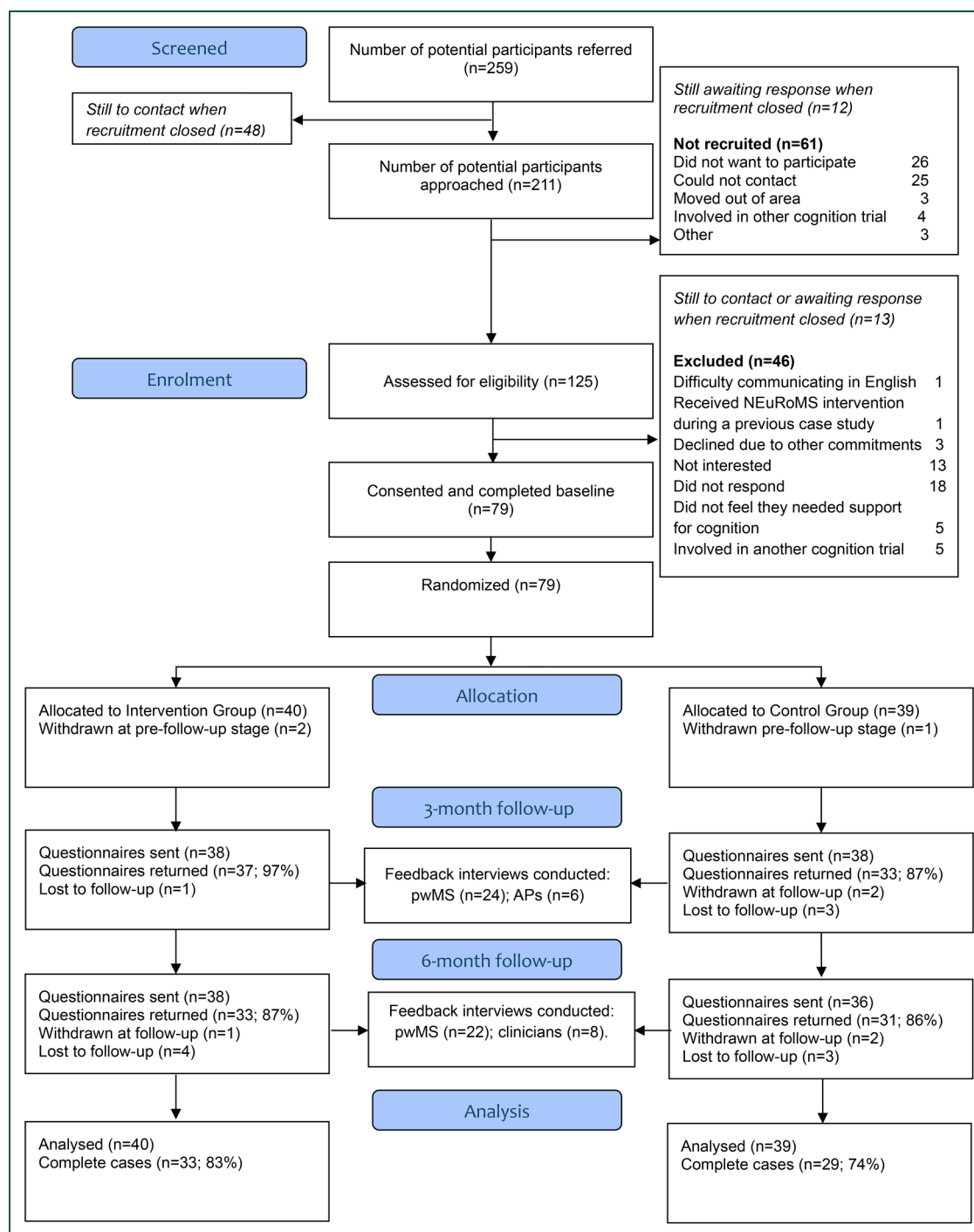


Figure 1. CONSORT flow diagram.

repetition, adding progress indicators and enabling save-and-return functionality to reduce burden.

Randomisation feasibility

All consented participants were randomised, with balanced allocation across sites (intervention n = 40; control n = 39).

No unblinding was reported. Two protocol deviations occurred: one incorrect allocation due to human error when reading the randomisation code, and one participant not receiving the intervention due to staffing absences.

Most pwMS understood the concept of randomisation and were happy with this aspect of the study when deciding to consent. Some suggested improvements regarding

Table 3. Participant demographic and clinical characteristics.

Characteristic	Descriptive	Intervention	Control	Total
Age (years)	N (missing)	40 (0)	39 (0)	79 (0)
	Mean (SD)	56.0 (11.2)	52.9 (11.7)	54.5 (11.5)
	Median [IQR]	55.5 [49, 63]	55.0 [44, 61]	55.0 [48, 62]
	Min, Max	22, 77	21, 72	21, 77
Gender	Woman	27 (67.5%)	28 (71.8%)	55 (69.6%)
	Man	12 (30.0%)	10 (25.6%)	22 (27.9%)
	Other	1 (2.5%)	0 (0%)	1 (1.3%)
	Prefer not to say	0 (0%)	1 (2.6%)	1 (1.3%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Ethnicity	White	38 (95.0%)	33 (84.6%)	71 (89.9%)
	Asian/Asian British	0 (0%)	1 (2.6%)	1 (1.3%)
	Black/ African/ Caribbean/Black British	2 (5.0%)	4 (10.3%)	6 (7.6%)
	Other ethnic group	0 (0%)	0 (0%)	0 (0%)
	Mixed/multiple ethnic Groups	0 (0%)	1 (2.6%)	1 (1.3%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Education	Below GCSE	4 (10.0%)	4 (10.3%)	8 (10.1%)
	GCSE	6 (15.0%)	6 (15.4%)	12 (15.2%)
	A-Level	10 (25.0%)	6 (15.4%)	16 (20.3%)
	NVQ	4 (10.0%)	1 (2.6%)	5 (6.3%)
	Degree	11 (27.5%)	17 (43.6%)	28 (35.4%)
	Higher degree	3 (7.5%)	4 (10.3%)	7 (8.9%)
	Not known	2 (5.0%)	1 (2.6%)	3 (3.8%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Employment	Not employed	10 (25.0%)	9 (23.1%)	19 (24.1%)
	Employed full-time	8 (20.0%)	8 (20.5%)	16 (20.3%)
	Employed part-time	3 (7.5%)	6 (15.4%)	9 (11.4%)
	Voluntary full-time	0 (0%)	0 (0%)	0 (0%)
	Voluntary part-time	2 (5.0%)	2 (5.1%)	4 (5.1%)
	In education full-time	0 (0%)	0 (0%)	0 (0%)

(continued)

Table 3. Continued.

Characteristic	Descriptive	Intervention	Control	Total
	In education part-time	1 (2.5%)	0 (0%)	1 (1.3%)
	Retired	16 (40.0%)	14 (35.9%)	30 (38.0%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Time since diagnosis (years)	N (missing)	40 (0)	39 (0)	79 (0)
	Mean (SD)	17.8 (10.2)	15.3 (11.4)	16.6 (10.8)
	Median [IQR]	16 [10.5, 23.5]	12 [7, 22]	14 [7, 23]
	Min, Max	1, 53	1, 42	1, 53
Type of MS	Relapsing-remitting MS	18 (45.0%)	24 (61.5%)	42 (53.2%)
	Primary progressive MS	5 (12.5%)	9 (23.1%)	14 (17.7%)
	Secondary progressive MS	15 (37.5%)	5 (12.8%)	20 (25.3%)
	Not known	2 (5.0%)	1 (2.6%)	3 (3.8%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Comorbidities	No	33 (82.5%)	34 (87.2%)	67 (84.8%)
	Yes	7 (17.5%)	5 (12.8%)	12 (15.2%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Symbol Substitution Task score	N (missing)	40 (0)	39 (0)	79 (0)
	Mean (SD)	28.5 (3.8)	28.1 (4.3)	28.3 (4.0)
	Median [IQR]	29 [26,31]	28 [25,32]	29 [26, 31]
	Min, Max	20, 34	21, 34	20, 34
Cognitive impairment Category	Mild	33 (82.5%)	31 (79.5%)	64 (81.0%)
	Moderate	7 (17.5%)	8 (20.5%)	15 (19.0%)

Note: GCSE = General Certificate of Secondary Education; IQR = interquartile range; MIN = minimum; Max = maximum; NVQ = National Vocational Qualification; SD = standard deviation.

how the randomisation process is explained (e.g., using analogies such as ‘tossing a coin’) to enhance clarity. Some control participants felt ‘unsuccessful’ at not receiving the intervention, though all expressed willingness to continue. A few believed they were ‘picked’ for intervention, while others expressed sympathy for control participants or enquired whether they would receive ‘extra’ support; nevertheless, all indicated they would have continued even if allocated to control, albeit with some disappointment.

Feasibility of NEuRoMS intervention

Of participants randomised to the intervention, 92% engaged; three withdrew before receiving any sessions (though two continued follow-ups). Session uptake and delivery characteristics are provided in Supplemental Material 3. PwMS and APs reported that intervention procedures were feasible and acceptable. Overall, pwMS described sessions as beneficial, particularly psychoeducation and learning new strategies, and reported positive changes when these were used.

Table 4. Feasibility outcomes – red/amber/green (RAG) ratings for progression to a definitive trial, by feasibility area.

Feasibility outcome	Rating	Suggested changes
Recruitment feasibility	Amber (Review)	- Longer recruitment period - Increase study sites - Contingency arrangements to ensure AP cover during absences/staff turnover.
Retention feasibility	Green (Go)	Revision to reminder procedures (e.g., more frequent and personalised reminders, varied mode of reminders).
Feasibility of self-report clinical outcome measures	Green (Go)	- Remove repetitive measures (e.g., Whooley Questions) - Consider using shorter versions of outcome measures (if available) - Provide questionnaire completion progress indicators on the online platform.
Randomisation feasibility	Green (Go)	- Improve Participant Information Sheet and the script used to explain randomisation process - Consider additional stratification variables (e.g., level of cognitive impairment (mild/moderate), MS type).
Feasibility of NEuRoMS intervention	Green (Go)	- Refinements to content and structure (e.g., simplifying workbook content) - Additional therapist training on goal-setting.
Feasibility of conducting a health economic evaluation	Green (Go)	Minor revisions to the Service Use Questionnaire to enhance content coverage and relevance, and improve clarity.
Exploration of efficacy	Green (Go)	Progress to definitive trial, adequately powered to detect a minimally clinically important effect size.

Note: AP, assistant psychologist.

PwMS found the number and length of sessions appropriate, though some experienced scheduling difficulties due to work commitments. The workbook was reportedly easy to follow and visually accessible, but some found the content overwhelming and overly technical. PwMS consistently praised APs' knowledge, flexibility and interpersonal skills.

Some pwMS and APs found goal-setting challenging, though most pwMS reported achieving their goals. APs reported that delivery was feasible overall, but felt some sections contained too much material for a single session, were not suitable for all participants, or included strategies (e.g., story method) that were difficult to implement.

Time-sampling of 28 recorded sessions (1211 min) from eight randomly selected participants showed 88% of coded time focused on intervention-specific content, with 12% on unrelated discussion or rapport building (Figure 2). The most frequently discussed components were goal-setting and progress (27%) and cognition/cognitive difficulties (17%).

All APs were rated as delivering the intervention at least 'adequately well'. Domain-level competency scores ranged from 2 to 3, with consistently high ratings for interpersonal style and communication skills, and greater variability in aspects of session structure (Supplemental Material 4).

Feasibility of a health economic evaluation

The health economic analysis identified key resource-use drivers associated with implementing the intervention, all captured from trial records. Completion rates for economic outcome measures were high, with EQ-5D-5L and ICECAP-A completed by 91% at 3 months and 87% at 6 months. The service use questionnaire (SUQ) had high return rates (87% at 3 months; 81% at 6 months), but some pwMS reported uncertainty about how to respond to certain items (e.g., prescribed medications).

Exploration of efficacy

Descriptive statistics for clinical outcomes are presented in Table 5. Adjusted means from the multilevel mixed-effects models are presented in Table 6 for the primary outcome and in Supplemental Material 5 for the secondary outcomes. Across outcomes, results were similar over time and between groups, with overlapping 95% CI. Participants with moderate cognitive impairment consistently showed poorer outcomes than those with mild impairment.

At 3 months, the observed difference on MSIS-Psych was 3.42 (95% CI 0.05–6.79), yielding an effect size of

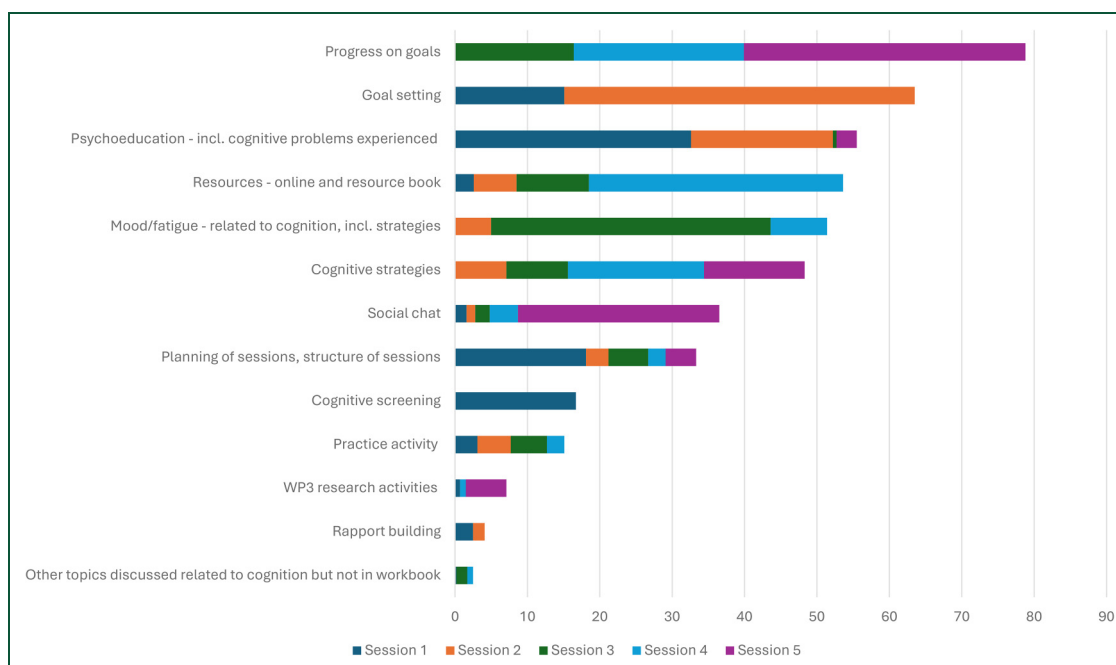


Figure 2. Frequency of intervention content discussed.

0.48 in favour of the intervention. Effect sizes for perceived cognitive difficulties, mood and self-efficacy ranged from 0.31 to 0.77, also favouring the intervention.

Interviewees described positive post-intervention changes, including achieving cognitive-specific goals, more effective strategy use, increased awareness of difficulties and associated improvements in mood. Participants also reported better fatigue management. These changes were reportedly sustained at 6 months, with continued improvements in planning and managing daily activities and strategy use. The process of working on goals was viewed as empowering and reinforced a sense that cognitive difficulties were manageable.

Across both groups, participants reported receiving no cognition-focused treatments as part of usual care, except one who reported having received pharmacological treatment.

Discussion

Our findings suggest that a definitive trial is feasible and that both the NEuRoMS intervention and trial procedures were acceptable, with pwMS and clinicians finding the intervention useful. Some refinements to the design and intervention, however, are required before progressing to a definitive trial (Table 4).

Most feasibility outcomes were rated Green, with recruitment rated Amber. Recruitment challenges were primarily due to staffing constraints arising from high turnover and extended absences among APs, which reduced monthly recruitment and led one site to pause recruitment for 3 months. However, recruitment

procedures were acceptable to participants, and consent rates were consistent with similar studies.²² To mitigate staffing-related disruption, the definitive trial will employ more than one AP per site, include additional sites, and extend the recruitment period.

Eighty percent of participants completed both follow-ups, demonstrating sustained engagement and long-term follow-up. Delays in some assessments were attributable to late reminders during a period of researcher absence, indicating operational factors rather than participant disengagement. Retention challenges are common in trials,²³ and evidence suggests that robust reminder procedures, particularly personalised, multi-component communication packages combining digital and non-digital reminders, are more effective than increasing reminder frequency alone.^{24,25} The definitive trial will implement these procedures, alongside contingency plans for staff absences.

High completion rates for the MSIS-Psych support its feasibility for longitudinal use and suitability as the primary outcome. In the definitive trial, SST will also be administered at follow-up as a secondary objective outcome to assess potential changes in objectively assessed cognitive performance. Cost-effectiveness data collection was also feasible, but the SUQ was lengthy. To reduce burden, measures assessing the same domains will be removed.

The definitive trial sample size was calculated *a priori* to detect an effect size of 0.33, equivalent to a three-point MSIS-Psych difference²⁶ assuming an SD of 9,²⁷ requiring 478 participants allowing for 20% attrition. Our findings suggest that this target is achievable and appropriate for detecting the planned effect size.

Table 5. Descriptive statistics for secondary outcome measures.

Measure	Time, group	N	Min	Max	Mean (SD)	Median [IQR]	95% confidence interval
MSIS-29 – Psychological subscale	Baseline, IG	40	12	43	23.8 (8.0)	22.5 [18.5, 28]	21.3, 26.4
	3 m, IG	37	12	42	22.3 (8.0)	21 [15, 27]	19.6, 24.9
	6 m, IG	33	11	43	21.3 (8.0)	19 [15, 27]	18.5, 24.1
	Baseline, CG	39	9	40	25.1 (8.5)	27 [17, 32]	22.3, 27.9
	3 m, CG	33	9	44	20.9 (8.9)	24 [19, 29]	20.9, 27.2
	6 m, CG	31	9	43	23.9 (9.0)	24 [16, 32]	20.6, 27.2
	Baseline, Total	79	9	43	24.5 (8.2)	24 [17, 31]	22.6, 26.3
	3 m, Total	70	9	44	23.1 (8.4)	21.5 [17, 29]	21.1, 25.1
	6 m, Total	64	9	43	22.6 (8.5)	21.5 [15.5, 29]	20.4, 24.7
MSIS-29 – Physical subscale	Baseline, IG	40	23	90	51.3 (18.2)	50.5 [35, 62.5]	45.5, 57.1
	3 m, IG	37	22	81	50.4 (17.3)	49 [34, 62]	44.6, 56.1
	6 m, IG	33	21	81	48.9 (18.6)	44 [31, 68]	42.3, 55.5
	Baseline, CG	39	20	89	51.9 (20.5)	49 [33, 67]	45.3, 58.5
	3 m, CG	33	20	94	50.3 (19.7)	49 [34, 65]	43.3, 57.3
	6 m, CG	32	20	100	52.0 (20.3)	48.5 [36.5, 65]	44.6, 59.3
	Baseline, Total	79	20	90	51.6 (19.2)	50 [35, 64]	47.3, 55.9
	3 m, Total	70	20	94	50.3 (18.3)	49 [34, 65]	46.0, 54.7
	6 m, Total	65	20	100	50.4 (19.4)	48 [32, 65]	45.6, 55.2
PDQ-20	Baseline, IG	40	3	71	34.3 (17.5)	33 [21, 42]	28.7, 39.9
	3 m, IG	37	2	61	29.3 (14.9)	31 [17, 39]	24.3, 34.3
	6 m, IG	33	2	60	28.7 (14.7)	29 [18, 39]	23.5, 33.9
	Baseline, CG	39	5	69	38 (19.0)	42 [20, 53]	31.8, 44.2
	3 m, CG	33	5	68	34.9 (19.5)	33 [20, 52]	28.0, 41.8
	6 m, CG	31	5	69	37.4 (19.5)	37 [18, 54]	30.3, 44.6
	Baseline, Total	79	3	71	36.1 (18.2)	36 [21, 50]	32.0, 40.2
	3 m, Total	70	2	68	31.9 (17.3)	31.5 [17, 43]	27.8, 36.1
	6 m, Total	64	2	69	32.9 (17.6)	34 [18, 45.5]	28.5, 37.3
PHQ-9	Baseline, IG	40	0	24	8.9 (5.5)	8 [5, 13]	7.1, 10.7

(continued)

Table 5. Continued.

Measure	Time, group	N	Min	Max	Mean (SD)	Median [IQR]	95% confidence interval
	3 m, IG	37	0	25	7 (5.4)	5 [3, 9]	5.2, 8.8
	6 m, IG	33	1	25	7.0 (5.4)	6 [3, 9]	5.1, 8.9
	Baseline, CG	39	0	25	9.9 (6.8)	11 [4, 14]	7.8, 12.1
	3 m, CG	33	0	25	10.2 (7.6)	9 [5, 16]	7.5, 12.9
	6 m, CG	31	0	26	9.2 (7.5)	7 [2, 15]	6.5, 12.0
	Baseline, Total	79	0	25	9.4 (6.2)	8 [5, 14]	8.0, 10.8
	3 m, Total	70	0	25	8.5 (6.7)	6.5 [3, 13]	6.9, 10.1
	6 m, Total	64	0	26	8.1 (6.5)	7 [2.5, 12]	6.5, 8.9
GAD-7	Baseline, IG	40	0	20	5.9 (5.0)	5 [1.5, 8.5]	4.3, 7.5
	3 m, IG	37	0	20	4.7 (5.0)	3 [1, 6]	3.0, 6.4
	6 m, IG	33	0	20	4.2 (4.6)	3 [1, 6]	2.6, 5.9
	Baseline, CG	39	0	21	7.0 (5.4)	6 [3, 12]	5.3, 8.8
	3 m, CG	33	0	21	7.1 (5.6)	6 [4, 10]	5.1, 9.1
	6 m, CG	31	0	19	6.9 (5.2)	6 [3, 11]	5.0, 8.9
	Baseline, Total	79	0	21	6.4 (5.2)	5 [2, 10]	5.3, 7.6
	3 m, Total	70	0	21	5.8 (5.4)	5 [2, 9]	4.5, 7.1
NEADL	6 m, Total	64	0	20	5.5 (5.1)	4 [1, 8.5]	4.3, 6.8
	Baseline, IG	40	0	22	14.6 (5.6)	15.5 [12, 19]	12.8, 16.4
	3 m, IG	37	0	22	14.8 (5.7)	15 [12, 20]	12.9, 16.7
	6 m, IG	33	0	22	15.1 (5.7)	16 [12, 20]	13.1, 17.1
	Baseline, CG	39	2	22	16.3 (5.3)	17 [11, 21]	14.6, 18.0
	3 m, CG	33	2	22	16.6 (5.2)	18 [14, 21]	14.8, 18.5
	6 m, CG	31	8	22	16.3 (4.4)	18 [13, 19]	14.7, 17.9
	Baseline, Total	79	0	22	15.4 (5.4)	17 [12, 20]	14.2, 16.6
MSSE	3 m, Total	70	0	22	15.7 (5.5)	16 [13, 21]	14.3, 17.0
	6 m, Total	64	0	22	15.7 (5.1)	16.5 [12.5, 19.5]	14.4, 17.0
	Baseline, IG	40	16	73	46.9 (13.6)	46.5 [38.5, 55.5]	42.5, 51.3
	3 m, IG	37	23	71	48.6 (12.2)	49 [40, 57]	44.6, 52.7

(continued)

Table 5. Continued.

Measure	Time, group	N	Min	Max	Mean (SD)	Median [IQR]	95% confidence interval
	6 m, IG	33	28	70	50.4 (12.0)	49 [42, 59]	46.2, 54.7
	Baseline, CG	39	24	67	46.5 (12.7)	46 [36, 58]	42.3, 50.6
	3 m, CG	33	23	73	46.8 (13.6)	45 [37, 59]	42.0, 51.7
	6 m, CG	31	20	70	47.3 (13.1)	43 [40, 59]	42.5, 52.1
	Baseline, Total	79	16	73	46.7 (13.1)	46 [37, 57]	43.8, 49.6
	3 m, Total	70	23	73	47.8 (12.8)	48 [38, 58]	44.7, 50.1
	6 m, Total	64	20	70	48.9 (12.5)	47.5 [41, 59]	45.8, 52.0
MSWDQ-23	Baseline, IG	11	3	55	28.3 (18.0)	30 [5, 46]	16.2, 40.4
	3 m, IG	10	11	49	28.0 (14.9)	26.5 [13, 43]	17.4, 38.6
	6 m, IG	9	0	43	21.6 (15.0)	22 [9, 30]	10.1, 33.1
	Baseline, CG	15	3	64	25.5 (22.2)	14 [9, 49]	13.2, 37.8
	3 m, CG	12	1	65	28.5 (23.9)	24 [7, 55]	13.3, 43.7
	6 m, CG	11	0	55	21.6 (21.3)	19 [1, 48]	7.3, 36.0
	Baseline, Total	26	3	64	26.7 (20.2)	27.5 [9, 46]	18.5, 34.8
	3 m, Total	22	1	65	28.3 (19.9)	25 [13, 48]	19.5, 37.1
	6 m, Total	20	0	55	21.6 (18.3)	20.5 [4, 34.5]	13.1, 30.2
Single item work and education question	Baseline, IG	25	1	5	3.2 (1.4)	3 [2, 4]	3, 4
	3 m, IG	21	1	5	3.1 (1.2)	3 [3, 4]	3, 4
	6 m, IG	22	1	5	2.8 (1.0)	3 [2, 3]	2, 3
	Baseline, CG	24	1	5	3.0 (1.3)	3 [2, 4]	2, 4
	3 m, CG	21	1	5	2.8 (1.3)	3 [2, 4]	2, 3
	6 m, CG	20	1	5	2.6 (1.5)	3 [1, 4]	2, 3
	Baseline, Total	49	1	5	3.1 (1.4)	3 [2, 4]	3, 3
	3 m, Total	42	1	5	3.0 (1.2)	3 [2, 4]	3, 3
	6 m, Total	42	1	5	2.7 (1.2)	3 [1, 3]	2, 3
Single item medication adherence question	Baseline, IG	39	1	5	2.0 (1.2)	2 [1, 3]	2, 2
	3 m, IG	36	1	5	1.8 (1.0)	1 [1, 2]	1, 2
	6 m, IG	33	1	5	1.7 (0.9)	2 [1, 2]	1, 2

(continued)

Table 5. Continued.

Measure	Time, group	N	Min	Max	Mean (SD)	Median [IQR]	95% confidence interval
	Baseline, CG	39	1	4	2.0 (0.9)	2 [1, 3]	2, 2
	3 m, CG	31	1	4	1.8 (0.9)	2 [1, 2]	1, 2
	6 m, CG	31	1	4	2.1 (1.0)	2 [1, 3]	2, 3
	Baseline, Total	78	1	5	2.0 (1.0)	2 [1, 3]	2, 2
	3 m, Total	68	1	5	1.8 (1.0)	2 [1, 2]	2, 2
	6 m, Total	64	1	5	1.9 (1.0)	2 [1, 2]	2, 2
	Time, Group	Requires further evaluation n (%)		Not depressed n (%)			
Whooley question*	Baseline, IG	27 (67.5%)		13 (32.5%)			
	3 m, IG	26 (70.3%)		11 (29.7%)			
	6 m, IG	19 (57.6%)		14 (42.4%)			
	Baseline, CG	24 (61.5%)		15 (38.5%)			
	3 m, CG	23 (69.7%)		10 (30.3%)			
	6 m, CG	20 (64.5%)		11 (35.5%)			
	Baseline, Total	51 (64.6%)		28 (35.4%)			
	3 m, Total	49 (70.0%)		21 (30.0%)			
	6 m, Total	39 (60.9%)		25 (39.1%)			

*The Whooley is a binary screening measure; continuous-data columns are not applicable.

Note: CG = control group; IG = intervention group; IQR = interquartile range; MIN = minimum; Max = maximum; SD = standard deviation; 3 m = 3-month follow-up; 6 m = 6-month follow-up. Refer to Table 2 for measure abbreviations.

Randomisation feasibility was supported by participants' willingness to continue regardless of allocation, though clearer explanations are needed to minimise misconceptions and ensure understanding that allocation is chance-based. This reflects wider evidence that randomisation and equipoise are difficult concepts to explain,^{28,29} highlighting the importance of explaining not only how randomisation works but also why it is essential for fairness, minimising bias and strengthening reliability of trial results. To reduce feelings of 'unsuccessfulness' among control participants, the definitive trial will strengthen communication about the value of both trial groups and the essential role of the control group in generating reliable evidence.

Intervention delivery was feasible, with most participants receiving the intended number and duration of sessions, although some variability was observed. However, there were some difficulties with goal-setting. Evidence suggests that effective goal-setting requires structured frameworks, enhanced clinician training and patient-centred

approaches.³⁰ The definitive trial will therefore incorporate additional training and structured goal-setting support for APs.

The intervention content was considered helpful, but not all elements were relevant for every participant, particularly those with milder difficulties, reinforcing the importance of person-centred, tailored, flexible rehabilitation approaches to improve engagement, satisfaction and outcomes.³¹ Although our intervention was tailored, feedback suggests that further refinement is needed, including clearer workbook content and strengthened AP training to support streamlined, proportionate use of resources for different levels of need. APs delivered the intervention competently with high fidelity. The same checklist will support rigorous process evaluation in the definitive trial,³² reducing risks associated with fidelity variation.³³

We observed a signal of efficacy in favour of the intervention, supported by qualitative evidence of gains and sustained behaviour change at 3 and 6 months. These results

Table 6. Adjusted means for the planned primary clinical outcome measure by time point and group, with differences presented.

	Descriptive	Baseline	3 m	6 m	3 m – baseline	6 m – baseline	6 m – 3 m
MSIS-27-Psych IG	Mean	23.05	21.70	20.88	-1.35	-2.16	-0.82
	SE	1.47	1.50	1.56	1.57	1.62	1.65
	95% CI	20.17, 25.92	18.75, 24.65	17.84, 23.93	-4.42, 1.73	-5.34, 1.01	-4.05, 2.41
MSIS-27-Psych CG	Mean	25.90	25.12	24.78	-0.78	-1.12	-0.35
	SE	1.49	1.54	1.59	1.64	1.67	1.72
	95% CI	22.99, 28.81	22.10, 28.15	21.66, 27.89	-3.98, 2.43	-4.39, 2.14	-3.72, 3.03
CG – IG	Mean	2.85	3.42	3.89			
	SE	1.64	1.72	1.82			
	95% CI	-0.36, 6.07	0.05, 6.79	0.32, 7.47			

Note: Comparisons of the differences are not available from the fitted model therefore, this section of the table is blank.

CG = control group; CI = confidence interval; IG = intervention group; IQR = interquartile range; MIN = minimum; Max = maximum; SE = standard error; 3 m = 3-month follow-up; 6 m = 6-month follow-up. Refer to Table 2 for measure abbreviations.

highlight the potential value of brief, targeted interventions delivered early in the course of cognitive impairment. This aligns with evidence that pwMS with mild-to-moderate impairment may benefit most from such interventions.⁸ Early rehabilitation has also been advocated for educational purposes,³⁴ enabling individuals to acquire and embed strategies while having sufficient cognitive capacity, before more severe impairment limits learning and adaptation, supporting broader calls for earlier identification of cognitive difficulties in routine care.³⁵

Strengths and limitations

Key strengths included systematic assessment of acceptability and feasibility, detailed fidelity evaluation and a multi-centre randomised design with an appropriate sample size for feasibility analyses. The mixed-methods approach enriched understanding by combining quantitative efficacy data with qualitative insights into behaviour change and cognitive management. Co-production with pwMS and stakeholders further strengthened the intervention's design, given that mild difficulties can be overlooked in routine care. A key limitation was the predominantly White sample (90%), with few participants from minoritised backgrounds. Although broadly representative of the UK MS population, this limits generalisability and underscores the need for more inclusive recruitment strategies. A further limitation is that SST scores were interpreted using raw thresholds, as demographic-adjusted norms were not yet available when the feasibility trial was initiated. We have since completed a norming study producing regression-based SST thresholds adjusted for age, gender and education (to be

published elsewhere), which will strengthen interpretation in future analyses.

Conclusion

The NEuRoMS intervention was feasible and acceptable for pwMS with mild-to-moderate cognitive difficulties, with a signal of efficacy in perceived psychological impact. The intervention was competently delivered with good fidelity. However, improvements are required to enhance recruitment, strengthen explanations of randomisation and expand AP training in delivering the intervention. A definitive trial (ISRCTN10285713) is now underway, incorporating refinements identified in this feasibility study.

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Ethical considerations

Ethical approval was granted by the Health Research Authority North West – Greater Manchester West Research Ethics Committee (20/NW/0454, 13/01/2021).

Consent to participate

All participants provided informed consent to take part in the study.

Consent for publication

No identifiable personal data, images or videos are included in this manuscript. Participants provided informed consent for the publication of anonymised quotations drawn from their interviews.

Author contributions

das Nair: Conceptualization; funding acquisition; investigation; methodology; resources; supervision; validation; writing – review and editing. **Topcu:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualisation; writing – original draft; writing – review and editing. **Goulden:** Data curation; formal analysis; methodology; visualisation; writing – review and editing. **Harris:** Conceptualization; formal analysis; methodology; writing – review and editing. **Mhizha-Murira:** Data curation; formal analysis; investigation; project administration; software; writing – review and editing. **Morris:** Investigation; project administration; resources; writing – review and editing. **Swain:** Investigation; project administration; resources; writing – review and editing. **Taylor:** Investigation; writing – review and editing. **Hancock:** Investigation; project

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Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

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