A Cognitive Occupation-Based programme for people with Multiple Sclerosis: definitive trial (COB-MS)

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Abstract

Cognitive difficulties can have significant impacts on daily function and quality of life of people with multiple sclerosis (MS). Although a common symptom of MS, it is often not treated in clinical care, despite the potential for devastating impacts. When treated, occupational therapists are the healthcare professionals most commonly responsible for the assessment and management of cognitive symptoms in MS. Despite this, no cognitive rehabilitation intervention has been developed that is measured by and taught through an occupational participation perspective. The Cognitive Occupation-Based programme for people with MS (COB-MS) was developed to address the clinical treatment deficit. The COB-MS is a personalised, patient-centred, holistic, occupational therapy, cognitive rehabilitation intervention. It is aimed at improving daily life functioning for people with MS who are experiencing cognitive difficulties.

The COB-MS has undergone extensive feasibility testing and has been found to be both feasible and acceptable by clinicians and participants with MS. The aim of this research is to estimate the clinical and cost-effectiveness of the COB-MS intervention relative to a treatment-as-usual control group. This study is a single-blind, three-arm, pragmatic randomised trial with two SWATs (described elsewhere). We will establish the effectiveness of both online and in-person delivery of the COB-MS, relative to control condition. We will complete an economic and process evaluation of COB-MS.

This definitive trial is led by the needs of the MS community at national and international levels and has a strong PPI-focus throughout. This research is innovative and very timely and links with priority research areas in multiple sclerosis rehabilitation, occupational therapy, and trial methodology, ensuring the international relevance of the research to the MS rehabilitation research community, knowledge-users, and those living with MS. The COB-MS team consists of experts in multiple disciplines, trial methodology, health economics, statistics, health service research, public and patient involvement, and related disciplines.

1. Background

It is estimated that 2.2-2.8 million people worldwide have multiple sclerosis (MS; Wallin et al., 2019; Walton et al., 2020), with approximately 9,000 people in Ireland (plus 5,500 in Northern Ireland) living with MS. MS is a complex disease that is characterised by inflammatory demyelination and degeneration with resulting damage to the white and grey matter of the central nervous system (Kalb et al., 2018; McGinley et al., 2021). Cognitive difficulties are a prevalent, distressing and debilitating symptom of multiple sclerosis (Sumowski et al., 2018). It is typically reported that up to 65% of people with MS experience a decline in their cognitive functioning (Amato et al., 2006; McKay et al. 2019; Olazarán, Cruz & Benito-León, 2009; Ruano et al., 2017), with memory, executive functions, processing speed and attention being the most affected areas (Langdon, 2011).

Cognitive difficulties have significant impacts on quality of life, increase the likelihood of being unemployed, having depression, and having difficulty managing self-care and daily life activities (Digiuseppe et al., 2018; Glanz et al., 2012; Mc Auliffe & Hynes, 2019). This can further result in a range of complex psychosocial needs. Very few people with MS receive intervention for cognitive difficulties (e.g Klein et al., 2019; Hynes et al., 2024) despite the debilitating impact that it can have. Cognitive difficulties, considered invisible symptoms of MS, are often experienced for the first time at a time when people are typically starting out in their careers, and may have young families to manage, which can mean that the impacts are considerable.

From an economic perspective, MS impacts not only the person with MS, and their ability to maintain employment, but also their families and society as a whole. People with MS who experience cognitive difficulties are 49% more likely to be unemployed than those not experiencing cognitive difficulties (Roessler et al., 2004). The economic burdens are particularly heavy for those with greater symptomology. In Ireland, MS is estimated to cost approximately €429million per year, including direct costs (e.g. hospital visits), indirect costs (e.g. time off work), and intangible costs (e.g. quality of life; MS Ireland, 2015). Through targeted rehabilitation, it is possible to reduce these costs as delaying disability in MS is estimated to save approximately €19million. Given the strain on health-care services, having an accessible and low-cost intervention is not only a national but a global priority, with tele/online interventions allowing greater access to those underserved by more traditional healthcare models (MSIF, 2021).

Occupational therapy is a client-centred health profession concerned with promoting health and well-being through occupation. The primary goal of occupational therapy is to enable people to participate in the activities of everyday life. Occupational therapists achieve this outcome by working with people and communities to enhance their ability to engage in the occupations they want to, need to, or are expected to do, or by modifying the occupation or the environment to better support their occupational engagement. (WFOT 2012, via www.wfot.org/about/about-occupationaltherapy). Although it is commonly occupational therapists who assess and treat cognitive dysfunction in MS in the UK (Klein et al., 2019) and Ireland (Hynes et al., 2024) there are few, if any, occupation-focused cognitive interventions to alleviate the decline in cognition for people with MS, and **no definitive trials have been conducted to date in this area**.

The overall evidence for cognitive rehabilitation in MS is promising, with short-term results in subjective memory, quality of life, verbal memory, and information processing found in a recent Cochrane review (Taylor et al., 2021). This review, and a number of other similar recent reviews, indicate that improving aspects of cognitive function was possible, but there are a number of important caveats to consider:

- Positive results were found in the short-term, but it is still unclear what longer-term impacts are seen.
- Many of the positive results were found on outcomes that mimicked the intervention that was taught to participants- e.g. participants trained on digit span tests and improved on digit span tests.
- There was very little evidence of transfer of training gains to everyday life tasks or outcomes that are ecologically valid.
- There is a strong focus on computerised, repetitive training in the interventions under study. Given the significant impacts on daily life that cognition has, it is vital to focus interventions on the areas of life (occupations) that are most significantly impacted, rather than targeting a specific cognitive function.
- It is still unclear if cognitive rehabilitation is cost-effective as very few studies have assessed this as an outcome of the intervention.

In addition to this, in a comprehensive review of rehabilitation research for people with progressive MS it was reported that insufficient evidence of effectiveness exists for cognitive rehabilitation (Feinstein et al., 2015) with this group of people. The authors of the Cochrane review (Taylor et al., 2021) have recommended that there is a need for robust, large-scale randomised controlled trials (RCTs) "*with better quality reporting, using ecologically valid outcome assessments (including health economic outcomes) assessed at longer-term time points*" to be certain about the effectiveness for people with MS.

The setting in which the intervention is delivered is also an important consideration with regards to cognitive rehabilitation, both from the perspective of the person with MS and the economic costs. 80-90% of interventions that focus on symptom management take place in community settings (Kobelt et al., 2006). Sláintecare (DoH, 2017) the ten-year programme to transform Irish health and social care services, The National Policy and Strategy for the Provision of Neuro-Rehabilitation Services (DoH, 2011), and the Model of Care for Specialist Rehabilitation Medicine (NCPRM, 2018) all promote the development of person-centred community-based care. This is further supported in the Strategy for Neuro-rehabilitation Services (2011) which aimed to develop and enhance neuro-rehabilitation services, though this implementation has been considerably slow to date (Burke at al., 2019).

There is an urgent need at an international level to develop the evidence-base to support people with MS to manage their cognitive difficulties. The Cognitive Occupation-Based programme for people with Multiple Sclerosis (COB-MS) has been developed to address the marked clinical gap that exists globally in the area of cognitive care for MS. Importantly, in this programme we are ensuring that we are addressing the needs of the MS community. We are achieving this by directly targeting the "My MS My Needs" report by MS Ireland (2017), the James Lind Alliance (JLA) Priority Setting Partnership for MS research (2013), the JLA Priority Setting for OT research (2020), the Progressive MS Alliance global research priorities (2014), and the ongoing input of patient experts. The COB-MS targets three of the top 10 MS Priority Research Areas (JLA, 2013)-cognition, (cognitive) fatigue, and self-management.

Patients have placed importance on ensuring that they are equipped with the information and training to be able to predict and deal with any problems they might face through their (unique) disease course. The COB-MS enables people with MS to identify, understand and learn new strategies to deal with their cognitive difficulties and provides a step-by-step evidence-based program that is specific to the difficulties seen in MS. This means that participants have access to a non-pharmacological treatment for cognition that focuses on the aspects of their own daily life that are important to them. Through the COB-MS it is also possible to target cognition at a much earlier stage. Using it as a

preventative treatment would ensure that people with MS would be equipped to face challenges at home and in the workplace when and if they arose. Currently in Ireland there are very few cognitive interventions being offered to patients in the same way that pharmacological treatments are (Hynes et al., 2024).

Researchers expert in the field of MS have also called for the development of effective treatments for cognitive difficulties, including a focus on holistic treatments (Sumowski et al., 2018). Six priorities in the area of treatment and prevention of cognitive deficits have been identified including studies of rigorous design (1), strong theoretical background (2), the use of structural and functional neuroimaging outcomes to explore mechanisms of intervention effects (3), research on modifiable lifestyle factors that may protect against cognitive decline (4), interventions focused on the daily-life of pwMS with a holistic approach to intervention (5), and interventions tailored to the needs of the pwMS (6). Further guidance in the area of trial design for MS rehabilitation trials has been provided by das Nair, de Groot, and Freeman (2019) and have been considered in the design of this definitive trial, in tandem with the feasibility results.

Further definitive evidence for cognitive rehabilitation in MS is required from large-scale RCTs using ecologically valid outcomes (Taylor et al., 2021) and clear reporting standards of intervention content (Mhiza-Murira et al., 2017). The COB-MS project, described in this application, aims to do just this. The COB-MS could have a significant clinical impact on the way in which health care professionals work with people with MS who have cognitive difficulties. There would exist an evidence-based openly available solution that has also assessed cost-effectiveness. The COB-MS has the potential to be generalised outside of Ireland due to its individualised approach. The low-cost associated with running the COB-MS means that it is accessible in various clinical and community settings.

Here, we aim to assess the clinical and cost-effectiveness of the COB-MS.

2. Research Question

Is the COB-MS a cost-effective and clinically effective intervention for improving daily life functioning for people with multiple sclerosis experiencing cognitive difficulties, in comparison to treatment as usual (TAU)?

The aim of this research is to estimate the clinical and cost-effectiveness of the COB-MS (online and in-person delivery) relative to TAU. We hypothesise that, in comparison with TAU, the COB-MS will improve daily life functioning for people with multiple sclerosis who are experiencing cognitive difficulties. Cognition, self-efficacy, and health-related quality-of-life are secondary outcomes. As part of the trial, we also aim to complete a mixed methods process evaluation of the COB-MS.

3. Design

COB-MS definitive intervention trial will be a pragmatic, national (eight locations nationwide), superiority randomised controlled trial (RCT) with a target recruitment of 365 people. This trial will be made of two COB-MS groups (online and in-person delivery) and a control usual care group. All people who meet the inclusion and exclusion criteria (e.g., diagnosis of MS, cognitive difficulties, age range, ability to give consent, absence of severe psychiatric or neurological comorbidities) will be included as participants. This ensures that the intervention is tested on the appropriate target group. The trial will start with an internal pilot, recruiting 83 people, considering economic and process evaluations. This internal pilot will happen in two locations and will assess go/no-go criteria for progression of the trial. The programme of work and work packages are based on the Medical Research Council's 'Framework for development and evaluation of RCTs for complex interventions to improve health' (Craig et al., 2008), which, following the development and feasibility work completed, focuses on evaluation of the COB-MS programme.

3.1. Internal Pilot

An internal pilot has been planned for six months of the trial (study month 6-12) and will include two locations (Galway and Dublin). Given the additional study arm in the definitive trial an internal pilot will provide important information and allow for the recalculation of sample size, as well as looking at the preselecting parameter and re-computing as needed. We will also test the feasibility of collecting data for within-trial cost effectiveness analysis.

In order to complete the trial in a timely manner and because of implications on resources, the internal pilot will not include the final data collection time point (12 months). This data will be collected at 12 months if the trial progresses. Given the additional study arm in the definitive trial (the feasibility trial only assessed the online delivery of the COB-MS) and other minor changes from feasibility trial, an internal pilot will provide important information and allow for sample size recalculation. The internal pilot will run in the same way in which the full trial is planned. The Trial Steering Committee (TSC) will decide on the viability of the trial and appropriateness of progression by reviewing processes of the internal pilot and key outcomes during that time. There will be a particular focus on trial recruitment, protocol adherence and outcome data. A traffic light system will be in place to assess progression and modifications that may be necessary.

With regards to recruitment, at each pilot location we are expecting a recruitment rate of approximately 14 participants per month. For protocol adherence, we will assess initial fidelity to treatment by observing 50% of COB-MS sessions. We will also monitor participant attendance rates. Any instance of off-protocol intervention will be recorded and discussed with the TSC. Outcome data will be monitored for completeness and quality. We will monitor rates of attrition or loss to follow-up. We will also assess levels of data completeness and report to TSC. No interim analysis is planned and so assessment of treatments and hazards is not planned, nor do we have criteria related to stopping trial for benefit.

In consultation with the TSC, we will modify as needed and continue to the full trial if appropriate. ACCEPT checklist (Charlesworth et al., 2013) will be used, in consultation with TSC and IDMC. A decision will be made as to whether pilot data can be included in the dataset. If data does not

compromise the integrity of the trial, it will be incorporated into the full dataset. Steps will be taken to reduce the likelihood of this happening, including research staff training and close monitoring of participant data completion of Patient-Reported Outcomes.

The internal pilot will also test the feasibility of collecting data for within-trial cost effectiveness analysis. During this phase, a model-based simulation (a mathematical and visual method of predicting and understanding problems over time), will also be developed by Professor Trepel, to: 1) provide prior estimate of cost effectiveness; 2) indicate the important drivers for the definitive study, and; 3) develop a basis updating with trial-based evidence and for extrapolations outcomes over a lifetime horizon (e.g. beyond definitive trial endpoint).

In line with best practice, we will ensure that there is detailed and systematic reporting around the decision-making process for stopping, amending or proceeding to a main trial.

3.1.1. Go/No Go Criteria

We will use a traffic light system, as recommended by Avery et al. (2017), green (go), amber (amend) and red (stop), which will allow for modification, in consultation with the TSC. This method was agreed with the TSC and aims to allow flexibility to correct any issues identified. The key areas of risk included in the criteria are trial recruitment, protocol adherence and outcomes. The criteria set need to be achieved for progression, but remediable issues can be dealt with in conjunction with the TSC. The research team, in collaboration with PPI panel and the TSC, will undertake a decision process to finalise the a priori threshold for progression. The following have been set:

- The goal is to recruit 83 participants within three months at the two pilot locations: Go (Green): average ≥ 27.66 participants/month; Review (Amber): average ≥ 16–27.66 participants /month; Stop (Red): average < 16 participants /month.
- Retention (participants staying in the study): Go (Green), ≥ 80% retained; Review (Amber): 50–79% retained; Stop (Red): ≤ 49% retained).
- The proportion of missing data will be explored, as well as percentage of participants with missing data (at 6-month time frame). Greater than 10% missing data will be discussed with the Data Monitoring Committee and appropriateness of progression or the need for amendment will be explored.

3.1.2. Discontinuation Criteria

Guidelines will be reviewed by the DMC, and any areas of disagreement will be addressed before starting the trial. Here we have set the following stopping rules:

- Change in opinion of the Research Ethics Committee.
- Safety concerns of participants or research staff.
- Statistical futility – if there is evidence (e.g. through very low recruitment rates) that there is low probability of a trial reaching its main objective even if it is completed as planned

3.2. Pragmatic RCT - Evaluation of clinical effectiveness of the COB-MS

Participants, with a diagnosis of MS and experiencing cognitive difficulties, will be randomly allocated to one of three trial arms, using a partially clustered design:

- In-person intervention arm- COB-MS delivered by occupational therapist in a community setting.
- Online intervention arm- COB-MS delivered by occupational therapist fully online.
- Control arm- TAU.

3.2.1. Inclusion/exclusion

Research staff will complete the consent process with people with MS and ensure eligibility. Participants with MS will be eligible to participate regardless of the type of MS.

The inclusion and exclusion criteria were piloted in the feasibility trial and feedback obtained (Dwyer et al., 2021a; Dwyer et al., 2021b), including:

a) aged 18 years of age or older,
b) have a diagnosis of multiple sclerosis, consistent with the 2024 McDonald Criteria for the Diagnosis of Multiple Sclerosis,
c) have cognitive difficulties as shown by a score of > 22 on the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) (Benedict et al., 2003),
d) not currently undergoing any other form of cognitive rehabilitation,
e) fluent in written and spoken English,
f) not experiencing an active relapse- clinically stable for three months,
g) can provide informed consent,
h) are a resident of the Republic of Ireland

Exclusion criteria for people with MS:

a) Significant cognitive impairment that would affect reliable participation or capacity to give informed consent,

b) Significant diagnosed neurological condition or organic brain damage (unrelated to MS)

3.2.2. Sampling strategy

People with MS will be recruited through advertising via newsletters, local radios, websites, social media, discussion boards, as well as posters and information leaflets posted in relevant clinics. Importantly, we will also post information on the trial through MS Ireland to 2000 people not using email or social media. Recruitment strategies were piloted through the feasibility study. Recruitment for the internal pilot is planned for three months, with the recruitment for the definitive trial planned for six months. See Figure 1 for CONSORT diagram of participant flow.

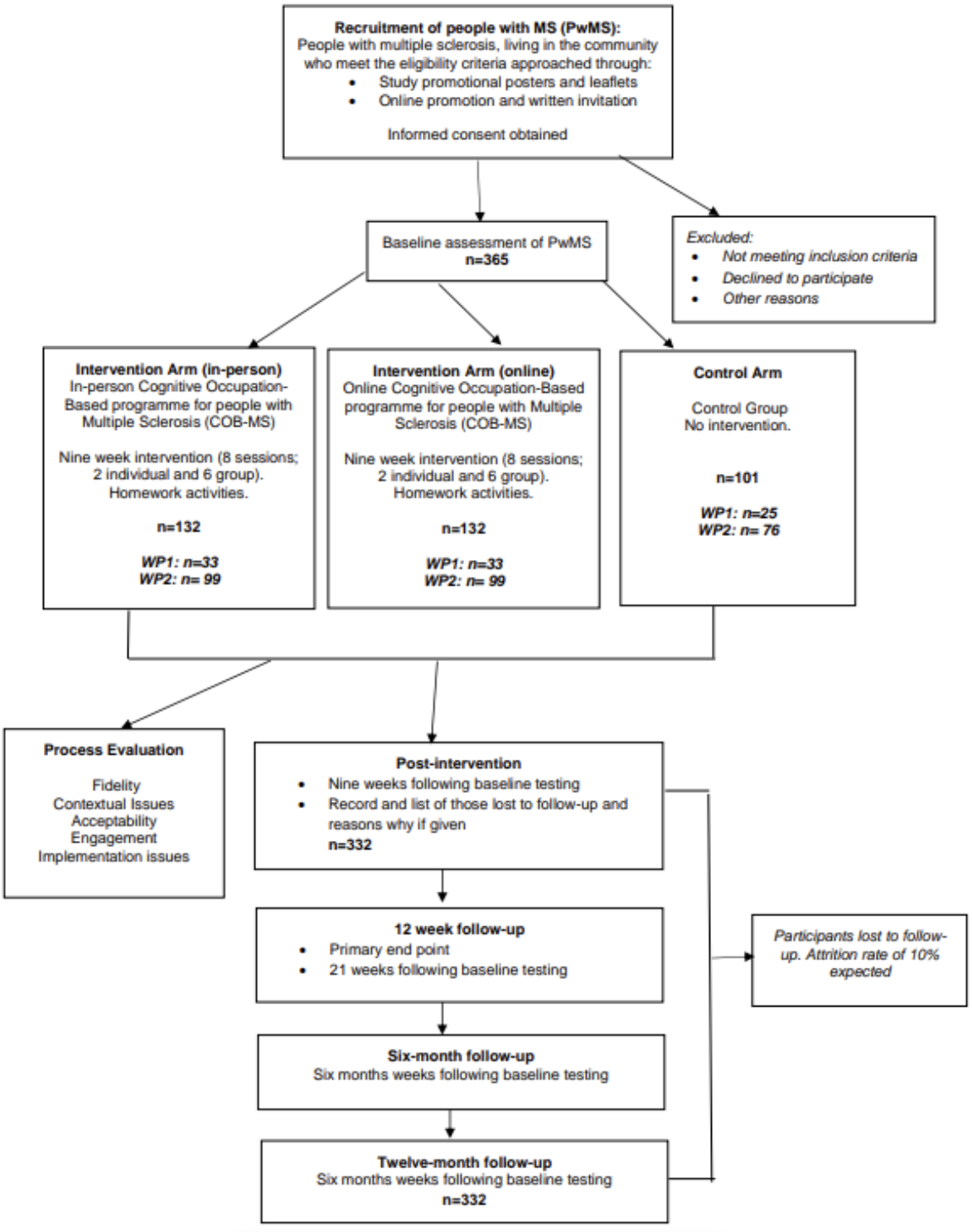


Figure 1. COB-MS CONSORT flowchart of study participants

3.2.3. Setting

The in-person arm will be community-based with study locations in MS Ireland centres or community venues that are accessible to participants. The provision of the intervention in a community setting is vital and aims to help with future implementation of the COB-MS. Many participants will also be familiar with MS Ireland and community centres which should reduce anxiety related to attending group (based on PPI feedback).

Data will be collected in Ireland. The intervention will be run at eight locations nationwide, but all data will be collected remotely- either online or postal (see section below). Having a uniform approach to data collection across locations will reduce some of the challenges associated with multi-location studies. This approach to data collection was also piloted through the feasibility trial.

3.2.4. Interventions

I. COB-MS

The Template for Intervention Description and Replication (TIDieR; Hoffman et al., 2014) checklist will be used here to describe the intervention.

a. Phrase that describes the intervention

An occupational therapy intervention aimed at improving daily life functioning for people with multiple sclerosis who are experiencing cognitive difficulties.

b. Rationale, theory, or goal of the elements essential to the intervention

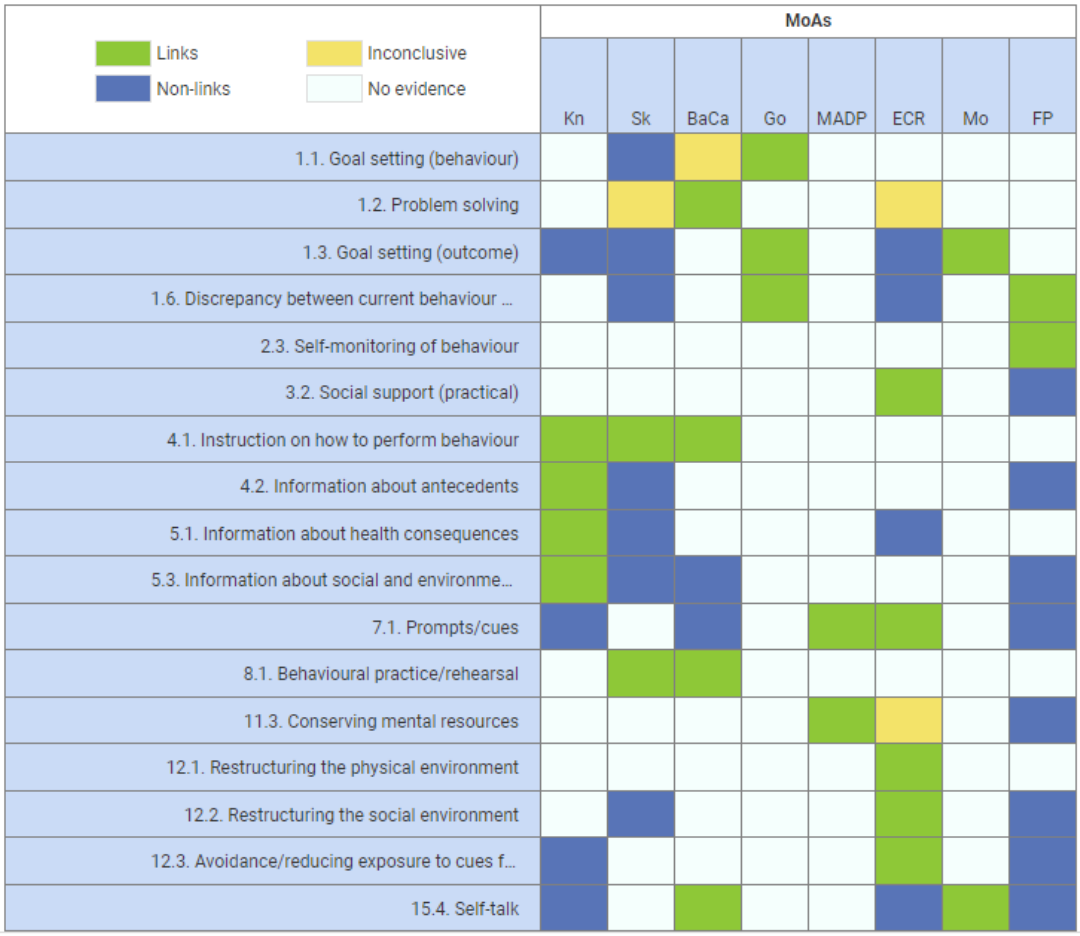
The COB-MS is a patient-centred holistic programme which consists of eight sessions- two individual and six group-based. It focuses on managing demands of employment and daily life through education, remediation and adaption using compensatory strategies, routines and learning new techniques that can be integrated into daily contexts. It recognises the impact of emotion, motivation and other non-cognitive functions.

The COB-MS looks at the context/environment within which the person lives in order to make strategies meaningful to the participant. The programme aims to help people meet their goals while managing their cognitive challenges. The group sessions focus on aspects of cognition and cognitive rehabilitation. There is an emphasis on group discussion and peer learning. Participants have a chance to practice strategies in the group and at home.

We aim, through the COB-MS, to equip people with MS with strategies to manage their own symptoms. Self-management interventions are relatively new in health research but have been found to be highly effective in the management of long-term conditions such as diabetes and arthritis. A number of steps have been taken in designing the COB-MS which addressed the maintenance of gains and continuation of strategies developed through the intervention – these include incorporating behaviour change principles into the COB-MS, integrating home activities into weekly routines, providing people with MS with handbooks which detail each COB-MS session, setting regular goals and having a definitive list of strategies that work for that person at the end of the last COB-MS session.

In the COB-MS the mechanisms of action [MoA; the processes through which Behaviour Change Technique (BCT; Michie et al., 2021 affects behaviour] can be seen in the heat-map below (Table 1). The Theory and Techniques Tool (Michie et al., 2021) online tool was used to visualise the 17 BCT and eight MoAs of the COB-MS and results are copied into the table below. Specifically, the eight MoAs are: Knowledge (Kn), Skill (Sk), Beliefs about Capabilities (BaCa), Goals (Go), Memory, attention & decision processes (MADP), Environmental context & resources (ECR), Motivation (Mo), and Feedback Processes (FP).

Table 1. COB-MS theoretical mechanisms of actions



c. Materials provided

The occupational therapist is provided with a facilitator handbook and people with MS are provided with a participant handbook that details the content of the intervention. The handbooks include the essential components of the intervention. Both intervention arms will be provided with a physical copy of the COB-MS handbook (large-print available on request). As the COB-MS is still subject to research and development, the handbook is not yet available publicly but has received ethical approval.

d. Procedures, activities, setting and/or processes used in the intervention

Each group session has a mixture of theory/background discussion on aspects of cognition (10mins) and strategies (15mins). This is followed by opportunities to practice strategies (15mins) and discuss usefulness, application to own life and goals (20mins). The strategies that are included in the handbook are evidence-based - they have either been found effective with an MS population [e.g. Story memory technique (Chiaravalloti et al., 2005)] or with a population with brain injury [e.g. Goal Management Training (Levine et al., 2000)]. The focus of COB-MS is on translation to daily life tasks and different areas of cognition in one intervention. Furthermore, occupational therapists will be provided with ongoing supervision. Table 2 below outlines the session content.

Table 2. COB-MS Session Content

Session and Format	***Brief Content of COB-MS Sessions***
Session 1 Individual	***Focus on You*** Initial meeting with the OT- briefing on what will be involved in the COB-MS. Goal setting with the person with MS on occupations that they wish to target
Session 2 Group	***You and Your Cognition*** Session will deal with education on the brain and the different areas of cognition. Discussion on how MS can impact cognition and commonly affected areas. Discussion on the impact of cognitive difficulties on day-to-day occupations.
Session 3 Group	***You, the Centrepiece*** How the cognitive difficulties affect you What changes can be made What can we learn that can help?
Session 4 Group	***You, The Person*** What changes can be made by you as a person What can we learn that can help? Further exploration of strategies
Session 5 Group	***Your Environment*** How does the environment impact cognition? What can we change that might help
Session 6 Group	***Focus on Doing*** How are our occupations and daily life affected? What can we do to help – integrate what has been covered to date and strategies that might be helpful Clear examples of how to adapt or remediate occupations.
Session 7 Group	***Seeking New Challenges*** Seeking new challenges Setting goals for yourself Keeping motivated, maintaining progress and adapting Group conclusion and debrief
Session 8 Individual	***Testing the Application*** Review goals and strategies used Set new goals if appropriate Plan for future Signpost to groups and services Debrief and summary

e. Intervention provider

COB-MS is designed to be run by CORU-registered occupational therapist who will be employed by the University of Galway. The occupational therapists will receive training on the COB-MS intervention and protocol, as well as ongoing support to ensure delivery of standardised intervention. By using multiple therapists to carry out the intervention, feasibility of the COB-MS in practice can be seen and we will address potential therapist effect.

f. Modes of delivery

Session one involves an initial meeting (online or in-person) with an occupational therapist who introduces the programme and helps the participant set personal goals. There are then six once-weekly group sessions with a small group (between 5-8 people). The group sessions are followed by a final individual session that takes place two weeks after the last group session. Feasibility results found sessions to average 60-70 minutes in length.

g. Location(s)

The COB-MS will take place in either a community setting or online, depending on allocation. The setting may vary per location but is planned to be a room in an MS Ireland centre. If this is not possible, then the budget allows for a community venue to be hired for the group intervention. Online sessions will use Zoom Workplace- this was found to be feasible and accepted in the feasibility trial. Each occupational therapist will run the COB-MS with approximately eight participants.

h. When and How Much?

There are eight COB-MS sessions which run over nine weeks. They are once-weekly with the final session happening two weeks after the penultimate session. The recommended duration spent on homework is 30 minutes per day 5 days/week, but this is likely to vary and will be monitored through the study. Each participant will receive the intervention once.

i. Tailoring

The intervention is planned to be personalised, through the setting of individual goals in the first session. Participants are encouraged to apply what they are learning in the group sessions to their own lives and goals. Participants can also personalise the intervention during one-to-one sessions with the occupational therapist. The intervention dose and content is the same for all participants and regardless of online or in-person delivery.

j. Modifications

The intervention should not be modified during the course of the study. Fidelity measures will be in place to address this.

k. Fidelity assessment

Key study considerations and actions are summarised in Table 3. Occupational therapists will keep a record of the intervention session content, length and other important information such as participant attendance after each session.

l. Extent of intervention delivered as planned

This data will be captured in the study to allow for complete fidelity testing and future intervention implementation planning.

Table 3. Fidelity checklist

Domain	Goal	Description	Fidelity measure
Study design	Operationalise the COB-MS intervention	COB-MS intervention was developed through high-level evidence, expert review and consultation	COB-MS handbook outlining the 'active ingredients' and intervention materials / templates provided to occupational therapist who will be the intervention provider.
	Specify the intervention dose	COB-MS arm: 8, one-hour sessions provided to the person with MS over 9 weeks.	OT use checklist to record the date, length and content of COB-MS sessions provided

		Control arm: Participants will also be asked to fill in form indicating any services/ interventions they have had during the nine-week period- OT being the most important to record here.	Participants will inform research staff through a written form if OT provision was received.
	Prevent contamination	Trained OT will be instructed not to pass their knowledge / facilitator's manual to untrained OTs, not participating in the study or people with MS	Monitor OT provision received to ensure does not overlap with COB-MS.
	Plan for implementation setbacks	Train additional health care providers (OTs) to ensure provision of COB-MS to all participants allocated to treatment arm	Monitor participant allocation and ensure OT contacts participant within 2 weeks of them being allocated to the either arm
		Develop a recruitment strategy to maximise recruitment of participants to time and target	Review and advise on implementation and success of recruitment strategy.
Intervention providers' training	Trainee characteristics	Intervention providers will be: Registered occupational therapist with prior experience of working in the community and/or with people who have multiple sclerosis	Monitor characteristics of occupational therapist
	Standardise the COB-MS training	Training on COB-MS to be provided to all OTs providing the intervention. Also: researchers explain study design and rationale / emphasise importance of fidelity, prevent contamination.	- Register of attendance. - Handbook provided to all OTs. - Completion of set training tasks by OTs, including reading the manual. - Addition of a brief assessment following training (new for definitive trial).
	Maintain intervention over time (i.e. prevent 'drift')	- Regular supervision with OT	- Record of supervision provided – type, frequency, content recorded - Future implementation – develop FAQ - Monitor participants drop-out rates per OT
Intervention delivery	Standardise intervention and monitor delivery	OT to provide the intervention as per the COB-MS Manual, using the standardised materials / templates.	- Review details of intervention sessions recorded by OT re: date, length, content and venue - OT required to keep reflective diary - Supervision and regular contact - Participant semi-structured interviews post intervention
	Minimise contamination	Trained OT will be instructed not to pass their knowledge or handbook to untrained OTs not participating in the study	Monitor OT provision received to ensure does not overlap with COB-MS.
Intervention receipt	Facilitate participants' understanding of	COB-MS materials produced in appropriate, user-friendly format, considering cognitive difficulties	COB-MS handbooks and material were developed in conjunction with people with MS and OTs (Hynes & Forwell, 2019) and

	the COB-MS intervention		updated with PPI members of feasibility trial (Joyce et al., 2021).
	Assess participants' ability to utilise the COB-MS intervention	Impact of intervention on participants / any changes of behaviour	- Participant semi structured interviews post intervention - Attendance and adherence to COB-MS intervention
Intervention enactment	Assess participants' ability to implement skills/goals addressed in practice	Impact of intervention on participants	- Review of goals set /level of achievement as participants progress through sessions - Suggestions/advice given by OT at the end of intervention and discussed with participants - Improvement on outcome measures maintained at follow-up

II. Usual care

It is expected that the risk of contamination will be low as cognitive rehabilitation is not standard care for patients with MS (Hynes et al., 2022). As part of the feasibility work completed, a national survey (Hynes et al., 2022) identified what constitutes usual practice in Ireland in cognitive care for MS. We found that only 34% of health care professionals (HCP) screen for cognitive difficulties in practice, 36% provide information on cognition to patients, and 39% of HCPs do not refer elsewhere if difficulties are detected. HCPs placed high importance on cognitive intervention but there appears to be very little consistency in cognitive assessment and treatment for people with MS (Hynes et al., 2022). Importantly, findings from the UK (Klein et al., 2019) and Ireland (Hynes et al., 2022) found that occupational therapists are the HCP mostly likely to assess and treat cognitive difficulties in MS.

Participants (across three arms) may be taking medication that has an effect on cognition–e.g. benzodiazepine antispasmodics, anticholinergic agents. Participants will continue with the pharmacological intervention but a record of this will be kept at each data point, and changes noted. This will be accounted for in the final analysis. All clinical services will be available as usual for the three study arms. Community and hospital-based occupational therapy will be monitored throughout the study, and a sensitivity analysis will be used to monitor the occupational therapy input received (if any) by participants. In order to reduce the chance of contamination occupational therapists trained in the COB-MS will be asked not to pass on their knowledge to non-COB-MS trained occupational therapists.

3.2.5. Data collection

3.2.5.1. Demographic Questionnaire

Demographic data of participants such as age, gender, the duration of diagnosis, etc. will be collected through a custom-designed demographic questionnaire. Moreover, their diagnosis and EDSS will be confirmed through clinicians where possible.

3.2.5.2. Outcome measures

There is currently no consensus on treatment outcomes that should be prioritised in MS care. The outcomes are based on existing best practice in the area of cognitive assessment in MS, the results of feasibility testing, and PPI. All outcomes chosen to have direct clinical relevance. The Minimal Assessment of Cognitive Function in Multiple Sclerosis (MSCFIMS) will be used which is a rationally

derived battery of assessments based on professional consensus regarding the fundamental domains of cognition to be assessed in MS. Outcomes will be assessed at baseline, 12-weeks, six-month, and 12-month. Qualitative outcomes will be collected in both intervention arms to further explore COB-MS outcomes. SPIRIT diagram (Chan et al., 2025) can be seen in Table 4.

Table 4. SPIRIT diagram (2025) of COB-MS outcomes

	TRIAL PERIOD							
	Enrolment		Post-randomization					Close-out
TIMEPOINT	*-1*	0	*Baseline*	*9 weeks (+2 weeks)*	*12 weeks (± 7 days)*	*6 month (± 14 days)*	*12 month (± 21 days)*	*13 months*
ENROLLMENT:								
Eligibility screen	X							
Informed consent	X							
Randomization		X						
INTERVENTION/ COMPARATOR:								
COB-MS			→	→				
Treatment as Usual			→	→				
ASSESSMENTS:								
Goal Attainment Scaling [P]			X		X	X	X	
The Multiple Sclerosis Impact Scale [P]			X		X	X	X	
Symbol Digit Modality Test [S]			X		X	X	X	
California Verbal Learning Test II [S}			X		X	X	X	
Trail Making Test [S}			X		X	X	X	
Brief Visuospatial Memory Test-Revised [S}			X		X	X	X	
Everyday Memory Questionnaire [S}			X		X	X	X	

Modified Fatigue Impact Scale-5-item [S}			X		X	X	X	
Generalised Self-Efficacy Scale [S}			X		X	X	X	
Patient Health Questionnaire [S}			X		X	X	X	
EQ-5D-5L [S}			X		X	X	X	
Quality-adjusted Life Year [S}			X		X	X	X	
Client Service Receipt Inventory [S}			X		X	X	X	
Quality of Life Alzheimer's Disease[S}			X		X	X	X	
Demographic and Clinical Information			X		X	X	X	
Qualitative outcomes				X				
Process Evaluation			X	X	X	X	X	
Safety Reporting			X	X	X	X	X	X

a. Primary Outcome Measures

The primary end point will be at 12 weeks.

Goal Attainment Scaling (GAS; Kiresuk & Sherman, 1968): allows participants to set meaningful goals relating to daily life which can be measured in a systematic way. It has shown excellent interrater reliability (r = 0.95) and construct validity (r = 0.92) in cognitive rehabilitation (Rockwood, Joyce, & Stolee, 1997). Goal attainment scaling does appear to show reliability, validity and sensitivity when utilized within a population of adults and older people (Hurn et al., 2006). The GAS has been used with people with MS (e.g. Khan, Pallant & Turner-Stokes, 2008; Stuifbergen et al., 2003) and with people with head injury/cognitive difficulty (Bouwens, Van Heugten& Verhey, 2009) in previous studies and has been shown to be responsive.

The Multiple Sclerosis Impact Scale (MSIS29; Hobart et al., 2001): has been added as an additional primary outcome based on the reviewer feedback and feasibility findings in order to overcome some of the limitations of the GAS. The MSIS is a 29-item scale (consisting of a 20-item physical sub-scale and 9-item psychological sub-scale) assessing MS impact according to a five-point Likert scale, with higher scores indicating higher levels of the impact. The MSIS-29 has high internal consistency and high test-retest reliability and has been validated in an Irish population (McGuigan & Hutchinson, 2004).

b. Secondary Outcome Measures

Symbol Digit Modality Test (SDMT; Smith, 1982): Within the MACFIMS, the SDMT appears to be the strongest predictor of future cognitive decline, thus supporting its sensitivity and construct validity (Amato et al., 2010). Similarly, a recent meta-analysis by Rao et al. (2014) investigated the criterion validity of the SDMT and found it to have the strongest correlation (r = 0.71) with several MRI measures among assessments of processing speed. Research has shown excellent test-retest reliability (r = 0.97) at 2-week (Benedict, 2005) and 4-week (Benedict et al., 2008) retest intervals for individuals with MS.

California Verbal Learning Test II (Woods et al. 2006): The CVLT-II is part of the Minimal Assessment of Cognitive Function In Multiple Sclerosis (MACFIMS) (Benedict et al., 2002). The MACFIMS is a rationally derived battery of assessments based on professional consensus regarding the fundamental domains of cognition to be assessed in MS. The interrater reliability of the CVLT-II ranges from 0.80 – 0.96 (Delis et al., 2000). Correlation coefficients for the CVLT-II and CVLT in recall and learning variables range from 0.72-0.80, supporting its construct validity (Delis et al., 2000).

Trail Making Test (Reitan,1992): The Trail Making Test (TMT) is included as a test of visual attention and task switching. The TMT has excellent construct validity, with correlation coefficients ranging from 0.73-0.90 with other measures such as the Wechsler Adult Intelligence Scale – III (Wechsler, 1999) (Sanchez-Cubillo et al., 2009). Interrater reliability for the TMT is also high (r = 0.96) (Bowie & Harvey, 2006).

Brief Visuospatial Memory Test-Revised (Benedict, 1997): Similar to the CVLT-II, the BVMT-R is part of the MACFIMS. Interrater reliability of the BVMT-R ranges from 0.96-0.97, and test-retest reliability coefficients ranges from 0.60-0.84 (Benedict et al., 1996). It has been used extensively with people with MS and does not have excessive motor demand.

Everyday Memory Questionnaire (EMQ; Royle & Lincoln, 2009): Research revealed Cronbach's alpha of 0.91 for the EMQ, showing good internal reliability.

Modified Fatigue Impact Scale-5-item (MFIS95; Fisk et al., 1994): MFIS-5 is a self-report measure to the impact of fatigue on participant's life. It looks at physical, cognitive and psychosocial impacts of fatigue. It has a Cronbach's alpha of .81 and discriminates between fatigue seen in MS and that seen in other conditions.

Generalised Self-Efficacy Scale (GSES; Schwarzer & Jerusalem, 1995): The GSES aims to predict participants' ability to cope with daily difficulties and adaptation to any stressful life events (Sherer et al., 1982). Cronbach's alphas ranged from .76 to .90 across 23 countries, with the majority in the high .80s.

Patient Health Questionnaire (PHQ-9): is a self-report screening tool for mood disorders, based on DSM-IV criteria for depression. It is a well-validated tool and has been used extensively with people with multiple sclerosis.

EQ-5D-5L: is a standardised measure of health-related quality of life. Five levels were chosen to increase sensitivity of the tool and reduce ceiling effects.

Quality-adjusted Life Year (QALY): will be used in cost-utility analysis as the measure of health benefits of COB-MS compared to usual care. This will yield an incremental QALY of COB-MS over usual care. An estimate of COB-MS direct costs by intervention group has been calculated.

Client Service Receipt Inventory (CSRI): will be collected at all follow up time points to measure downstream resource use and will inform the cost analysis in determine cost-effectiveness of COB-MS. However, the CSRI is a generic measurement instrument and, with respect particularly to medication and health service use in the target population with MS, the pilot phase will provide a

purpose-adapted version of the CSRI to measure nuance of service use in MS population and to be relevant to the Irish health system.

Quality of Life Alzheimer's Disease (QOL-AD): is a validated 13-item questionnaire that measures overall well-being in people with Alzheimer's disease (AD), covering physical, emotional, social, and functional domains. It can be completed by the person themselves or by a caregiver and is widely used to assess the impact of interventions on quality of life. This will be included only in conjunction with PPI input and used specifically for cost-effectiveness calculations.

3.2.5.3. Qualitative data

Interviews and focus groups (depending on the needs of participants) will be conducted in order to evaluate the impact of the intervention from a qualitative perspective. This data will be collected from 20% of both intervention arms, though it will not be a requirement of participation. Stratified purposeful sampling will be used and pre-selected parameters using low-inference variables will assist with selection.

Steps will be taken to ensure the trustworthiness of qualitative data and to increase the credibility of the findings. These include immersion in the data to develop rich descriptions, triangulation strategies to capture different dimensions of the data, member-checking to increase validity of findings, ensuring a good rapport between researcher and participant to increase the likelihood of collecting useful data and using reflection throughout.

An inductive, thematic analysis will inform a framework analysis. Framework analysis is informed both by the inductive analysis and by the Theoretical Domains Framework. Analysis will be a rigorous, iterative and recursive process: characterised by continual reading and re-reading of the data and study aims, e.g. exploring the presence/absence of new themes in previous data, posing further questions of the data.

3.2.6. Sample size and Power Calculation

There are two primary outcome measures, the Goal Attainment Scaling GAS and the MS Impact Scale MSIS both measured at 12-week follow-up. Estimates of average GAS values in two of the trial arms (COB-MS online and Usual Care) were obtained from the analysis of the feasibility study data along with the estimated variability and intracluster correlation coefficient. The internal Pilot Phase will inform us of the average GAS score in the in-person intervention arm along with the relevant summaries for the MSIS scores. The current sample size is based on a hypothesised 3 units difference in mean GAS scores between usual care and on-line groups and a 6 units difference in mean GAS scores between usual care and in-person groups, with a common SD = 10.5. Based on these assumptions, a sample of 276 participants, i.e. 92 in each group, will achieve over 90% power to detect differences among the means using a one-way ANOVA test with a 0.025 significance level. However, a clustering effect may occur in the intervention arms due to the therapy being delivered in groups. Following the approach by Roberts and Roberts (2005) for group therapy trials, the optimum allocation ratio is 1.3 in favour of the intervention arms, assuming an intracluster correlation coefficient of 0.1 and groups of size 8. A sample of 332 participants (15 groups of 8 participants in each of the COB-MS arms plus 92 in the control arm) will achieve 90% power to detect differences among the means. This sample size will also achieve an 80% power to detect a difference of 3 points on the MSIS scores between usual care and online groups and 4.5 points between usual care and in-person groups, assuming a standard deviation of 9. Note that the significant level is set at 0.025 in the

two individual tests to ensure a family-wise error rate of 0.05. Feasibility results indicate a 10% attrition rate which would inflate the sample to 365 (101 control, 132 in each intervention arm).

3.2.7. Allocation

Prior to allocation participants will be provided with a video that will explain randomisation process and the importance of aspects such as retention, blinding and contamination. Once groups have been randomised, participants will be notified of their allocation.

- ***Randomisation***

Randomisation will be conducted through a purpose-designed computer-generated system. The web-based service Sealed Envelope will be used to complete the allocation.
Participants will be allocated to the three arms using allocation ratio of 1.3 in favour of the intervention arms to allow for clustering of the intervention arm, using randomly permuted blocks.
Once approximately sixteen participants have been recruited who would be able to attend the same COB-MS group, allocation will take place. Participants' details will be passed to their allocated OTs to initiate contact following allocation.

- ***Blinding***

The study will be single-blinded. The following people/groups will be masked to participant allocation: all research staff collecting outcome measure data (not to include the qualitative data), statisticians and those involved in data analysis, the Independent Steering Trial Committee and Data Monitoring Committee. It will not be possible to mask the participants, nor the occupational therapists providing the intervention.
A number of strategies will be in place to minimise the risk that unblinding will happen (Lowe et al., 2011):

a. Participants will be asked to conceal their group identity to research staff who are conducting follow-up outcome measure assessment.
b. The importance of maintaining blind will be stressed to research assistants.
c. Blinded research staff will not have access to any data that might unblind them.
d. Following each assessment, blinded researchers will record which group they thought the participant had been allocated to and their degree of certainty.
e. If a blinded researcher is unblinded, this will be recorded along with the reason for unblinding. The data will remain in the study.
f. The rate of unblinding will be reported. Unblinded data that remains in the study will be factored into the final analysis.

3.2.8. Data Analysis

Data analysis and reporting will follow 2010 CONSORT guidelines. We will report on demographic and clinical characteristics, and number of participants included in each analysis. The estimated effect size and 95% confidence interval will be reported for each group on primary and secondary outcomes. Analysis will take place once all data has been collected. Serious adverse events will also be reported.
Means and standard deviations (SD) (or medians and IQR as appropriate) will be used for continuous variables and counts and percentages for categorical outcomes. The retention rate will be estimated using a 95% confidence interval (CI). Estimates (mean and SDs) of the primary outcome variables, GAS and MSIS score, and treatment effect at week 12 will be reported.

The primary efficacy analysis will be performed using linear mixed models incorporating a random intercept term to take into account the cluster effect due to the intervention being delivered in groups. Efficacy for the secondary outcomes will be summarised and analysed in a similar fashion.
The pattern of missingness will be explored and, if plausible, a sensitivity analysis using multiple imputation MI will be carried out, comparing the results of the primary and secondary complete-case analysis with those obtained using MI.
Planned sub-group analysis will take place to assess the effect of the intervention at the level of the therapist, by gender, and baseline score on MSNQ. The planned subgroup analysis will only be conducted if a sufficient number of participants are available per group.

3.3. Health Economic Evaluation

We will conduct a full economic evaluation alongside the clinical trial. The goal is, by estimate the cost-effectiveness from the perspective of the Ireland health system and also from a wider societal perspective (to consider intervention effect to reduce risk of lost productivity and demands for informal care), to help inform healthcare decision makers on whether to allocate resource to COB-MS nationally.
Data from each arm will be collected on participants resource use (to estimate costs) and their health-related quality of life (to estimate quality adjusted life years or QALY) and an Incremental Cost Effectiveness Ratio (ICER) will be calculated formally as:

- ICER = ($COST_{COB\text{-}MS}$ - COSTTAU) / ($EFFECT_{COB\text{-}MS}$ - EFFECTTAU)

Health state utilities will be estimated using the EQ5D5L and QOL-AD and QALYs will be estimated using an area-under-the-curve approach. Total cost will be the sum of cost associated with COB-MS (based on specific data on fidelity to the 9-week program) and cost consequences (based on a bespoke resource use tool developed during year 1).
Ireland has previously indicated a willingness-to-pay threshold of €45,000 per QALY and national guidelines for economic evaluation of health technologies in Ireland (HIQA 2020) stipulate that studies should report “the probability of an ICER being below €20,000 and €45,000 per QALY). To calculate these probabilities of being cost effective, uncertainty analysis will perform bootstrapping of the joint distribution of total costs and QALY.
In addition to this trial based economic evaluation, a simple simulation model will also be developed to extrapolate cost effectiveness beyond the trial endpoint (i.e. over a lifetime horizon). Furthermore, the simulation, in combination with the trial data, will examine the relationship of fidelity to the COB-MS sessions and how this influences cost effectiveness. Finally, from the societal perspective, the model will also examine the longer-term effect of lost productivity and increasing demand for informal care.

3.4. Process Evaluation

A mixed method process evaluation will be used to interpret the findings of the definitive trial in the context of the health economics data in order to assist in the implementation of the COB-MS. A detailed assessment of treatment fidelity will take place, along with estimates of contamination, and engagement with the intervention. The aim is to measure fidelity of the COB-MS, identify factors that could affect implementation in practice, and environmental and other contexts that impact on engagement with the COB-MS.

3.4.1. Fidelity

A number of fidelity measures have been included and are available in Table 3. Occupational therapists will be required to detail the content of each COB-MS sessions and detail any participant-level differences that may exist. The data collected will be compared to the intended intervention. Data will identify components of the intervention that were adhered to by the occupational therapists and the participants.

A fidelity checklist, based on the COB-MS logic model (Figure 2.) and handbook, will be completed by all occupational therapists and a random selection of participants from each location.

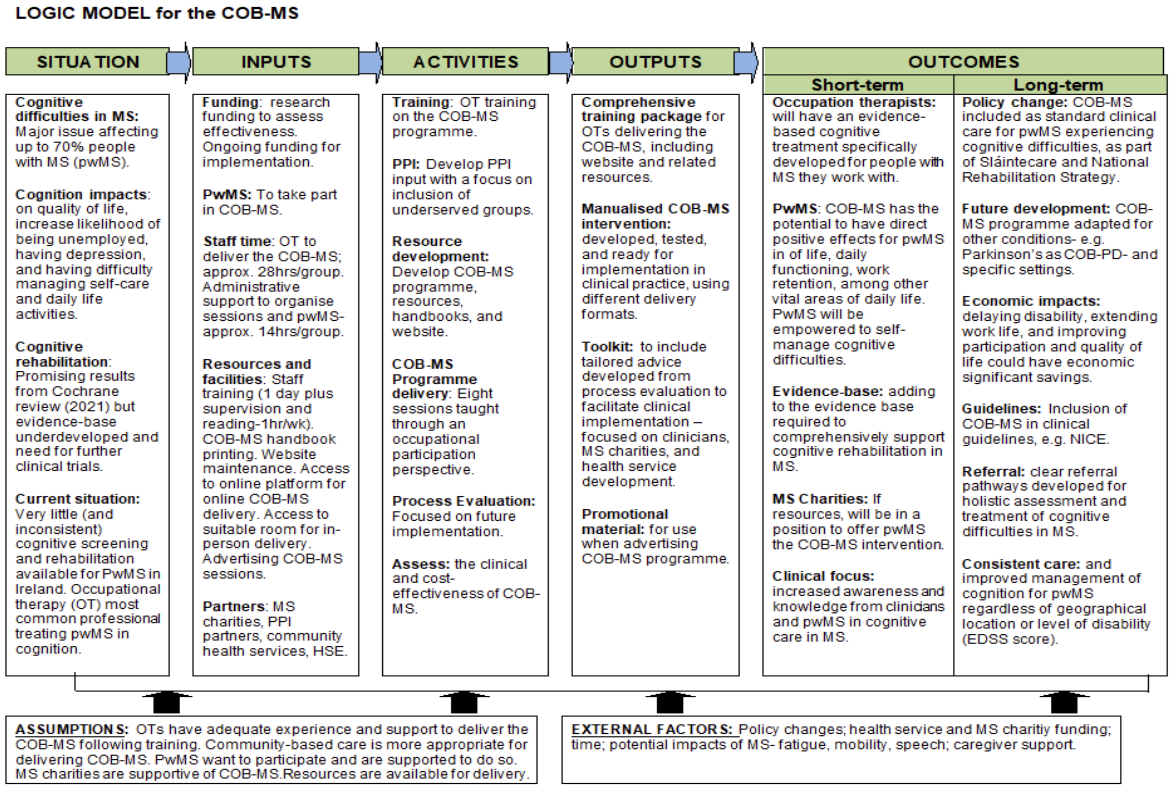


Figure 2. COB-MS Logic Model

3.4.2. Engagement with the intervention

Occupational therapists will record participant attendance at each group session as a measure of engagement with the intervention. Engagement with the intervention will be used as a proxy for compliance with weekly home-based activities. Engagement will be recorded by participants in their handbook. This will include self-monitoring of completion of home-based activities and rating on a weekly basis taking account of effort, intention, time spent and actual completion. This will be collected at the end of the final COB-MS session to assess accessibility and acceptability (including tolerance) of the intervention.

3.4.3. Contextual factors

We will develop a description of the locations throughout the process through surveying occupational therapists during the intervention delivery period- this is for online and in-person delivery. A trained research assistant will also observe the COB-MS training and the delivery of random COB-MS sessions

across therapists and across locations. A checklist will guide the research assistant in this- the focus will be both on fidelity to treatment and the contextual factors.
Occupational therapists will be required to maintain a structured reflective diary that will be updated (at a minimum) following each COB-MS session. Occupational therapists delivering the intervention will also be interviewed at the end of their time delivering the COB-MS. The aim will be to provide feedback on the intervention, the delivery method, training, and to identify potential implementation factors.

4. Data Management Plan

A FAIR Data Management Plan (Wilkinson et al.,2016) will be used, ensuring data is findable, accessible, interoperable, and reusable. A completed data management plan will be submitted to the HRB funder at the beginning of the study and with the final report. The DMP Online Digital Curation Centre checklist will be used to guide creation:
http://www.dcc.ac.uk/sites/default/files/documents/resource/DMP/DMP_Checklist_2013.pdf in conjunction with the Clinical Research Facility at the University of Galway.
Data sets will be made openly available with a CC-BY license, at the following locations: 1) Irish Social Science Data Archive (ISSDA) http://www.ucd.ie/issda/data/ and 2) Irish Qualitative Data Archive (IQDA) at https://www.maynoothuniversity.ie/iqda.

The HRB Clinical Research Facility (HRB-CRF) will assist with setting up the database to be used for the study. This is for the entire sample population. The database will be developed by the HRB-CRF in consultation with the PI and statistician on the team. DFdiscover will be used as the Clinical Data Management System (CDMS) for this study. The system supports electronic data capture, data validation, query management, and audit trail functionality. Site personnel will primarily use DFWeb, the web-based component of DFdiscover, which enables secure online data entry and review without requiring local software installation. In addition, DFexplore, the desktop client application of DFdiscover, can be installed for authorized users when required. Both interfaces provide access to study-specific electronic Case Report Forms (eCRFs) according to assigned user roles and permissions. Access to the system will be controlled through unique user credentials, and all data transactions will be recorded in an audit trail in compliance with applicable regulatory requirements.
The Archival of the data will be done as follow:

- Archival of the electronic data management files for the study by the data developer using clinical data management systems,
- Archival of paper data management files by the data manager or delegate,
- Archival of site-specific data by the site principal investigator and held within the site files.

The HRB-CRF will also monitor the database for the lifetime of the trial. Monitoring of the trial will ensure appropriate reporting to sponsors. Monitoring will take place at the research site (University of Galway). Monitoring arrangements are set in line with the risk and complexity of the trial. The study is considered low risk and so monitoring should be in line with this. Monitoring would include the following:

- Investigating whether trial is being implemented according to the approved protocol
- Randomly select 20% of Case Report Forms- check for completeness and consistency
- Monitor informed consent and adverse events reporting

5. Dissemination and knowledge exchange

Our knowledge exchange plan not only includes dissemination through traditional avenues, such as international peer-reviewed publications and conference presentations, but also dissemination to lay audiences living with MS and caring for PwMS. Thus, knowledge exchange of the research program's findings will target a broad audience, including the researcher community, PwMS, funding bodies and healthcare providers. With respect to traditional means of dissemination, findings from the research program will be published through international, high impact peer-reviewed journals and presented at relevant international conferences. All publications pertaining to the COB-MS will be Open Access publications. The Open Access aspect is important in order to improve transparency and validity of research and to keep the public aware of progress. University of Galway transformative publishing agreements which allow for Open Access publication will be used – e.g. Multiple Sclerosis Journal. We also intend to publish in HRB Open Research, which we have experience publishing in and favour the rapid and open process associated.

With respect to non-traditional means of research dissemination, such strategies will be engaged in order to enhance accessibility and better advertise the program to the public for purposes of successful future recruitment and subsequent implementation. Such strategies include utilising relevant websites (e.g. in the Irish context: hse.ie, hea.ie, education.ie and psychologytoday.com); university press releases for television, newspaper, radio and established media websites; as well as social media. Social media presence (i.e. updates and maintenance) will be managed through a partnership of the trial manager and PPI embedded patient researcher, focusing on established MS groups, international MS societies and relevant news outlets. A dedicated COB-MS website has been developed and will be maintained to keep the public up to date with program progress and findings, as well as links to Open Access publications. All results will be disseminated regardless of the outcomes. All data will be shared at appropriate repositories in order to reinforce the transparency of the COB-MS.

In addition to assessing the clinical and cost-effectiveness of the COB-MS intervention, it is a goal of the research program to co-develop implementation strands that will support the delivery and long-term implementation of the intervention – the process and principles of designing for dissemination (Brownson et al., 2013) will allow for effective dissemination of findings to relevant stakeholders. For example, in addition to engaging a PPI advisory panel, the research program will recruit an advisory group of healthcare practitioners, those working in healthcare systems, and employers that will advise on implementation.

The primary impact of these strategies and, indeed, the research program will be the availability of a fully developed and tested cognitive rehabilitation intervention. Researchers will liaise with the Health Service Executive, health promotion services, MS societies and Public & Patient Involvement, more broadly, regarding how best to promote the results to PwMS, healthcare practitioners, researchers and health-policy decision-makers. Impact will also be made through helping to enhance MS rehabilitation and management; ease extant MS rehabilitation health services; and fill extant gaps in research on cognitive rehabilitation for people with MS.

6. Public and Patient Involvement

Planned Involvement of Patients & Public in this trial (see also Figure 3)

PPI members will be involved in all decisions made and help with planning. Across the trial, there will be areas in which PPI members will contribute. There will be a particular focus on the process evaluation where there will be a real need for PPI when looking at COB-MS acceptability.

- Co-applicant: Robert Joyce, who was the Embedded Patient Researcher (EPR) in the Feasibility Study, will use his experience to mentor and train the EPR's in this study so they can contribute effectively at all project stages.
- Collaborators: Martha Killilea from PPI Ignite - Galway will provide guidance over the course of the study. MS Ireland will also support the trial.
- Trial Steering Committee: This will have two PPI members who will provide oversight from a patient perspective.
- Trial Management Group: This will include a representative of the MS Ireland and the Embedded Patient Researchers.
- Patient Advisory Panel: A panel will be recruited which will be representative of the MS Community in Ireland. A balance of genders, age, illness profile (PPMS, SPMS & RRMS), rural and urban, and socio-economic profile. It will also include, if possible, caregivers of people living with MS.
- Embedded Patient Researchers: Two EPR have been employed (Joan Jordan and Emma Rogan). Having two viewpoints will benefit the trial and will help if one of the EPR's has medical issues which would require time away from the trial.

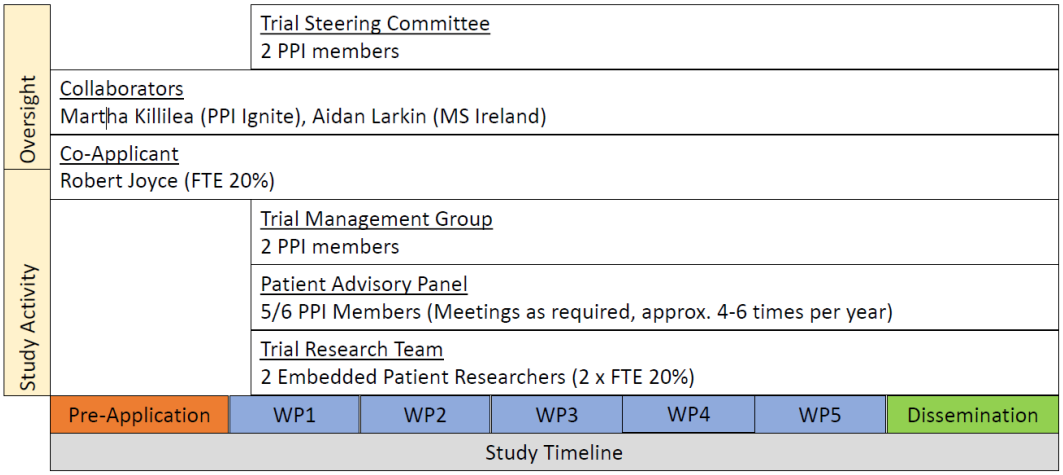


Figure 3. PPI Inclusion Chart

7. Trial Management, Governance and Safety Monitoring

The study will be conducted according to Good Clinical Practice (GCP) Guidelines, Declaration of Helsinki, GDPR. The following procedures will be in place to ensure appropriate trial management, governance and safety monitoring:

7.1. Trial Oversight Committees

7.1.1. Trial Management Group (TMG)

A Trial Management Group (with agreed Terms of Reference) has been established. Membership of this group is from the research team (as described in the ethics application) and when needed representatives from MS Ireland will join the meetings. Terms of Reference will be agreed upon at the first meeting. This group will meet bimonthly and will be responsible for ensuring timely delivery of the activities. At trial set-up this group will be meeting more regularly. The regularity will be decided at the initial meeting. A meeting will also be held before a TSC meeting to plan the agenda and required meeting papers. Key team responsibilities will be decided on at the initial meeting including the arrangements for the day-to-day management of the trail – e.g. randomisation, data handling and coordination.

The responsibilities of this group will be in the overseeing of the daily management and running of the COB-MS trial. They will manage the overall conduct of the trail and ensure timely progression. This group will include the PI, research staff on the trial, the statistician, qualitative expert, and representative from MS Ireland. The research assistants responsible for data management will be on the TMG. The embedded patient researchers will also be a member of the TMG.

Group meetings will ensure that TMG members are kept up to date with the progress of the trial. Monitoring progress is key to the success of this trial and the TMG is essential to this. Potential risks to the study success will be discussed at meetings and an action plan put in place for same.

7.1.2. Trial Steering Committee (TSC)

The COB-MS trial will be monitored by an independent Trial Steering Committee, following guidance set out by the NIHR. The role of the TSC is to provide oversight of the trial on behalf of the sponsor and funder and ensure that the trial is conducted in accordance with the principles of GCP and relevant regulations. This committee will meet three-four times a year and will be chaired by an independent academic with relevant experience of trial management and conduct. Membership will include a majority of independent voting members (minimum of 75%). A quoracy of 67% (two-thirds of members) will be required on all decisions made by the TSC. The members of this committee do not have any direct involvement in the running of the trial. The PI will be on the TSC as a non-independent member. Members will include statistician, clinician, trial methodologist, two PPI members, academic researchers with expertise in condition and methodology, and independent chair. Membership will be agreed with the funder. When relevant, members of the TMG will attend TSC meeting to present an update on progress. The PI will also highlight any particular issues for discussion and requests for guidance at meetings.

The committee will provide expert advice and monitoring that is independent of the research team and the institution involved. Any issues that might impact on the trial will be discussed by the committee. The TSC will focus on the progress of the trial, adherence to the protocol and participant safety. The terms of reference of the committee have been drafted (developed using MRC Clinical Trials Unit template TSC Charter version 1.02, 13-Mar-2006) and will be agreed upon at the beginning of the first meeting of the TSC. This group will decide when an Independent Data Monitoring and Ethics Committee (DMEC) needs to be convened.

Specific roles of the TSC are as follows:

- To provide expert oversight of the trial.
- To maintain confidentiality of all trial information that is not already in the public domain.
- To finalise the Go/No Go criteria from internal pilot to full trial.

- To make a decision on progression following the internal pilot, based on the Go-No Go criteria.
- To make decisions as to the future continuation (or otherwise) of the trial/s.
- To monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems.
- To approve the protocol before enactment and following Sponsor and REC approval.
- To review regular reports of the trial.
- To assess the impact and relevance of any accumulating external evidence.
- To monitor completion of CRFs and comment on strategies from TMG to encourage satisfactory completion in the future.
- To monitor follow-up rates and review strategies from TMG to deal with problems.
- To approve any amendments to the protocol, where appropriate, prior to Sponsor and REC approval.
- To oversee the timely reporting of trial results.
- To approve / comment on the statistical analysis plan, where appropriate to expertise.
- To approve / comment on the main trial manuscript.

The independent membership of the TSC will be for the duration of the trial, if possible for members. PPI members can share attendance at meetings, if preferred.

7.1.3. Independent Data Monitoring Committee (IDMC)

As this trial is considered to be low risk the TSC will assume the role of the IDMC. The IDMC terms of reference have been drafted and will be agreed before the start of the trial. This document will outline any stopping rules and any planned interim data analyses during the recruitment phase of the trial.

All members of the IDMC will be independent of the trial. They will be made up of 2-4 members of the TSC and will include a statistician, clinician and independent chair. The trial statistician will present data to the IDMC at meetings. Recommendations made by the IDMC will be reviewed by the entire TSC.

The IDMC will not need to meet at every TSC meeting. The meetings will be approximately every 10 months following recruitment. This will be reviewed as required and the IDMC may wish to meet more frequently. The IDMC will have unblinded access to the data. There are no interim analyses planned but the IDMC may decide that this is required. If this happens, then the IDMC will review the data.

The IDMC are responsible for the data that comes from the trial. They are particularly interested in safety and efficacy, and make recommendations to the TSC regarding any safety issues. Along with the TSC, they decide if there are any safety issues that should be brought to the attention of participants. They are also responsible for decision concerning any ethical reasons why the trial should not continue. The IDMC will review and make recommendations around the proposed type of analyses. They will also review plans for subgroup analysis. The IDMC will be key in deciding if the design for analysis chosen is the most appropriate for drawing conclusions about the aims of the trial.

7.1.4. Trial Registration

Prior to initiation of the study the COB-MS trial will be registered on the ISRCTN registry. This will be publicly accessible. Results will also be available in open access repository within twelve months of trial completion and will be submitted for publication, regardless of the study outcome. Outputs will be shared with participants once available.

8. Potential Risks and Management

8.1. Trial Risks

All the potential risks that can happen in COB-MS trial, their probabilities, impacts and how to manage them are listed in table 5.

Table 5. Risk management in COB-MS

Potential Risks	Likelihood	Impact	Mitigation Measure
COB-MS intervention	Rare/Remote	Negligible	No anticipated harm associated with this intervention. All participants will be able to provide informed consent
Slow Recruitment	Possible	Moderate	Recruitment will be monitored closely across locations and from internal pilot stage. Location-specific strategies will be used if recruitment is slow in a particular location- e.g. contacting local radio and press.
Participant Distress	Unlikely	Minor	There is some chance that people may become upset when discussing cognitive difficulties but research staff will have skills to deal with this. If participants are experiencing on-going distress then they will be directed to emotional and support services. A distress protocol for participants has been drafted.
Participant Burden	Unlikely	Minor	Likelihood of participant burden has been reduced by removing number of outcome measures, and one data point collection. We will work closely with the PPI group to ensure burden is low. Data will be collected remotely.
Impact of the COB-MS in practice	Possible	Major	Feasibility work has identified barriers and facilitators to COB-MS in practice. PPI Advisory group, MS Ireland, and occupational therapists will be involved in developing and finalising a feasible implementation plan that is relevant and sustainable across Ireland.
Recruitment of junior research staff.	Likely	Minor	We will provide researcher training, supervision, and support throughout. Research staff (research assistants, postdoctoral researchers, embedded patient researchers, and occupational therapist) are required to have regular supervision.
Data Breach	Unlikely	Extreme	Data Breach Procedure for University of Galway will be followed (see Section 3.8)
Incomplete data set	Unlikely	Moderate	Data collection plan has been developed with PPI members, and considerations from feasibility trial. Logic model and PPI used to select outcomes.
Confidentiality (during COB-MS sessions)	Possible	Moderate	Participants not expected to share personal data with others in the group. Because of the very nature of a group intervention, confidentiality and anonymity cannot be guaranteed but participants will be asked not to share information outside of the group discussions with others. This will be monitored by the occupational therapist.

Control group disappointment	Possible	Minor	Participants allocated to the control group may be disappointed with their allocation. Video has been drafted that shows importance of control group.

8.2. Adverse Events and Safeguarding

Participants will be monitored for adverse events throughout the trial period, defined as any untoward medical occurrence during the trial. Although there is no pharmaceutical product administered as part of this study, assessments of causality and severity will be collected. Safeguarding alerts will also be monitored. A line listing of adverse events will be considered a secondary outcome of the trial.

If a patient becomes ill or relapses during the course of participation in course of the trial, this should be managed via normal standard of care.

In the event of an adverse event, the clinician investigator(s) is available to advise, and direct further care/investigation in conjunction with the patient's doctors will be considered.

8.2.1. Adverse and Serious Adverse Events

Based on GCP definitions, adverse events (AE) include any unfavourable medical occurrence in a trial participant administered the investigational product. The adverse event does not necessarily have a causal relationship with the treatment. Moreover, any unfavourable medical occurrence that is considered serious at any dose if it:

• Results in death,

• Is life-threatening,

• Requires inpatient hospitalisation or prolongation of existing hospitalisation,

• Results in persistent or significant disability/incapacity, or

• Is a congenital anomaly/birth defect, is considered serious adverse event (SAE). Serious adverse events such as death; or medical events that are: life threatening, or require hospitalisation, or result in disability or incapacity, or are otherwise considered significant will be recorded.

A reporting procedure will be in place for all serious adverse events and all team members will be aware of the correct procedures. This will be detailed in the Trial Master File and is summarised in Figure 4.

Immediate reporting will be followed by a detailed, written report. Follow-up reports will use participant ID numbers rather than any identifying personal information. SAE forms will be used to detail the SAE. All SAEs forms will involve the PI and will be tracked on the case report files and followed-up by the PI.

Non-serious adverse events will be recorded as part of the secondary outcomes of the study (Figure 4).

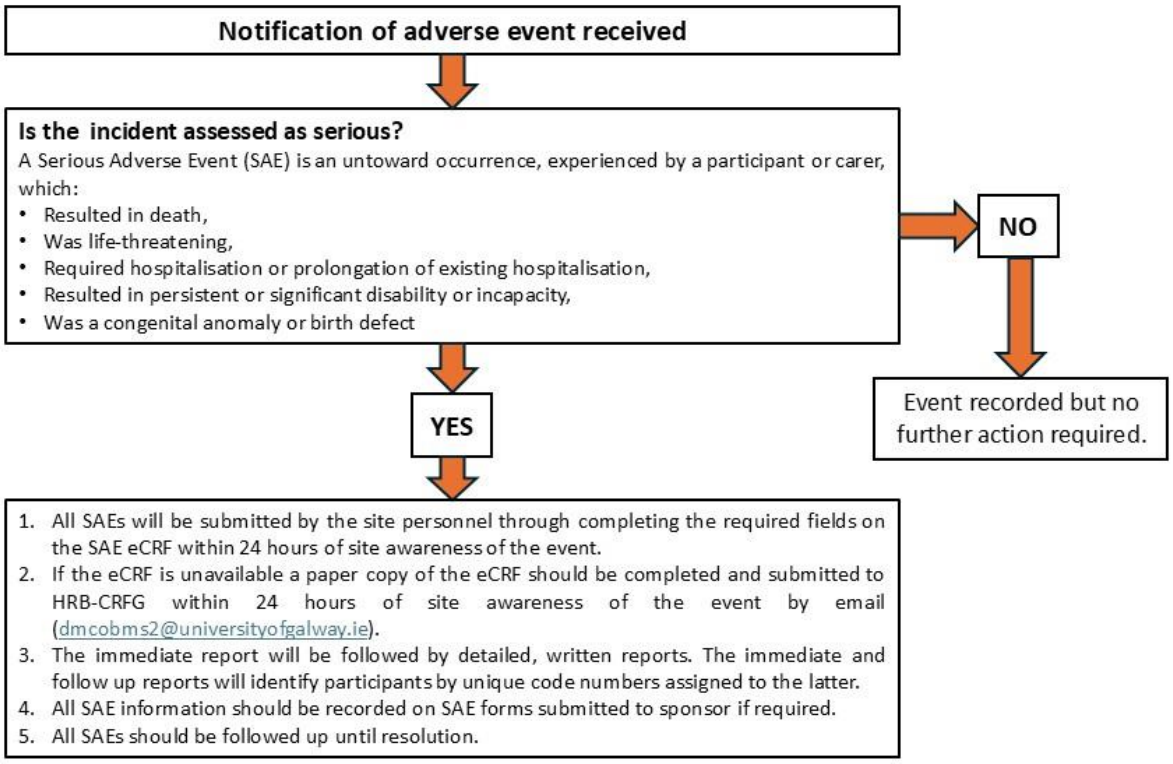


Figure 4. Serious adverse event reporting procedure.

8.2.2. Safeguarding

Safeguarding alerts (cases where action has been taken for the protection of vulnerable adults -dealing with suspected abuse or neglect of participants) will be recorded. Safeguarding alerts may relate to physical, emotional/psychological, sexual, financial or material abuse, neglect or acts of omission, domestic abuse, institutional abuse, or discriminatory abuse. Any safeguarding concern will be managed in accordance with the study safeguarding policy, sponsor requirements, and local statutory safeguarding procedures, including escalation to the appropriate safeguarding authority where required.

Abuse or neglect will not be recorded as an adverse event unless it results in an untoward medical occurrence. Instances of abuse will be captured as an event of special interest. Any resulting medical signs or symptoms will be reported as AEs or SAEs in accordance with standard safety reporting requirements.

8.2.3. Harms

There is no anticipated harm associated with this intervention or trial. No invasive intervention will take place. All participants will be able to provide informed consent and will be clear on what they are consenting to with regards to their data, as per General Data Protection Regulation EU 2016/679. If a participant withdraws from the study, this will be noted and reported as appropriate. Their details will be 'flagged' to ensure that no further contact is made by the research team. The study will not interfere with or limited the current treatment of each participant.

A Trial Operations Manual will be used to ensure consistency of all processes. All research and clinical staff involved in the research activities will be trained, supervised and supported.

Health data will be collected from participants. This will be anonymised and will consist of current medications and treatments (including any treatments that may have been paid for and provided outside of the country), and any prior cognitive intervention. Participants will not be expected to share any personal data with others in the group. It is important to note that because of the very nature of a group intervention, confidentiality and anonymity cannot be guaranteed but participants will be asked not to share information outside of the group discussions with others.

There is minimal risk to participants. There is some chance that people may become upset when discussing cognitive difficulties, but research staff will have skills to deal with this. If participants are experiencing on-going distress, then they will be directed to emotional and support services. They will be encouraged to seek support or intervention from GP and/or treating neurologist.

Participants allocated to the control group may be disappointed with their allocation. Every effort will be made to retain participants through the study.

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