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REFUEL-MS: Clinical and Cost-Effectiveness RCT

Submission date 09/04/2025	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 20/06/2025	**Overall study status** Ongoing	
Last Edited 10/11/2026	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Although 9/10 people living with MS report fatigue as a symptom, fewer than a third have been offered any treatment for fatigue as part of their routine care. Of these people, only 9% were offered behavioural treatments. Our overall research programme aimed to work with people with MS to create a digital intervention to help reduce fatigue and then to test how well this intervention – called REFUEL-MS – works in real life. REFUEL-MS is an app that includes physical activity, balance exercises, and cognitive behavioural therapy (CBT) techniques. These were included because previous research has found that they are all effective at reducing MS fatigue. This current study aims to test how well the REFUEL-MS app is at reducing MS-related fatigue compared to usual care and to make sure it is safe for patients.
REFUEL-MS is a patient-led app that people with MS can access on a smartphone or tablet. Patient-led means there are opportunities for patients to choose the content that is most relevant to them (cognitive behavioural therapy, physical activity, or balance exercises), set personal goals, and track progress. The intervention also includes support from a REFUEL-MS healthcare professional through regular virtual appointments and app-based messages. The REFUEL-MS app is not intended to replace the existing MS medical care of participants.

Who can participate?
People living with MS can take part if they:
1. Are aged 18 years and over
2. Have a confirmed diagnosis of MS
3. Are able to read and communicate in English
4. Are a resident of England, Wales or Scotland
5. Are able to see and use a smartphone or tablet
6. Experience fatigue

We are particularly interested in involving participants who are not currently well represented in MS research. This includes those who are older, male, LGBTQ+, from minoritised ethnic backgrounds, live with progressive types of MS, varying levels of disability, lower digital literacy, and lower socioeconomic status. REFUEL-MS is designed to be suitable for individuals with different needs. Participants who do not have a suitable device can be loaned one for the duration of the trial.
We will be recruiting 378 people with MS from the UK MS Register, Guy's and St Thomas' NHS Foundation Trust, and community groups.

What does the study involve?
Participants who are eligible and consent will complete an online questionnaire. Participants will then be randomly assigned to one of two groups. One group will get access to the REFUEL-MS programme via the app and the other group will continue their usual care. For both groups, the study will last for 16 weeks.
All participants will be asked to complete online questionnaires about their fatigue, physical activity, mood and quality of life at 4, 6 and 12 months after starting the study. All participants will also receive a monthly phone call from the research team to check how they are doing and if anything unexpected has happened since the last call. Some participants will also be invited to take part in an interview about their experience of using REFUEL-MS.

What are the possible benefits and risks of taking part?
Taking part in this study could improve treatments for MS-related fatigue and support future research. The risks are small, as REFUEL-MS can be used from home and tailored to suit individual needs.
Participant safety is very important to us and the research team will regularly contact participants to check if it is suitable for them to continue in the study. We also understand that MS can come with challenges like anxiety and depression, so along with monthly check-in calls, we will provide information on additional support in the Participant Information Sheet.
We know that completing questionnaires can be time-consuming so we are offering participants a £5 voucher when they complete the questionnaires at 6 and 12 months.

Where is the study run from?
King’s College London (UK)

When is the study starting and how long is it expected to run for?
March 2025 to March 2027

Who is funding the study?
1. National Institute for Health and Care Research (NIHR) (UK)
2. MS Society (UK)

Who is the main contact?
Professor Rona Moss-Morris or Harriet Mortimer, refuel-ms@kcl.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
350492

Central Portfolio Management System (CPMS)
67673

National Institute for Health and Care Research (NIHR)
203290

Protocol serial number
CI/2025/0011GB

Study information

Scientific Title
REFUEL-MS: A two-arm parallel group randomised controlled trial of the clinical and cost-effectiveness of a digital CBT, balance and exercise intervention (REFUEL-MS) for treating fatigue in multiple sclerosis (MS)

Acronym
REFUEL-MS

Study objectives
We hypothesise that REFUEL-MS, a blended digital self-management treatment for fatigue in MS, will be more (clinically and cost) effective than Treatment-As-Usual (TAU) at reducing fatigue severity in people with MS experiencing high levels of fatigue.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 16/07/2025, London - Stanmore Research Ethics Committee (Meeting held by video-conference via Zoom, London, N/A, United Kingdom; +44 (0)2071048208; stanmore.rec@hra.nhs.uk), ref: 25/LO/0256

Primary study design
Interventional

Study design
Randomized controlled trial

Study type(s)
Efficacy, Quality of life, Safety, Treatment

Health condition(s) or problem(s) studied
Multiple sclerosis

Interventions
This study will involve randomising participants to one of two groups (1:1), to compare the REFUEL-MS app, a digital, healthcare professional (HCP) supported self-management treatment for MS-related fatigue, with usual care (treatment-as-usual; TAU) for a period of 16 weeks. Participants in the two groups will complete assessments of fatigue (primary), physical activity, mood, and quality of life at 4, 6, and 12 months. In addition, a qualitative interview study will be conducted with a diverse sample of pwMS who trialed REFUEL-MS and the HCPs supporting the intervention. This should inform our understanding of the factors impacting engagement with REFUEL-MS, perceptions of its effectiveness and potential implementation in routine MS care.

Participant Selection:
The target total sample size of 378 (189 randomly allocated per arm) people living with MS (pwMS) who meet the eligibility criteria will be recruited through the NHS and the UK MS Register (UKMSR). To address the lack of representativeness of previous trials of fatigue interventions, we also aim to recruit a percentage of people from minoritised or traditionally underserved groups. If we are unable to recruit sufficient people from these groups through the UKMSR and NHS, we aim to recruit through targeted community groups.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Refuel MS

Primary outcome(s)
Fatigue severity measured by the Chalder Fatigue Questionnaire (CFQ) at 6-months post-randomisation

Key secondary outcome(s)
Current secondary outcome measures as of 27/08/2025:

1. Fatigue impact measured by the Fatigue Severity Scale (FSS) that captures the impact of fatigue on daily functioning at 4, 6 and 12 months post-randomisation
2. Clinically meaningful improvement in fatigue severity, defined as a reduction of >2.3 points from baseline in the total CFQ score, consistent with estimates of the minimum clinically important difference (binary outcome) at 4 and 12 months post-randomisation
3. Clinically meaningful improvement in fatigue impact, defined as a reduction of ≥0.45 points from baseline in the mean FSS score (binary outcome)
4. Depression severity using the Patient Health Questionnaire (PHQ-9) at 4, 6 and 12 months post-randomisation
5. Anxiety severity using the Generalised Anxiety Disorder scale (GAD-7) at 4, 6 and 12 months post-randomisation
6. General quality of life captured by the EQ-5D-5L at 4, 6 and 12 months post-randomisation
7. MS-specific quality of life captured by the MSIS v29 at 4, 6 and 12 months post-randomisation
8. Physical Activity using the International Physical Activity Questionnaire short form (IPAQ-SF) at 4, 6 and 12 months post-randomisation
9. Health and social care utilisation using a Modified Adult Service Use Schedule (ADSUS) at 6- and 12-month post-randomisation
10. Safety, assessed through collection of Adverse Events and Serious Adverse Events throughout the trial (monthly until 6 months then again at 12 months post-randomisation)

Previous secondary outcome measures:

1. Fatigue impact measured by the Fatigue Severity Scale (FSS) that captures the impact of fatigue on daily functioning at 4, 6 and 12 months post-randomisation
2. Clinically meaningful improvement in fatigue severity, defined as a reduction of >2.3 points from baseline in the total CFQ score, consistent with estimates of the minimum clinically important difference (binary outcome) at 4 and 12 months post-randomisation
3. Clinically meaningful improvement in fatigue impact, defined as a reduction of ≥0.45 points from baseline in the mean FSS score (binary outcome)
4. Depression severity using the Patient Health Questionnaire (PHQ-9) at 4, 6 and 12 months post-randomisation
5. Anxiety severity using the Generalised Anxiety Disorder scale (GAD-7) at 4, 6 and 12 months post-randomisation
6. General quality of life captured by the EQ-5D-5L at 4, 6 and 12 months post-randomisation
7. MS-specific quality of life captured by the MSIS v29 at 4, 6 and 12 months post-randomisation
8. Health and social care utilisation using a Modified Adult Service Use Schedule (ADSUS) at 6- and 12-month post-randomisation
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Completion date
05/03/2027

Eligibility

Key inclusion criteria
People living with MS will be eligible if they:
1. Are 18 years of age and over
2. Able to read and communicate in English

3. Are a resident in England, Wales or Scotland
4. Have a confirmed diagnosis of MS
5. Have sufficient vision and manual abilities to use a smartphone or tablet
6. Experience clinical levels of fatigue, scoring ≥4 on the Chalder Fatigue Questionnaire (CFQ), when using bimodal scoring

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
99 Years

Sex
All

Total final enrolment
380

Key exclusion criteria
Potential participants will be excluded if they:
1. Currently undertaking another behavioural or exercise/balance fatigue management programme, other behavioural treatments*
2. Have started on a new disease-modifying treatment for their MS within the last 6 months**
3. Have started a new antidepressant or fatigue medication within the past 3 months**
4. Are currently experiencing severe mental health problems, including psychosis, bipolar disorder or active thoughts of self-harm that are not being appropriately managed, assessed by self-report
5. Score of 11 or under out of 15 on the Mini Montreal Cognitive Assessment, which denotes moderate or severe cognitive impairment (MoCA)
6. Are unable to give informed consent (for example, due to reduced mental capacity)

*These participants will have the option of being recontacted by the trial team once they have completed their current treatment to be rescreened for entry into the trial.

**These participants will have the option of being recontacted by the trial team once they have been on their treatment for sufficient time to be rescreened for entry into the trial.

Please note, participants will only be recontacted up until the end of the recruitment period (likely October 2025), as this is the last possible timepoint for enrolment on the trial in order to complete 12-month data collection.

Date of first enrolment

21/08/2025

Date of final enrolment
05/03/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Guy's and St Thomas NHS Foundation Trust
Guy's Hospital
Great Maze Pond
London
England
SE1 9RT

Study participating centre
King's College London
Health Psychology Section
Bermondsey Wing
Guy's Campus
Great Maze Pond
London
England
SE1 9RT

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
Guy's and St Thomas' NHS Foundation Trust

ROR
https://ror.org/00j161312

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Multiple Sclerosis Society

Alternative Name(s)
mssocietyuk, MS Society UK, Multiple Sclerosis Society UK, Multiple Sclerosis Society of Great Britain and Northern Ireland, The MS Society, MS Society

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		11/08/2026	10/11/2026	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes