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A Randomised Controlled Trial with parallel process evaluation and health economic analysis to evaluate a nutritional management intervention, OptiCALS, for patients with Amyotrophic Lateral Sclerosis: Study Protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-096098
Article Type:	Protocol
Date Submitted by the Author:	04-Nov-2024
Complete List of Authors:	<p>Peace, Arron; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research White, David; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Hackney, Gemma; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Bradburn, Mike; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Norman, Paul; University of Sheffield, Department of Psychology White, Sean; Sheffield Teaching Hospitals NHS Foundation Trust Al-Chalabi, Ammar; King's College London, Department of Neuroscience Baird, Wendy; The University of Sheffield, Sheffield Centre for Health and Related Research Beever, Daniel; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Cade, Janet; University of Leeds, School of Food Science and Nutrition Coates, Elizabeth; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Cooper, Cindy; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Ezaydi, Naseeb; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Halliday, Vanessa; The University of Sheffield, Sheffield Centre for Health and Related Research Shaw, Pamela; The University of Sheffield, 6Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational Neuroscience Stavroulakis, Haris; The University of Sheffield, 6Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational Neuroscience Waterhouse, Simon; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research Young, Tracey; The University of Sheffield, School of Health and Related Research McDermott, Christopher; The University of Sheffield, 6Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational Neuroscience</p>

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	Maguire, Chin; The University of Sheffield, Clinical Trials Unit, Sheffield Centre for Health and Related Research
Keywords:	Health, NEUROLOGY, Motor neurone disease < NEUROLOGY, NUTRITION & DIETETICS

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Manuscripts

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3 **A Randomised Controlled Trial with parallel process evaluation and health economic analysis to evaluate a**
4 **nutritional management intervention, OptiCALS, for patients with Amyotrophic Lateral Sclerosis: Study**
5 **Protocol**
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8 Arron Peace¹, David White^{1*}, Gemma Hackney¹, Mike Bradburn¹, Paul Norman², Sean White³, Ammar Al-
9 Chalabi⁴, Wendy Baird⁷, Daniel Beever¹, Janet Cade⁵, Elizabeth Coates¹, Cindy Cooper¹, Naseeb Ezaydi¹,
10 Vanessa Halliday⁷, Chin Maguire⁴, Pamela Shaw⁶, Haris Stavroulakis⁶, Simon Waterhouse¹, Tracey Young⁷
11 and Christopher McDermott⁶, on behalf of the HighCALS group.
12
13

14
15 *Corresponding author: d.a.white@sheffield.ac.uk
16

17 ¹Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research. University of Sheffield.
18

19 ²Department of Psychology, University of Sheffield
20

21 ³Sheffield Teaching Hospitals NHS Foundation Trust
22

23 ⁴Department of Neuroscience, Kings College London
24

25 ⁵School of Food Science and Nutrition, University of Leeds
26

27 ⁶Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational
28 Neuroscience (SITraN). University of Sheffield
29

30 ⁷Sheffield Centre for Health and Related Research, University of Sheffield
31

32 ⁸ King's College London, Maurice Wohl Clinical Neuroscience Institute, Department of Basic and Clinical
33 Neuroscience
34

35 **ABSTRACT**

36 **Introduction**

37 Amyotrophic lateral sclerosis (ALS) is a devastating illness which leads to muscle weakness and death usually
38 within around 3 years of diagnosis. People with ALS (pwALS) often lose weight due to raised energy requirements
39 and symptoms of the disease presenting significant challenges to taking adequate oral diet, with those who lose
40 more weight being at a greater chance of earlier death. There is also some evidence to suggest that a higher
41 calorie diet may benefit the disease course in pwALS, but further research is needed.
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46 **Methods and analysis**

47 Two armed, parallel group, superiority, open labelled, RCT, with internal pilot, to assess the effectiveness of an
48 early high calorie diet on functional outcomes in ALS, comprising two treatment arms): 1) Standard care, 2)
49 Standard care with additional active management using the OptiCALS complex intervention to achieve a high
50 calorie diet (initially randomised 1:1, then 1:2 following a protocol amendment). Using a food first approach,
51 pwALS will be encouraged and supported to follow a diet that meets an individualised calorie target from food
52 before prescribing oral nutritional supplements. 259 pwALS will be recruited from up to 20 ALS centres across
53 the United Kingdom and Republic of Ireland and followed-up for a period of 12 months. Primary outcome is
54 functional change measured over 12 months, using the ALSFRS-R. Secondary end points include measures of
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functional health, quality of life, calorie intake and weight, as well as time to gastrostomy and survival. A Health economic analysis and process evaluation will also be undertaken.

STRENGTHS AND LIMITATIONS

- The study builds upon 4 years of formative research exploring attitudes, as well as enablers and barriers, to nutritional support for pwALS developed with specialists, pwALS and their carers.
- The intervention is designed to be delivered in the NHS, by non-specialists enabling an easier roll-out into clinical services if found to be beneficial.
- The study allows data collection and intervention delivery remotely. This enables participants to access the intervention where it may not otherwise be feasible due to disability.
- Due to the nature of the intervention it is not possible to blind participants and investigators to treatment allocation; however, blinded outcome assessors are used to facilitate remote data collection. The use of remote data collection may risk inaccuracies in some outcome measures (height, weight, spirometry).

Ethics and dissemination

The trial was approved by Greater Manchester – North West Research Ethics Committee, reference 20/NW/0334 on 8th of September 2020. We will publish the study findings in peer-reviewed academic journals and present at local, national and international conferences where possible.

Patient and Public Engagement

Patients and the public have been involved in all aspects of the study. The OptiCALS clinical trial builds on the back of 5 years of work (HighCALS programme) designed to understand the current national service models, the beliefs of stakeholders and the development of behaviour change strategies to support and improve nutritional interventions. The OptiCALS trial has been developed in collaboration with a variety of stakeholders including clinicians, nutritionists, psychologists as well as people living with MND, and their carers. This includes early consultation on study design, outcome measures and recruitment strategies. The OptiCALS Program Steering Committee consist of clinicians, methodologists and PPI members and meet regularly to offer continued input in to the conduct, analysis, publication and future work of the study.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a devastating neurodegenerative disorder. The annual incidence is 1.5-2.5 per 100,000 with usual survival of around 3 years (1, 2). Affected individuals experience a progressive weakness of limb muscles, loss of speech, chewing and swallowing problems, eventually succumbing to the consequences of respiratory failure due to respiratory

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3 muscle weakness (3). There is no curative treatment for ALS (4). Riluzole, the only drug treatment to have an
4 effect on survival, slows progression by approximately three months (5).
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7 Malnutrition and weight loss are well recognised poor prognostic factors in ALS (4, 6, 7). Body Mass Index
8 (BMI) is an independent predictor of survival in ALS, with higher BMI (i.e. 30-35) having a protective effect and
9 lower BMI associated with a worse prognosis (8). In patients with weight loss of 5% or more at diagnosis, there
10 is a two-fold increase in risk of death, compared to those who have lost less than 5% of their usual pre-morbid
11 weight (7, 9-11). This is compounded by hypermetabolism, with resting energy expenditure being, significantly
12 higher than in healthy individuals (12-16). Post-diagnostic changes in BMI have been shown to predict survival,
13 with those with a slower decline in BMI or increase in weight showing better prognosis (16,17).
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18 Current guidance on nutritional management with regard to assessment of nutritional status, total daily energy
19 expenditure calculations, appropriate dietary intake or oral nutritional supplementation are based upon weak
20 evidence. Surveys indicate a lack of knowledge in healthcare professions regarding the nutritional management
21 of ALS (29). The poor evidence base may also help explain the poor nutritional outcomes observed in pwALS (18-
22 20).
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27 Metabolic defects and an energy deficit are an early feature of ALS pathology and not simply a consequence of
28 denervation and advanced disease (1, 21). Encouragingly, correction of the energy deficit with a high calorie diet
29 extended life by 20% in an ALS mouse model (22). Moreover, in ALS patients, a small pilot study indicated a
30 potential survival advantage and tolerability of a high calorie diet (23). Two recent randomised trials have
31 investigated this further, but both studies have limitations. A single centre RCT of 88 pwALS compared nutritional
32 counselling (with or without a mHealth app) versus standard care (24). The study had low power and failed to
33 show a significant difference in weight but did signal a potential benefit of increased calorie intake on functional
34 decline. Ludolph et al recruited 201 pwALS to a RCT comparing a high-fat nutritional supplement with placebo
35 (25). The study showed no overall benefit on survival but did detect a significant benefit in fast-progressing
36 patients. It is not clear whether the intervention increased calorie intake as this was not reported. The study also
37 experienced high drop-out. In addition, two recent small-scale systematic reviews with meta-analyses showed
38 no significant difference in ALSFRS-R in pwALS taking a high calorie supplementation compared with control
39 groups. It was highlighted that studies included were insufficiently powered, and therefore the reviews
40 concluded that a high quality, large-scale RCT was required (26, 27).
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49 There is a need for a high quality, adequately powered RCT, comparing a complex nutritional intervention to
50 standard care, in order to confirm the potential of a high calorie diet to influence the disease course in ALS. The
51 National Institute for Health Research (NIHR) funded the HighCALS Programme Grant to meet this need. It
52 comprises a comprehensive programme of research to develop and evaluate an intervention, OptiCALS, to
53 increase calorie intake in pwALS. Earlier work packages developed and piloted the OptiCALS intervention
54 (28-32). The study described in this protocol will evaluate that intervention.
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59 OBJECTIVES

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1. A randomised controlled trial to determine the effect of the OptiCALS intervention on both clinical and participant related outcomes.
2. A process evaluation to facilitate interpretation of the RCT results and offer insights about how best to deliver the intervention in the real world.
3. A health economic evaluation to assess the cost-effectiveness of the OptiCALS intervention relative to current standard treatments available in the NHS.

METHODS AND ANALYSIS

Trial Design

Two armed, parallel group, superiority, open labelled, RCT, with internal pilot, to assess the effectiveness of an early high calorie diet on functional outcomes in ALS.

Adaptations in response to the COVID-19 pandemic

The OptiCALS study has undergone significant changes to make the study safe and deliverable during the COVID-19 pandemic. In the original study design, participants would have to attend hospital visits to enable all data collection, as well as the delivery of the study intervention. After a delay to study launch, the study was redesigned to enable participant consent, data collection and intervention to be delivered remotely. This allowed the delivery of the study in a COVID-19 safe manner. Where participants attend hospital during a data collection window, participant blood is also collected for analysis. As the intervention was designed to be deliverable online, there were no changes made to intervention.

Participant identification

Participants are recruited from up to 20 sites delivering care to people with ALS.

Inclusion and exclusion criteria

Inclusion Criteria for pwALS:

1. Age 18 years or older.
2. Diagnosis of ALS by the Gold Coast criteria
3. Within 2 and a half years of onset of muscle weakness
4. Stabilised on riluzole for one month or not on riluzole.

Inclusion criteria for caregivers:

1. Aged 18 years and over.
2. Primary informal caregiver of a person with ALS who has consented to participate in the trial (either living with the person with ALS or a close family member or friend).

Exclusion Criteria for pwALS only:

1. Comorbidity that would affect survival or metabolic state (e.g. unstable thyroid disease or unstable diabetes mellitus).
2. Using a gastrostomy tube for feeding (those using a gastrostomy tube for fluid or medication are not excluded).
3. BMI \geq 35kg/m².

Exclusion Criteria for pwALS and caregivers:

4. Lacking capacity to provide fully informed written consent, verbal consent (for those who cannot provide written consent), or consent via the use of a communication aid.
5. Previous participation in the HighCALS research programme
6. Unable to understand written and spoken English

Participant approach and recruitment

A sample of pwALS will be identified by local hospital systems (notes, electronic systems) or through self-identification via study advertising (local posters/leaflets, social media, MNDA, patient organisation websites). Those pwALS who are potentially eligible will be approached with an introductory letter, Participant Information Sheet (PIS) and Consent Form either via post, during a face-to-face routine clinic visit, or via email/post during/following a routine remote clinic appointment. Those potential participants sent the information via email or in the post will be followed up within a week by the researcher / healthcare professional to discuss the study over the phone and answer any further questions.

Remote consent procedures

If a face-to-face visit is not possible, a remote consent appointment will be arranged to take place via video or phone call, where either: 1) consent will be collected electronically (by email); 2) full verbal consent will be audio recorded using an encrypted Dictaphone, with the permission of the potential participant; 3) the paper consent form will be completed by the participant and returned by post; or, 4) an independent witness will join the call and sign consent on behalf of the participant.

Randomisation

Participants will be allocated to one of two groups: standard treatment; standard treatment plus OptiCALS intervention (originally in a 1:1 ratio, amended during the study to a 1:2 ratio). Randomisation is via a web-based randomisation system, employing non-deterministic minimisation by including a random element into the allocation algorithm. The minimisation factors will be:

- Study site
- ALSFRS-R trajectory since symptom onset (a measure of functional decline that can predict individuals with fast and slow disease progression)

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3 - Riluzole use
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5 The minimisation will be hosted by the CTRU randomisation system, SCRAM – a remote secure server internet-
6 based system. Access to the allocation list will only be granted to those responsible for cleaning the data and
7 preparing unblinded data summaries during the recruitment and follow-up. For all other members of the trial
8 team, the allocations will be concealed until recruitment and data collection are complete.
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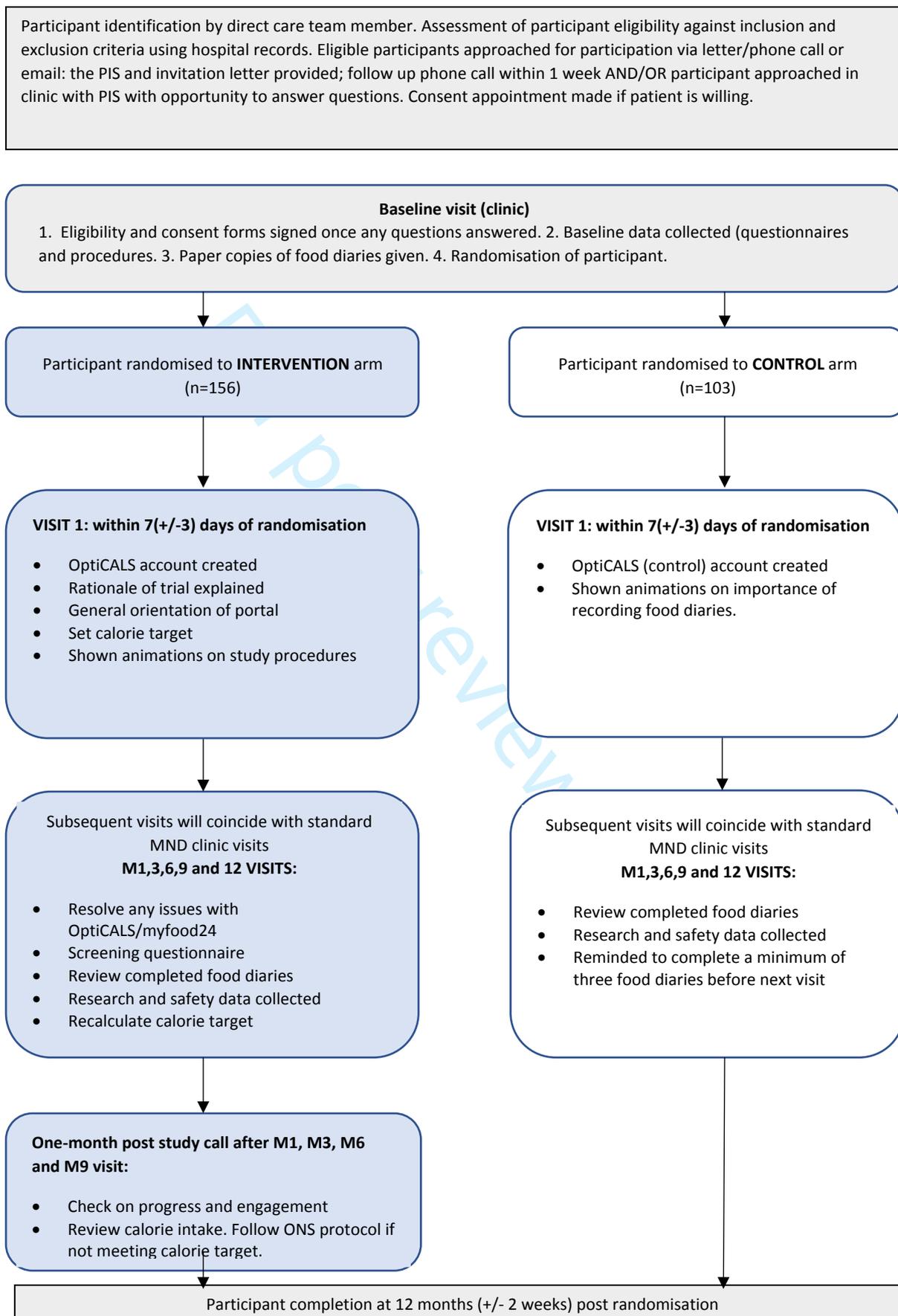
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12 A CTRU statistician who is not otherwise associated with the trial will generate the allocation sequence.

13 Named persons on the delegation log, who are trained in research procedures, will allocate participants by
14 logging into SCRAM and entering basic demographic information.
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17 **Blinding**
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19 The outcome assessors will be blinded to treatment allocation during the trial recruitment and follow-up. Site
20 staff who are delivering the intervention will not be responsible for collecting study outcome measures. Any
21 instances of unblinding of the outcome assessor will be documented within the CRF and be reported as a
22 secondary outcome. Study statisticians, health economists and those collecting outcome data will remain
23 blinded while the study is ongoing.
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Figure 1 Participant flow diagram



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Study Intervention

The OptiCALS portal will allow estimation of the participant's total daily energy expenditure (TDEE) using the ALS specific Kasarskis equation (33). At the first intervention study visit, an initial calorie target will be set based on the participant's current calorie intake and their TDEE estimate (whichever is higher). At subsequent intervention study visits, the calorie target will be adjusted taking into account the participant's current BMI, weight direction and TDEE estimate. Patients who are losing weight will be set a calorie target that is 400 calories above their current calorie intake, unless their current calorie intake is more than 400 calories below the TDEE estimate, in which case the TDEE estimate will be their calorie target.

Participants will work with their healthcare professional to develop a dietary strategy using a food fortification first approach (with or without Oral Nutritional Supplements (ONS)) to meet their calorie target and in doing so, maintain or increase their weight. Specific areas of the portal provide information and resources for pwALS, carers, and healthcare professionals to help overcome barriers to eating a high calorie diet. These are summarised in Table 1 below. The need for ONS and/or enteral feeding will be reviewed systematically throughout the study, and discussed when participants are unable to meet their calorie target through a food first approach.

The OptiCALS portal has five modules, with further sub-sections.

Table 1: Intervention modules

Module	Description
My Food Diary	<ul style="list-style-type: none"> Record dietary intake (A minimum of 3 days food diaries will be collected prior to each study visit to provide an estimate of current calorie intake) Estimate daily calorie intake
How am I doing?	<ul style="list-style-type: none"> Presents participants with their individualised calorie target Presents charts/graphs indicating current calorie intake versus calorie target Presents charts/graphs of participants' weight
All Resources	<ul style="list-style-type: none"> A range of resources and advice to help participants to meet their calorie targets, including animations, videos, text, PDFs and links to resources external to OptiCALS
My Resources	<ul style="list-style-type: none"> An area to save specific pages from within OptiCALS in one area. Individual pages on OptiCALS can be saved by the healthcare professional, participant and/or carer to the My Resources page. Allow participants to write individual action plans about how they will meet their calorie target Allow participants to view a list of saved 'quick wins', i.e. foods and their calorie values that can be introduced to help them meet their calorie target
Why boost my calories and weight?	<ul style="list-style-type: none"> Provides participants and carers with the rationale for why it is important to boost calories and increase weight in ALS

Intervention providers, support and training

RCT sites will allocate, or employ, members of staff from the ALS team to deliver the research and intervention procedures locally. Members of the central project team will support healthcare professionals in the delivery of the intervention:

- All healthcare professionals delivering the intervention will attend a training session run by the central project team before they are able to deliver the intervention to trial participants.
- Ongoing ad hoc support in answering questions, e.g. how to tailor the intervention to participants, via an online discussion group embedded into the healthcare professional area of the OptiCALS portal.

Training will include a face-to-face or virtual (if necessary) session where RCT healthcare professionals will be orientated to the portal from logging on through to discussing calorie needs and tailoring the intervention. A user guide for healthcare professionals will form part of the materials they use to facilitate intervention sessions with trial participants. Healthcare professionals will complete session logs to ensure delivery of the intervention as intended and these will both facilitate tailoring the intervention to individual participant needs as well as ensuring ongoing fidelity monitoring. Participants without access to the equipment necessary to engage with the OptiCALS intervention (i.e. an internet enabled device) will be provided with these, including access to a video call enabled device where clinic visits are not possible.

Intervention procedures: Overview of visits

The intervention will be delivered by the healthcare professional primarily during face-to-face sessions if possible, or via telephone / video calls if necessary over the course of the participant's involvement, from the first intervention visit to 12 months post randomisation.

Prior to starting the intervention, both intervention and control participants will meet with the food diary reviewer to be trained how to log food diary entries on to the myfood24 system area of the portal using three food diaries that they will have been asked to complete before the intervention visit. They will also be familiarised with the portal, ahead of their first visit.

Intervention Visit 1: Week 1

The first intervention visit will take place approximately 1-2 weeks after recruitment into the trial and will be arranged at a convenient time and place (via telephone / video call if necessary) for the participant and carer, with sufficient time to carry out the tasks (approximately 2 hours). The healthcare professional will login to the participant's account.. At this visit, the key tasks will be to generally orientate the participants and/or carer to the modules within the portal but, more importantly, to explain the rationale for the trial, i.e. the importance of increasing calorie intake to maintain or increase weight.

The healthcare professional will direct the participant to the 'How I am doing: calories?' page of the website to view their current calorie intake. The healthcare professional will then complete the ALSFRS-6 questions with the participant to calculate the participant's total daily energy expenditure (TDEE) using the ALS specific Kasarskis equation, that is embedded into the healthcare professional part of OptiCALS portal. This (or the

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3 participant's current calorie intake, if higher) will be used as the initial calorie target. Participants will be directed
4 to the 'Calorie Boosting Quick Wins' page and encouraged to identify foods that could be easily added to their
5 daily diet to help them meet their calorie target. The participant will be asked to complete, and enter, another
6 three food diary entries before their next intervention visit.
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9 10 Intervention Visit 2-5: Months 1, 3, 6 and 9

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12 At subsequent intervention visits or video/phone calls, the researcher / healthcare professional will review the
13 three food diaries completed by the participant and ensure they provide an accurate record of what they ate
14 and drank. These visits will last approximately 1 hour. The healthcare professional will complete the ALSFRS-6
15 questions again and enter the participant's current weight. This information, along with the participant's current
16 calorie intake, will be used to adjust the participant's calorie target.
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20 Any issues relating to the accessibility and use of myfood24 or the OptiCALS website will be discussed by the
21 healthcare professional delivering the intervention and support given to resolve these. The healthcare
22 professional will direct the participant to the 'How I am doing: calories?' page to identify if there is a calorie
23 deficit and then view the 'Calorie Boosting Quick Wins' or discuss the use of oral nutritional supplements to
24 bridge any calorie gap, as appropriate to each participant. The healthcare professional will also complete a
25 screening questionnaire which will suggest specific pages that can be saved to the participant's 'My Resources'
26 section of the OptiCALS website to help them boost the number of calories in their diet and/or manage common
27 barriers to eating a high calorie diet. Finally, participants will be informed that they will receive a follow-up call
28 in a month and will be asked to complete, and enter, three additional food diary entries in the week before the
29 follow up call. Onward referral for dietetic advice, gastrostomy, and speech and language therapy will be as per
30 standard clinical practice. The PI at each site will communicate with the Dietitian the rationale for the trial and
31 request that they attempt to meet the calorie target set in OptiCALS when devising dietetic treatment plans. If
32 participants are required to start ONS as a result of their inability to meet their calorie target, then they will
33 initially be provided with a sample pack to try before an order is submitted. This will be followed up by a brief
34 phone call from the healthcare professional to check that they are happy with the ONS products provided.
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37 38 39 40 41 42 43 44 Follow-up Phone Calls After Intervention Visits 2-5: Months 2, 4, 7 and 10

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46 All participants will receive a follow-up phone call from their healthcare professional one month after each
47 intervention visit to review their current calorie intake and any changes that have, or haven't, been made to
48 meet the new calorie target. Participants will be asked to complete, and enter, three additional food diary entries
49 in the week before their next intervention visit.
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52 53 Final intervention visit: Month 12

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55 At the final intervention visit, the researcher / healthcare professional will review their final three food diaries.
56 Participants will continue to be able to access the OptiCALS portal until the study ends. However, following the
57 end of the 12 month trial period, no further calorie targets will be set by the supporting healthcare professionals.
58 Also, the healthcare professionals will only continue to discuss the use of OptiCALS in clinic visits if they feel they
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3 have the resource to provide this support. There will be no expectation for the healthcare professionals to
4 continue to provide this support and they will no longer receive excess treatment costs for this time.
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7 The participant's GP and neurologist will be notified with an end of trial letter. If the participant is taking oral
8 nutritional supplements at the end of the trial period, the PI will write to the participant's GP and neurologist
9 (and dietitian if involved), advising them that the participant has finished the trial and informing them of the
10 specific oral nutritional supplement they have been taking, including the dose and calorie value, so that the same
11 supplement or a similar product can be continued as part of standard care.
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15 **Usual care**

16 Usual care participants will receive the current standard nutritional management at each study site. Prior to
17 their first visit, they will receive training on the myfood24 system. They will complete the myfood24 diary data
18 through the 'my food diary' module, the only section of the OptiCALS portal available to the control arm
19 participants. OptiCALS intervention modules will not be available to control arm participants, carers, and other
20 health professionals at the sites and, as such, will not be used to influence dietary management.
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26 **STUDY OUTCOMES**

27 Participants will be followed up at week 1, month 1, month 3 and then at three month intervals until month 12
28 or until death if this is earlier. Survival status of each participant will be reassessed at the end of the study
29 (between 12 and 35 months post-randomisation depending on when the patient was recruited). All outcome
30 measures will be collected by a blinded assessor, except blood samples, calorie intake, adverse events and
31 acceptability of the intervention. Where clinic visits are not possible (e.g. if shielding due to Covid-19) data will
32 be collected at the participants' home, either in person (if feasible), via video call, or via phone call if a video call
33 is not possible. Where physical measures are to be collected via video or phone call, participants will be sent any
34 equipment needed to complete these in advance of the appointment, as well as being directed to information
35 about taking the measures in a separate section of the OptiCALS portal, including step by step videos. Training
36 will also be provided by the blinded assessor prior to any measurements being taken. If neither a face-to-face or
37 remote follow up appointment can be arranged, the questionnaire outcomes ALSFRS-R, WHOQOL-BREF, EQ5D-
38 3L, Healthcare resource use and acceptability questionnaire (intervention group only) can be self-completed by
39 post or electronically via email.
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49 **Primary outcome**

50 Functional change over 1 year as measured longitudinally by the ALS Functional Rating Scale (ALSFRSR) (34), a
51 validated rating instrument for monitoring the progression of disability in patients with ALS that correlates with
52 survival and quality of life.
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57 **Secondary outcomes**

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3 **CAFS:** This analysis ranks clinical outcomes on the basis of survival and change in ALSFRSR scores (35). Each
4 patient's outcome is compared to every other patient's outcome, assigned a score, and the summed scores are
5 ranked. The mean rank score for each treatment group can then be calculated.
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8 **Quality of life for patients: WHOQOL-BREF:** A 26-item quality of life measure validated for use in pwALS (36).
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10 **EQ-5D-3L:** A standardised measure of health status, covering five areas with three scoring options for each,
11 developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and
12 economic appraisal (37). Preference-based utility weights will be applied to EQ-5D-3L responses using UK
13 population based values from the UK value set (38). Utility values range from 1-perfect health to 0 death, with
14 negative scores indicating states worse than death. This will be completed by both patients and carers.
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18 **Respiratory function: Slow vital capacity (SVC):** A measure of respiratory muscle strength shown to correlate
19 with survival in ALS, taken by spirometry. FEV6 will also be taken via spirometry. Participants will be supplied
20 with handheld spirometers. Participants who are able to use a smartphone-reliant spirometer will take SVC and
21 FEV6 measurements. Participants who cannot use a smartphone-reliant spirometer will take FEV6
22 measurements only. Both measurements are considered acceptable alternatives based on existing literature
23 (39-43).
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28 **Anthropometric assessments:** Triceps skin fold, mid arm circumference and calf circumference measurements
29 will be taken using standardised methods (44). Given the asymmetry in ALS the mean values taken from both
30 upper and lower extremities will be used. Fat mass and fat free mass will then be estimated. If outcomes are
31 measured remotely, triceps skin fold will not be taken and calf circumference will be used as the primary method
32 of fat mass and fat free mass estimation.
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36 **Overall survival:** Defined as time from randomisation to date of death. Surviving patients will be censored at the
37 date last known to be alive
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40 **Total calorie intake:** Self-completed by participants via myfood24.org (accessed via the OptiCALS portal).
41 Participants will be asked to complete, and enter, three food diary entries in the week before each study visit.
42 Access to an internet-enabled device will be provided for participants if needed.
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46 **Change in weight:** % weight change throughout the study period
47

48 **Change in Body Mass Index (BMI):** The BMI calculation divides an adult's weight in kilograms by their height in
49 metres squared. An existing record of measured height will be used if available in the patient notes. If no
50 measured height is available, this will be taken remotely.
51
52

53 **Time to gastrostomy:** Defined as time from randomisation to date of gastrostomy procedure. If no procedure is
54 recorded patients will be censored at the date last known to be without gastrostomy.
55
56

57 **Acceptability of the intervention (intervention group only):** Self-reported using a bespoke 11-item
58 questionnaire structured around the Theoretical Framework of Acceptability (45).
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3 **Healthcare resource use:** A questionnaire to measure use of healthcare services, used in the calculation of the
4 cost-effectiveness of the intervention.
5

6 **Adverse events.**

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9 **Blood tests:** Fasting lipids, albumin, lactate, renal function, thyroid function, neurofilament (Nf) serum,
10 creatinine and C-reactive protein. If face to face visits are not possible, these measures will not be taken. The
11 funding for analysis of Nf samples is via separate charitable funding, and as such, samples may be stored and
12 analysed centrally beyond the completion of the trial.
13
14

15 **Safety**

16
17 Adverse events (AEs) may be identified at any point during the study via routine follow-up, contact from the
18 participant and/or carer, on site or remote monitoring or other sources (medical notes etc.). Participants and/or
19 carers can inform site healthcare professionals of adverse events at any point of the follow up period. Related
20 Serious Adverse Events (SAEs) will be reported to the Sponsor, Research Ethics Committee and the Project
21 Steering Committee providing safety oversight for the study.
22
23

24 There are no Adverse Events excluded from collection although expected events related to ALS disease
25 progression will not be reported as a SAE, unless the event is more severe than would normally be expected for
26 a participant or if the investigator considers there to be a causal relationship between the trial intervention and
27 the event.
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30 **Participant retention**

31 Participant retention is promoted through regular communication from the research team which clearly explains
32 the importance of completing outcome data regardless of study arm. This message is reinforced at enrolment
33 and all follow-up points. A flexible approach to study visits, and delivery of intervention also aims to maximise
34 participant retention, including a series of withdrawal options aiming to minimise participant burden, whilst
35 maximising retention and data collection. Where participants are finding participation in the study challenging,
36 but otherwise want to continue in the trial, options for reduced data collection throughout the remainder of the
37 study will be discussed.
38
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40 **Intervention completion and withdrawal**

41 Study completion is defined as 12 months after the date of randomisation. There are 3 withdrawal options
42 available to participants:
43
44

- 45 1. Withdrawal from the OptiCALS intervention only, i.e. no further intervention delivery visits but the
46 participant remains in the trial. The participant and/or clinician can make the decision to discontinue the
47 intervention for any reason.
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2. Withdrawal from the OptiCALS trial, but with consent for the collection of essential routine data from hospital notes, i.e. survival status / cause of death and ALSFRS-R scores, where available. No further intervention or research visits will be conducted with the participant.

3. Withdrawal from the OptiCALS trial entirely, with no consent given to collect essential routine data. Unless specified by the participant, all data collected up to this point will be used in the analysis and no further intervention or research visits will be conducted.

Where participants have withdrawn, but consent to routine clinical data being collected, ALSFRS-R will be collected from their medical records along with survival status.

Sample Size

The sample size was derived by simulation using the PRO-ACT ALS clinical trials data repository to estimate the parameters of interest (46). The ALSFRS-R at entry was assumed to have a mean (SD) of 37 (6) and a mean monthly decline of 1 unit over the 12-month duration of follow-up, with successive values following with an AR1 correlation with $\rho=0.9$. A difference of +0.25 units per month (i.e. a monthly decline of 0.75 in the intervention arm versus 1.00 in the control arm) was taken as a clinically meaningful effect. The probability of death in each three month period was assumed zero up to month 3 and estimated as $91 \times \exp[-0.115 \times (\text{ALSFRS-R at previous visit}) - 3.95]$ thereafter, equating to a 18% death rate for the control group and 15% in the intervention at twelve months; these participants are included in the analysis and allocated a functional score of zero. Withdrawal was assumed to occur at a rate of 5% per quarter in both groups, again starting after the month 3 visit. With a two-sided alpha of 5%, a power of 85% and with the first 100 participants allocated in a 1:1 ratio and the remaining participants allocated 1:2 (standard care vs OptiCALS intervention), this requires a sample size of 103 in the standard care arm and 156 in the OptiCALS intervention arm, $n=259$ participants in total.

DATA ANALYSIS

Primary outcome

The primary outcome ALSFRS-R will be analysed longitudinally using a mixed model including time, treatment and their interaction together with variables used in the minimisation process. The area between the two ALSFRS-R curves will be derived using a linear combination of the coefficients for treatment and the interaction of treatment with time, and will be presented alongside its 95% confidence interval and p-value. The difference in ALSFRS-R will also be quantified separately at each timepoint.

The primary analysis will be intention-to treat and will include all patients for whom data are collected or who have died; an ALSFRS-R functionality score will be assigned for all timepoints scheduled after the date of death. Sensitivity analyses will be performed to assess the robustness of the findings to distributional assumptions, baseline characteristics and imbalance, missing data and non-adherence (47).

Secondary outcome

Secondary outcomes will be analysed and reported in the same manner as the primary outcome, with the exception of time to event outcomes which will be analysed using Cox regression, and the combined analysis of function and survival which is a rank-based (non-parametric) test described in Berry et al. (35). Analyses will be performed on an intention-to-treat basis and all statistical tests will be two-tailed at 5% significance level. Further details will be provided in a full statistical analysis plan.

Process evaluation

Alongside the RCT, a mixed-methods process evaluation will be undertaken. This includes qualitative interviews with pwALS, their carers and healthcare professionals (HCPs) to explore context, implementation and mechanisms of impact. Analysis of a sample of audio-recorded consultations and HCP intervention visit logs will be used to assess fidelity of intervention delivery. In addition to this, quantitative data will be collected using surveys administered to the intervention arm to investigate the acceptability of the intervention and data analytics on intervention usage.

All interviews will be transcribed verbatim for analysis. Observation notes will be written up after each visit and reflexive notes will be written up after each qualitative interview to help with data interpretation. The qualitative data will be analysed thematically (48), within the broader framework for process evaluations recommended by the Medical Research Council (49). To understand the wider implementation issues, the analysis will draw upon Normalisation Process Theory (50) and the Theoretical Framework of Acceptability (45). To consider influences on the behaviour of individual pwALS, the COM-B model will be used as an overarching theoretical framework [62]. NVivo software (QSR International) will be used to help structure the analysis.

Health economics

A cost-utility analysis will be undertaken using the resource use, EQ-5D-3L and mortality data from the trial. The analysis will take a NHS and a broader societal perspective, with an additional analysis that incorporates carer QALYs within the incremental cost-effectiveness ratio (ICER). This will be supplemented with decision analytic modelling to estimate lifetime cost-effectiveness for the patient cohort recruited to the study.

Patient and Public Involvement

People with lived experience of ALS (pwALS) were involved in all areas of the programme. This included earlier research exploring enablers and barriers to eating for pwALS, intervention development and data collection. Patient and Public Involvement was incorporated in the delivery of the study, through membership in the Steering and Management committees.

ETHICS AND DISSEMINATION

Governance

Sheffield Clinical Trials Research Unit on behalf of the sponsor (Sheffield Teaching Hospitals NHS Foundation Trust) coordinates the trial. The Chief Investigator, project co-applicants, members of the data management team, sponsor, trial manager and other representatives form the Project Management group, who oversee the operation of the trial and through which amendments will be communicated. The Project Steering Committee, comprised of clinicians, statisticians, trialists and PPI representatives provides independent oversight. The independent PSC also undertake the activities of the DMEC providing data monitoring and oversight.

Ethical approval

The trial was approved by Greater Manchester – North West Research Ethics Committee, reference 20/NW/0334 on 8th of September 2020. The committee will be notified of amendments to the trial as appropriate.

ISRCTN Registration

The program was registered on the ISRCTN registry on 7/12/20 reference: ISRCTN30588041.

Dissemination

We will publish the study findings in peer-reviewed academic journals and present at local, national and international conferences where possible. We will publish a short summary of the results on the OptiCALS trial website, accessed by trial participants as well as relevant interest groups.

Acknowledgements

Authors' contributions

CM, DW, AA-C, WB, MB, JC, EC, CC, VH, PN, PS, HS, SW and TY contributed to funding acquisition and study design. CM, AP, DW, GH, DB, MB, EC, SD, NE, CM, PN, ES, SW, SW, JW and TY contributed to development of the protocol and study procedures. AP, DW, GH and CM produced the initial draft of this paper. All authors contributed to reviewing and revising the final version prior to submission.

The 'HighCALS group' consists of the named authors and Elaine Scott, Jonathan Woodward and Shamila Ditta.

Funding statement

This work was funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (PGfAR) programme grant number RP-PG-1016-20006 and supported by NIHR Sheffield Biomedical Research Centre. CM is supported by an NIHR Professor Award.

Competing interest's statement

AA-C is an NIHR Senior Investigator (NIHR202421). He has been supported by an EU Joint Programme - Neurodegenerative Disease Research (JPND) project through the following funding organisations under the aegis of JPND - www.jpnd.eu (United Kingdom, Medical Research Council (MR/L501529/1; MR/R024804/1) and Economic and Social Research Council (ES/L008238/1)) and through the Motor Neurone Disease Association, My Name's Doddie Foundation, and Alan Davidson Foundation. This study represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. AAC reports consultancies or advisory boards for Amylyx, Apellis, Biogen, Brainstorm, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Qoralis, Sano, Sanofi, and Wave Pharmaceuticals

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BMJ Open

A Randomised Controlled Trial with parallel process evaluation and health economic analysis to evaluate a nutritional management intervention, OptiCALS, for patients with Amyotrophic Lateral Sclerosis: Study Protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-096098.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Apr-2025
Complete List of Authors:	<p>Peace, Arron; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>White, David; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Hackney, Gemma; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Bradburn, Mike; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Norman, Paul; University of Sheffield, Department of Psychology</p> <p>White, Sean; Sheffield Teaching Hospitals NHS Foundation Trust</p> <p>Al-Chalabi, Ammar; King's College London, Department of Neuroscience</p> <p>Baird, Wendy; The University of Sheffield, Sheffield Centre for Health and Related Research</p> <p>Beever, Daniel; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Cade, Janet; University of Leeds, School of Food Science and Nutrition</p> <p>Coates, Elizabeth; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Cooper, Cindy; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Ezaydi, Naseeb; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Halliday, Vanessa; The University of Sheffield, Sheffield Centre for Health and Related Research</p> <p>Shaw, Pamela; The University of Sheffield, 6Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational Neuroscience</p> <p>Stavroulakis, Haris; The University of Sheffield, 6Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational Neuroscience</p> <p>Waterhouse, Simon; The University of Sheffield, Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research</p> <p>Young, Tracey; The University of Sheffield, School of Health and Related Research</p> <p>McDermott, Christopher; The University of Sheffield, 6Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational Neuroscience</p> <p>Maguire, Chin; The University of Sheffield, Clinical Trials Unit, Sheffield</p>

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	Centre for Health and Related Research Group, HighCALs ; The University of Sheffield
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Nutrition and metabolism
Keywords:	Health, NEUROLOGY, Motor neurone disease < NEUROLOGY, NUTRITION & DIETETICS



BMJ Open: first published as 10.1136/bmjopen-2024-096098 on 27 May 2025. Downloaded from <http://bmjopen.bmj.com/> on June 7, 2025 at Agence Bibliographique de l'Enseignement Supérieur (ABES).
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3 **A Randomised Controlled Trial with parallel process evaluation and health economic analysis to evaluate a**
4 **nutritional management intervention, OptiCALS, for patients with Amyotrophic Lateral Sclerosis: Study**
5 **Protocol**
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8 **Arron Peace¹, David White^{1*}, Gemma Hackney¹, Mike Bradburn¹, Paul Norman², Sean White³, Ammar Al-**
9 **Chalabi⁴, Wendy Baird⁷, Daniel Beever¹, Janet Cade⁵, Elizabeth Coates¹, Cindy Cooper¹, Naseeb Ezaydi¹,**
10 **Vanessa Halliday⁷, Chin Maguire¹, Pamela Shaw⁶, Haris Stavroulakis⁶, Simon Waterhouse¹, Tracey Young⁷**
11 **and Christopher McDermott⁶, on behalf of the HighCALS group.**
12
13

14
15 ***Corresponding author: d.a.white@sheffield.ac.uk**
16

17 **¹Sheffield Clinical Trials Unit, Sheffield Centre for Health and Related Research. University of Sheffield.**

18 **²Department of Psychology, University of Sheffield**

19 **³Sheffield Teaching Hospitals NHS Foundation Trust**

20 **⁴Department of Neuroscience, Kings College London**

21 **⁵School of Food Science and Nutrition, University of Leeds**

22 **⁶Division of Neuroscience. School of Medicine and Population Health. Sheffield Institute for Translational**
23 **Neuroscience (SITraN). University of Sheffield**

24 **⁷Sheffield Centre for Health and Related Research, University of Sheffield**

25 **⁸ King's College London, Maurice Wohl Clinical Neuroscience Institute, Department of Basic and Clinical**
26 **Neuroscience**
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33 **ABSTRACT**

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35 **Introduction**

36
37 Amyotrophic lateral sclerosis (ALS) is a devastating illness which leads to muscle weakness and death usually
38 within around 3 years of diagnosis. People with ALS (pwALS) often lose weight due to raised energy requirements
39 and symptoms of the disease presenting significant challenges to taking adequate oral diet, with those who lose
40 more weight being at a greater chance of earlier death. There is also some evidence to suggest that a higher
41 calorie diet may benefit the disease course in pwALS, but further research is needed.
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46 **Methods and analysis**

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48 Two armed, parallel group, superiority, open labelled, Randomised Controlled Trial (RCT), with internal pilot, to
49 assess the effectiveness of an early high calorie diet on functional outcomes in ALS, comprising two treatment
50 arms): 1) Standard care, 2) Standard care with additional active management using the OptiCALS complex
51 intervention to achieve a high calorie diet (initially randomised 1:1, then 1:2 following a protocol amendment).
52 Using a food first approach, pwALS will be encouraged and supported to follow a diet that meets an
53 individualised calorie target from food before prescribing oral nutritional supplements. 259 pwALS will be
54 recruited from up to 20 ALS centres across the United Kingdom and Republic of Ireland and followed-up for a
55 period of 12 months. Primary outcome is functional change measured over 12 months, using the Revised
56 Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRRS-R). Secondary end points include measures of
57 functional health, quality of life, calorie intake and weight, as well as time to gastrostomy and survival. A
58 Health economic analysis and process evaluation will also be undertaken. Participant recruitment is expected
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3 to complete in Sept '25, and participant follow-up is expected to complete in Sept '26. The results of this study
4 are expected in March '27.
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8 **Ethics and dissemination**

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10 The trial was approved by Greater Manchester – North West Research Ethics Committee, reference
11 20/NW/0334 on 8th of September 2020. We will publish the study findings in peer-reviewed academic journals
12 and present at local, national and international conferences where possible.
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16 **STRENGTHS AND LIMITATIONS**

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18
19 - The study builds upon 4 years of formative research exploring attitudes, as well as enablers and barriers,
20 to nutritional support for pwALS developed with specialists, pwALS and their carers.
21
22 - The intervention is designed to be delivered in the NHS, by non-specialists enabling an easier roll-out
23 into clinical services if found to be beneficial.
24
25 - The study allows data collection and intervention delivery remotely. This enables participants to access
26 the intervention where it may not otherwise be feasible due to disability.
27
28 - Due to the nature of the intervention it is not possible to blind participants and investigators to
29 treatment allocation; however, blinded outcome assessors are used to facilitate remote data collection.
30
31 The use of remote data collection may risk inaccuracies in some outcome measures (height, weight,
32 spirometry).
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37 **INTRODUCTION**

38
39 Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a devastating
40 neurodegenerative disorder. The annual incidence is 1.5-2.5 per 100,000 with usual survival of around 3 years
41 [1, 2]. Affected individuals experience a progressive weakness of limb muscles, loss of speech, chewing and
42 swallowing problems, eventually succumbing to the consequences of respiratory failure due to respiratory
43 muscle weakness [3]. There is no curative treatment for ALS [4]. Riluzole, the only drug treatment to have an
44 effect on survival, slows progression by approximately three months [5].
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49 Malnutrition and weight loss are well recognised poor prognostic factors in ALS [4, 6, 7]. Body Mass Index
50 (BMI) is an independent predictor of survival in ALS, with higher BMI (i.e. 30-35) having a protective effect and
51 lower BMI associated with a worse prognosis [8]. In patients with weight loss of 5% or more at diagnosis, there
52 is a two-fold increase in risk of death, compared to those who have lost less than 5% of their usual pre-morbid
53 weight [7, 9-11]. This is compounded by hypermetabolism, with resting energy expenditure being, significantly
54 higher than in healthy individuals [12-16]. Post-diagnostic changes in BMI have been shown to predict survival,
55 with those with a slower decline in BMI or increase in weight showing better prognosis [16,17].
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3 Current guidance on nutritional management with regard to assessment of nutritional status, total daily energy
4 expenditure calculations, appropriate dietary intake or oral nutritional supplementation are based upon weak
5 evidence. Surveys indicate a lack of knowledge in healthcare professions regarding the nutritional management
6 of ALS (29). The poor evidence base may also help explain the poor nutritional outcomes observed in pwALS)
7 [18-20].
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10
11 Metabolic defects and an energy deficit are an early feature of ALS pathology and not simply a consequence of
12 denervation and advanced disease [1, 21]. Encouragingly, correction of the energy deficit with a high calorie diet
13 extended life by 20% in an ALS mouse model [22]. Moreover, in ALS patients, a small pilot study indicated a
14 potential survival advantage and tolerability of a high calorie diet [23]. Two recent randomised trials have
15 investigated this further, but both studies have limitations. A single centre RCT of 88 pwALS compared nutritional
16 counselling (with or without a mHealth app) versus standard care [24]. The study had low power and failed to
17 show a significant difference in weight but did signal a potential benefit of increased calorie intake on functional
18 decline. Ludolph et al recruited 201 pwALS to a RCT comparing a high-fat nutritional supplement with placebo
19 [25]. The study showed no overall benefit on survival but did detect a significant benefit in fast-progressing
20 patients. It is not clear whether the intervention increased calorie intake as this was not reported. The study also
21 experienced high drop-out. In addition, two recent small-scale systematic reviews with meta-analyses showed
22 no significant difference in ALSFRS-R in pwALS taking a high calorie supplementation compared with control
23 groups. It was highlighted that studies included were insufficiently powered, and therefore the reviews
24 concluded that a high quality, large-scale RCT was required [26, 27].
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28 There is a need for a high quality, adequately powered RCT, comparing a complex nutritional intervention to
29 standard care, in order to confirm the potential of a high calorie diet to influence the disease course in ALS. The
30 National Institute for Health Research (NIHR) funded the HighCALS Programme Grant to meet this need. It
31 comprises a comprehensive programme of research to develop and evaluate an intervention, OptiCALS, to
32 increase calorie intake in pwALS. Earlier work packages developed and piloted the OptiCALS intervention
33 [28-32]. The study described in this protocol will evaluate that intervention.
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36 37 38 39 40 41 42 43 44 **OBJECTIVES**

- 45 1. A randomised controlled trial to determine the effect of the OptiCALS intervention on both clinical and
46 participant related outcomes.
- 47 2. A process evaluation to facilitate interpretation of the RCT results and offer insights about how best to deliver
48 the intervention in the real world.
- 49 3. A health economic evaluation to assess the cost-effectiveness of the OptiCALS intervention relative to current
50 standard treatments available in the UK National Health Service (NHS).
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54 55 56 57 58 **METHODS AND ANALYSIS**

Trial Design

Two armed, parallel group, superiority, open labelled, RCT, with internal pilot, to assess the effectiveness of an early high calorie diet on functional outcomes in ALS.

Adaptations in response to the COVID-19 pandemic

The OptiCALS study has undergone significant changes to make the study safe and deliverable during the COVID-19 pandemic. In the original study design, participants would have to attend hospital visits to enable all data collection, as well as the delivery of the study intervention. After a delay to study launch, the study was redesigned to enable participant consent, data collection and intervention to be delivered remotely. This allowed the delivery of the study in a COVID-19 safe manner. Where participants attend hospital during a data collection window, participant blood is also collected for analysis. As the intervention was designed to be deliverable online, there were no changes made to intervention.

Participant identification

Participants are recruited from up to 20 sites delivering care to people with ALS.

Inclusion and exclusion criteria

Inclusion Criteria for pwALS:

1. Age 18 years or older.
2. Diagnosis of ALS by the Gold Coast criteria
3. Within 2 and a half years of onset of muscle weakness
4. Stabilised on riluzole for one month or not on riluzole.

Inclusion criteria for caregivers:

1. Aged 18 years and over.
2. Primary informal caregiver of a person with ALS who has consented to participate in the trial (either living with the person with ALS or a close family member or friend).

Exclusion Criteria for pwALS only:

1. Comorbidity that would affect survival or metabolic state (e.g. unstable thyroid disease or unstable diabetes mellitus).
2. Using a gastrostomy tube for feeding (those using a gastrostomy tube for fluid or medication are not excluded).
3. BMI \geq 35kg/m².

Exclusion Criteria for pwALS and caregivers:

4. Lacking capacity to provide fully informed written consent, verbal consent (for those who cannot provide written consent), or consent via the use of a communication aid.
5. Previous participation in the HighCALS research programme
6. Unable to understand written and spoken English

Participant approach and recruitment

A sample of pwALS will be identified by local hospital systems (notes, electronic systems) or through self-identification via study advertising (local posters/leaflets, social media, Motor Neuron Disease Association, patient organisation websites). Those pwALS who are potentially eligible will be approached with an introductory letter, Participant Information Sheet (PIS) and Consent Form either via post, during a face-to-face routine clinic visit, or via email/post during/following a routine remote clinic appointment. Those potential participants sent the information via email or in the post will be followed up within a week by the researcher / healthcare professional to discuss the study over the phone and answer any further questions. Example participant consent forms are attached as supplementary materials to this manuscript.

Remote consent procedures

If a face-to-face visit is not possible, a remote consent appointment will be arranged to take place via video or phone call, where either: 1) consent will be collected electronically (by email); 2) full verbal consent will be audio recorded using an encrypted Dictaphone, with the permission of the potential participant; 3) the paper consent form will be completed by the participant and returned by post; or, 4) an independent witness will join the call and sign consent on behalf of the participant.

Randomisation

Participants will be allocated to one of two groups: standard treatment; standard treatment plus OptiCALS intervention (originally in a 1:1 ratio, amended during the study to a 1:2 ratio). Randomisation is via a web-based randomisation system, employing non-deterministic minimisation by including a random element into the allocation algorithm. The minimisation factors will be:

- Study site
- ALSFRS-R trajectory since symptom onset (a measure of functional decline that can predict individuals with fast and slow disease progression)
- Riluzole use

The minimisation will be hosted by the Sheffield Clinical Trial Research Unit (CTRU) randomisation system, SCRAM – a remote secure server internet-based system. Access to the allocation list will only be granted to those responsible for cleaning the data and preparing unblinded data summaries during the recruitment and follow-up. For all other members of the trial team, the allocations will be concealed until recruitment and data collection are complete.

A CTRU statistician who is not otherwise associated with the trial will generate the allocation sequence. Named persons on the delegation log, who are trained in research procedures, will allocate participants by logging into SCRAM and entering basic demographic information.

Blinding

The outcome assessors will be blinded to treatment allocation during the trial recruitment and follow-up. Site staff who are delivering the intervention will not be responsible for collecting study outcome measures. Any instances of unblinding of the outcome assessor will be documented within the Case Report Form (CRF) and be reported as a secondary outcome. Study statisticians, health economists and those collecting outcome data will remain blinded while the study is ongoing.

Study Intervention

The OptiCALS portal will allow estimation of the participant's total daily energy expenditure (TDEE) using the ALS specific Kasarskis equation [33]. At the first intervention study visit, an initial calorie target will be set based on the participant's current calorie intake and their TDEE estimate (whichever is higher). At subsequent intervention study visits, the calorie target will be adjusted taking into account the participant's current BMI, weight direction and TDEE estimate. Patients who are losing weight will be set a calorie target that is 400 calories above their current calorie intake, unless their current calorie intake is more than 400 calories below the TDEE estimate, in which case the TDEE estimate will be their calorie target. The study process is outlined in Figure 1.

Participants will work with their healthcare professional to develop a dietary strategy using a food fortification first approach (with or without Oral Nutritional Supplements (ONS)) to meet their calorie target and in doing so, maintain or increase their weight. Specific areas of the portal provide information and resources for pwALS, carers, and healthcare professionals to help overcome barriers to eating a high calorie diet. These are summarised in Table 1 below. The need for ONS and/or enteral feeding will be reviewed systematically throughout the study, and discussed when participants are unable to meet their calorie target through a food first approach.

The OptiCALS portal has five modules, with further sub-sections.

Table 1: Intervention modules

Module	Description
My Food Diary	<ul style="list-style-type: none"> Record dietary intake (A minimum of 3 days food diaries will be collected prior to each study visit to provide an estimate of current calorie intake) Estimate daily calorie intake
How am I doing?	<ul style="list-style-type: none"> Presents participants with their individualised calorie target Presents charts/graphs indicating current calorie intake versus calorie target Presents charts/graphs of participants' weight
All Resources	<ul style="list-style-type: none"> A range of resources and advice to help participants to meet their calorie targets, including animations, videos, text, PDFs and links to resources external to OptiCALS

My Resources	<ul style="list-style-type: none"> • An area to save specific pages from within OptiCALS in one area. Individual pages on OptiCALS can be saved by the healthcare professional, participant and/or carer to the My Resources page. • Allow participants to write individual action plans about how they will meet their calorie target • Allow participants to view a list of saved 'quick wins', i.e. foods and their calorie values that can be introduced to help them meet their calorie target
Why boost my calories and weight?	<ul style="list-style-type: none"> • Provides participants and carers with the rationale for why it is important to boost calories and increase weight in ALS

Intervention providers, support and training

RCT sites will allocate, or employ, members of staff from the ALS team to deliver the research and intervention procedures locally. Members of the central project team will support healthcare professionals in the delivery of the intervention:

- All healthcare professionals delivering the intervention will attend a training session run by the central project team before they are able to deliver the intervention to trial participants.
- Ongoing ad hoc support in answering questions, e.g. how to tailor the intervention to participants, via an online discussion group embedded into the healthcare professional area of the OptiCALS portal.

Training will include a face-to-face or virtual (if necessary) session where RCT healthcare professionals will be orientated to the portal from logging on through to discussing calorie needs and tailoring the intervention. A user guide for healthcare professionals will form part of the materials they use to facilitate intervention sessions with trial participants. Healthcare professionals will complete session logs to ensure delivery of the intervention as intended and these will both facilitate tailoring the intervention to individual participant needs as well as ensuring ongoing fidelity monitoring. Participants without access to the equipment necessary to engage with the OptiCALS intervention (i.e. an internet enabled device) will be provided with these, including access to a video call enabled device where clinic visits are not possible.

Intervention procedures: Overview of visits

The intervention will be delivered by the healthcare professional primarily during face-to-face sessions if possible, or via telephone / video calls if necessary over the course of the participant's involvement, from the first intervention visit to 12 months post randomisation.

Prior to starting the intervention, both intervention and control participants will meet with the food diary reviewer to be trained how to log food diary entries on to the myfood24 system area of the portal using three food diaries that they will have been asked to complete before the intervention visit. They will also be familiarised with the portal, ahead of their first visit.

Intervention Visit 1: Week 1

The first intervention visit will take place approximately 1-2 weeks after recruitment into the trial and will be arranged at a convenient time and place (via telephone / video call if necessary) for the participant and carer, with sufficient time to carry out the tasks (approximately 2 hours). The healthcare professional will login to the participant's account. At this visit, the key tasks will be to generally orientate the participants and/or carer to the modules within the portal but, more importantly, to explain the rationale for the trial, i.e. the importance of increasing calorie intake to maintain or increase weight.

The healthcare professional will direct the participant to the 'How I am doing: calories?' page of the website to view their current calorie intake. The healthcare professional will then complete the ALSFRS-6 questions with the participant to calculate the participant's total daily energy expenditure (TDEE) using the ALS specific Kasarskis equation, that is embedded into the healthcare professional part of OptiCALS portal. This (or the participant's current calorie intake, if higher) will be used as the initial calorie target. Participants will be directed to the 'Calorie Boosting Quick Wins' page and encouraged to identify foods that could be easily added to their daily diet to help them meet their calorie target. The participant will be asked to complete, and enter, another three food diary entries before their next intervention visit.

Intervention Visit 2-5: Months 1, 3, 6 and 9

At subsequent intervention visits or video/phone calls, the researcher / healthcare professional will review the three food diaries completed by the participant and ensure they provide an accurate record of what they ate and drank. These visits will last approximately 1 hour. The healthcare professional will complete the ALSFRS-6 questions again and enter the participant's current weight. This information, along with the participant's current calorie intake, will be used to adjust the participant's calorie target.

Any issues relating to the accessibility and use of myfood24 or the OptiCALS website will be discussed by the healthcare professional delivering the intervention and support given to resolve these. The healthcare professional will direct the participant to the 'How I am doing: calories?' page to identify if there is a calorie deficit and then view the 'Calorie Boosting Quick Wins' or discuss the use of oral nutritional supplements to bridge any calorie gap, as appropriate to each participant. The healthcare professional will also complete a screening questionnaire which will suggest specific pages that can be saved to the participant's 'My Resources' section of the OptiCALS website to help them boost the number of calories in their diet and/or manage common barriers to eating a high calorie diet. Finally, participants will be informed that they will receive a follow-up call in a month and will be asked to complete, and enter, three additional food diary entries in the week before the follow up call. Onward referral for dietetic advice, gastrostomy, and speech and language therapy will be as per standard clinical practice. The Principal Investigator (PI) at each site will communicate with the Dietitian the rationale for the trial and request that they attempt to meet the calorie target set in OptiCALS when devising dietetic treatment plans. If participants are required to start ONS as a result of their inability to meet their calorie target, then they will initially be provided with a sample pack to try before an order is submitted. This will be

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3 followed up by a brief phone call from the healthcare professional to check that they are happy with the ONS
4 products provided.
5

6 Follow-up Phone Calls After Intervention Visits 2-5: Months 2, 4, 7 and 10

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9 All participants will receive a follow-up phone call from their healthcare professional one month after each
10 intervention visit to review their current calorie intake and any changes that have, or haven't, been made to
11 meet the new calorie target. Participants will be asked to complete, and enter, three additional food diary entries
12 in the week before their next intervention visit.
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15 Final intervention visit: Month 12

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18 At the final intervention visit, the researcher / healthcare professional will review their final three food diaries.
19 Participants will continue to be able to access the OptiCALS portal until the study ends. However, following the
20 end of the 12 month trial period, no further calorie targets will be set by the supporting healthcare professionals.
21 Also, the healthcare professionals will only continue to discuss the use of OptiCALS in clinic visits if they feel they
22 have the resource to provide this support. There will be no expectation for the healthcare professionals to
23 continue to provide this support and they will no longer receive excess treatment costs for this time.
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28 The participant's General Practitioner (GP) and Neurologist will be notified with an end of trial letter. If the
29 participant is taking oral nutritional supplements at the end of the trial period, the PI will write to the
30 participant's GP and neurologist (and dietitian if involved), advising them that the participant has finished the
31 trial and informing them of the specific oral nutritional supplement they have been taking, including the dose
32 and calorie value, so that the same supplement or a similar product can be continued as part of standard care.
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36 **Usual care**

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38 Usual care participants will receive the current standard nutritional management at each study site. Prior to
39 their first visit, they will receive training on the myfood24 system. They will complete the myfood24 diary data
40 through the 'my food diary' module, the only section of the OptiCALS portal available to the control arm
41 participants. OptiCALS intervention modules will not be available to control arm participants, carers, and other
42 health professionals at the sites and, as such, will not be used to influence dietary management.
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47 **STUDY OUTCOMES**

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49 Participants will be followed up at week 1, month 1, month 3 and then at three month intervals until month 12
50 or until death if this is earlier. Survival status of each participant will be reassessed at the end of the study
51 (between 12 and 35 months post-randomisation depending on when the patient was recruited). All outcome
52 measures will be collected by a blinded assessor, except blood samples, calorie intake, adverse events and
53 acceptability of the intervention. Where clinic visits are not possible (e.g. if shielding due to Covid-19) data will
54 be collected at the participants' home, either in person (if feasible), via video call, or via phone call if a video call
55 is not possible. Where physical measures are to be collected via video or phone call, participants will be sent any
56 equipment needed to complete these in advance of the appointment, as well as being directed to information
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3 about taking the measures in a separate section of the OptiCALS portal, including step by step videos. Training
4 will also be provided by the blinded assessor prior to any measurements being taken. If neither a face-to-face or
5 remote follow up appointment can be arranged, the questionnaire outcomes ALSFRS-R, WHOQOL-BREF, EQ5D-
6 3L, Healthcare resource use and acceptability questionnaire (intervention group only) can be self-completed by
7 post or electronically via email.
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10 11 12 **Primary outcome**

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14 Functional change over 1 year as measured longitudinally by the ALS Functional Rating Scale (ALSFRSR) [34], a
15 validated rating instrument for monitoring the progression of disability in patients with ALS that correlates with
16 survival and quality of life.
17
18

19 20 **Secondary outcomes**

21
22 **CAFS:** This analysis ranks clinical outcomes on the basis of survival and change in ALSFRSR scores [35]. Each
23 patient's outcome is compared to every other patient's outcome, assigned a score, and the summed scores are
24 ranked. The mean rank score for each treatment group can then be calculated.
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28 **Quality of life for patients: WHOQOL-BREF:** A 26-item quality of life measure validated for use in pwALS [36].
29

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31 **EQ-5D-3L:** A standardised measure of health status, covering five areas with three scoring options for each,
32 developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and
33 economic appraisal [37]. Preference-based utility weights will be applied to EQ-5D-3L responses using UK
34 population based values from the UK value set [38]. Utility values range from 1-perfect health to 0 death, with
35 negative scores indicating states worse than death. This will be completed by both patients and carers.
36
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39 **Respiratory function: Slow vital capacity (SVC):** A measure of respiratory muscle strength shown to correlate
40 with survival in ALS, taken by spirometry. FEV6 will also be taken via spirometry. Participants will be supplied
41 with handheld spirometers. Participants who are able to use a smartphone-reliant spirometer will take SVC and
42 FEV6 measurements. Participants who cannot use a smartphone-reliant spirometer will take FEV6
43 measurements only. Both measurements are considered acceptable alternatives based on existing literature
44 [39-43].
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48 **Anthropometric assessments:** Triceps skin fold, mid arm circumference and calf circumference measurements
49 will be taken using standardised methods [44]. Given the asymmetry in ALS the mean values taken from both
50 upper and lower extremities will be used. Fat mass and fat free mass will then be estimated. If outcomes are
51 measured remotely, triceps skin fold will not be taken and calf circumference will be used as the primary method
52 of fat mass and fat free mass estimation.
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56 **Overall survival:** Defined as time from randomisation to date of death. Surviving patients will be censored at the
57 date last known to be alive
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3 **Total calorie intake:** Self-completed by participants via myfood24.org (accessed via the OptiCALS portal).
4 Participants will be asked to complete, and enter, three food diary entries in the week before each study visit.
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6 Access to an internet-enabled device will be provided for participants if needed.
7

8 **Change in weight:** % weight change throughout the study period
9

10 **Change in Body Mass Index (BMI):** The BMI calculation divides an adult's weight in kilograms by their height in
11 metres squared. An existing record of measured height will be used if available in the patient notes. If no
12 measured height is available, this will be taken remotely.
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15 **Time to gastrostomy:** Defined as time from randomisation to date of gastrostomy procedure. If no procedure is
16 recorded patients will be censored at the date last known to be without gastrostomy.
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19 **Acceptability of the intervention (intervention group only):** Self-reported using a bespoke 11-item
20 questionnaire structured around the Theoretical Framework of Acceptability [45].
21
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23 **Healthcare resource use:** A questionnaire to measure use of healthcare services, used in the calculation of the
24 cost-effectiveness of the intervention.
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26

27 **Adverse events.**

28 **Blood tests:** Fasting lipids, albumin, lactate, renal function, thyroid function, neurofilament (Nf) serum,
29 creatinine and C-reactive protein. If face to face visits are not possible, these measures will not be taken. The
30 funding for analysis of Nf samples is via separate charitable funding, and as such, samples may be stored and
31 analysed centrally beyond the completion of the trial.
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36 **Safety**

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39 Adverse events (AEs) may be identified at any point during the study via routine follow-up, contact from the
40 participant and/or carer, on site or remote monitoring or other sources (medical notes etc.). Participants and/or
41 carers can inform site healthcare professionals of adverse events at any point of the follow up period. Related
42 Serious Adverse Events (SAEs) will be reported to the Sponsor, Research Ethics Committee and the Project
43 Steering Committee providing safety oversight for the study.
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48 There are no Adverse Events excluded from collection although expected events related to ALS disease
49 progression will not be reported as a SAE, unless the event is more severe than would normally be expected for
50 a participant or if the investigator considers there to be a causal relationship between the trial intervention and
51 the event.
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55 **Participant retention**

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57 Participant retention is promoted through regular communication from the research team which clearly explains
58 the importance of completing outcome data regardless of study arm. This message is reinforced at enrolment
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3 and all follow-up points. A flexible approach to study visits, and delivery of intervention also aims to maximise
4 participant retention, including a series of withdrawal options aiming to minimise participant burden, whilst
5 maximising retention and data collection. Where participants are finding participation in the study challenging,
6 but otherwise want to continue in the trial, options for reduced data collection throughout the remainder of the
7 study will be discussed.
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11 **Intervention completion and withdrawal**

12 Study completion is defined as 12 months after the date of randomisation. There are 3 withdrawal options
13 available to participants:
14

- 15 1. Withdrawal from the OptiCALS intervention only, i.e. no further intervention delivery visits but the
16 participant remains in the trial. The participant and/or clinician can make the decision to discontinue the
17 intervention for any reason.
- 18 2. Withdrawal from the OptiCALS trial, but with consent for the collection of essential routine data from
19 hospital notes, i.e. survival status / cause of death and ALSFRS scores, where available. No further intervention
20 or research visits will be conducted with the participant.
- 21 3. Withdrawal from the OptiCALS trial entirely, with no consent given to collect essential routine data.
22 Unless specified by the participant, all data collected up to this point will be used in the analysis and no further
23 intervention or research visits will be conducted.
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33 Where participants have withdrawn, but consent to routine clinical data being collected, ALSFRS-R will be
34 collected from their medical records along with survival status.
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37 **Uptake of intervention**

38 The intervention comprises several components (see table 1), each of which can be measured by the number of
39 times accessed and the time span over which patients continue to engage with it. Each component will be
40 summarised individually, and visual displays will depict how each individual engages with each component
41 across time. For purposes of the analysis, these will be used to provide an overall assessment (blind to outcome)
42 of whether each participant had engaged sufficiently to be considered “compliant” with the intervention.
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49 **Sample Size**

50 The sample size was derived by simulation with parameters estimated from the PRO-ACT ALS clinical trials data
51 repository [46]. The ALSFRS-R at entry was assumed to have a mean (SD) of 37 (6) and a mean monthly decline
52 of 1 unit over the 12-month duration of follow-up, with successive values following with an autoregressive (AR1)
53 correlation structure with $\rho=0.9$. A difference of +0.25 units per month (i.e. a monthly decline of 0.75 in the
54 intervention arm versus 1.00 in the control arm) was taken as a clinically meaningful effect. The probability of
55 death was assumed to depend on the last known ALSFRS-R with the probability of death in each three month
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3 period assumed zero up to month 3 and then as $91 * \exp[-0.115 * (\text{ALSFRS-R at previous visit}) - 3.95]$ thereafter,
4 equating to a 18% death rate for the control group and 15% in the intervention at twelve months. These
5 parameters were based on fitting a Cox regression model for survival in which ALSFRS-R score was a time
6 dependent covariate. Participants that die are included in the analysis and allocated a functional score of zero.
7
8 Withdrawal was assumed to occur at a rate of 5% per quarter in both groups, again starting after the month 3
9 visit. With a two-sided alpha of 5%, a power of 85% and with the first 100 participants allocated in a 1:1 ratio
10 and the remaining participants allocated 1:2 (standard care vs OptiCALS intervention), this requires a sample
11 size of 103 in the standard care arm and 156 in the OptiCALS intervention arm, n=259 participants in total.
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16 DATA ANALYSIS

17 Primary outcome

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19 The primary outcome ALSFRS-R will be analysed longitudinally using a multi-level linear mixed effect model
20 estimated by restricted maximum likelihood (REML). The fixed effect covariates will be time, treatment and their
21 interaction together with variables used in the minimisation process. The recruitment centre will be
22 incorporated as a random intercept in which participants are nested within their centre. If this model fails to
23 convergence, the centre effect will be removed and the simpler model will be fitted. The area between the two
24 ALSFRS-R curves will be derived using a linear combination of the coefficients for treatment and the interaction
25 of treatment with time, and will be presented alongside its 95% confidence interval and p-value. The difference
26 in ALSFRS-R will also be quantified separately at each timepoint.
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35 The primary analysis will be intention-to treat and will include all patients for whom data are collected or who
36 have died; an ALSFRS-R functionality score will be assigned for all timepoints scheduled after the date of death.
37 Sensitivity analyses will be performed to assess the robustness of the findings to distributional assumptions,
38 baseline characteristics and imbalance, missing data and non-adherence [47].
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42 Secondary outcome

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44 Secondary outcomes will be analysed and reported in the same manner as the primary outcome, with the
45 exception of time to event outcomes which will be analysed using Cox regression, and the combined analysis of
46 function and survival which is a rank-based (non-parametric) test described in Berry et al. [35]. Analyses will
47 be performed on an intention-to-treat basis and all statistical tests will be two-tailed at 5% significance level.
48 Further details will be provided in a full statistical analysis plan.
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53 Process evaluation

54
55 Alongside the RCT, a mixed-methods process evaluation will be undertaken. This includes qualitative interviews
56 with pwALS, their carers and healthcare professionals (HCPs) to explore context, implementation and
57 mechanisms of impact. Where possible we will approach patients and carers for separate interviews however if
58 preferred they will be given the choice to interview together, for example, to support with speech difficulties.
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3 Analysis of a sample of audio-recorded consultations and HCP intervention visit logs will be used to assess fidelity
4 of intervention delivery. In addition to this, quantitative data will be collected using surveys administered to the
5 intervention arm to investigate the acceptability of the intervention and data analytics on intervention usage.
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9 All interviews will be transcribed verbatim for analysis. Observation notes will be written up after each visit and
10 reflexive notes will be written up after each qualitative interview to help with data interpretation. The qualitative
11 data will be analysed thematically [48], within the broader framework for process evaluations recommended by
12 the Medical Research Council [49]. To understand the wider implementation issues, the analysis will draw upon
13 Normalisation Process Theory [50] and the Theoretical Framework of Acceptability [45]. To consider influences
14 on the behaviour of individual pwALS, the COM-B model will be used as an overarching theoretical framework
15 [62]. NVivo software (QSR International) will be used to help structure the analysis.
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18

21 **Health economics**

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23 A cost-utility analysis will be undertaken using the resource use, EQ-5D-3L and mortality data from the trial. The
24 analysis will take a NHS and a broader societal perspective, with an additional analysis that incorporates carer
25 QALYs within the incremental cost-effectiveness ratio (ICER). This will be supplemented with decision analytic
26 modelling to estimate lifetime cost-effectiveness for the patient cohort recruited to the study.
27
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31 **Patient and Public Involvement**

35 Patient and Public Engagement

36
37 Patients and the public have been involved in all aspects of the study. The OptiCALS clinical trial builds on the
38 back of 5 years of work (HighCALS programme) designed to understand the current national service models, the
39 beliefs of stakeholders and the development of behaviour change strategies to support and improve nutritional
40 interventions. The OptiCALS trial has been developed in collaboration with a variety of stakeholders including
41 clinicians, nutritionists, psychologists as well as people living with MND, and their carers. This includes early
42 consultation on study design, outcome measures and recruitment strategies. The OptiCALS Program Steering
43 Committee consist of clinicians, methodologists and PPI members and meet regularly to offer continued input
44 into the conduct, analysis, publication and future work of the study.
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53 **ETHICS AND DISSEMINATION**

56 **Governance**

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58 Sheffield Clinical Trials Research Unit on behalf of the sponsor (Sheffield Teaching Hospitals NHS Foundation
59 Trust) coordinates the trial. The Chief Investigator, project co-applicants, members of the data management
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3 team, sponsor, trial manager and other representatives form the Project Management group, who oversee the
4 operation of the trial and through which amendments will be communicated. The Project Steering Committee,
5 comprised of clinicians, statisticians, trialists and PPI representatives provides independent oversight. The
6 independent PSC also undertake the activities of the Data Monitoring Ethics Committee (DMEC) providing data
7 monitoring and oversight.
8
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10 11 **Ethical approval**

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14 The trial was approved by Greater Manchester – North West Research Ethics Committee, reference
15 20/NW/0334 on 8th of September 2020. The committee will be notified of amendments to the trial as
16 appropriate.
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19 **ISRCTN Registration**

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22 The program was registered on the ISRCTN registry on 7/12/20 reference: ISRCTN30588041.
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25 **Dissemination**

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27 We will publish the study findings in peer-reviewed academic journals and present at local, national and
28 international conferences where possible. We will publish a short summary of the results on the OptiCALS trial
29 website, accessed by trial participants as well as relevant interest groups.
30
31

32 **Acknowledgements**

33 **Authors' contributions**

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36 CM, DW, AA-C, WB, MB, JC, EC, CC, VH, PN, PS, HS, SW and TY contributed to funding acquisition and study
37 design. CM, AP, DW, GH, DB, MB, EC, SD, NE, CM, PN, ES, SW, SW, JW and TY contributed to development of the
38 protocol and study procedures. AP, DW, GH and CM produced the initial draft of this paper. All authors
39 contributed to reviewing and revising the final version prior to submission. David White will act as guarantor.
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44 **Contributor contributions**

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47 The 'HighCALS group' consists of the named authors and Elaine Scott, Jonathan Woodward and Shamila Ditta.
48 All of which contributed to development of the protocol, and study procedures.
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51 **Funding statement**

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54 This work was funded by the National Institute for Health Research (NIHR) Programme Grants for Applied
55 Research (PGfAR) programme grant number RP-PG-1016-20006 and supported by NIHR Sheffield Biomedical
56 Research Centre. CM is supported by an NIHR Professor Award.
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59 **Competing interest's statement**

AA-C is an NIHR Senior Investigator (NIHR202421). He has been supported by an EU Joint Programme - Neurodegenerative Disease Research (JPND) project through the following funding organisations under the aegis of JPND - www.jpnd.eu (United Kingdom, Medical Research Council (MR/L501529/1; MR/R024804/1) and Economic and Social Research Council (ES/L008238/1)) and through the Motor Neurone Disease Association, My Name's Doddie Foundation, and Alan Davidson Foundation. This study represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. AAC reports consultancies or advisory boards for Amylyx, Apellis, Biogen, Brainstorm, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Qoralis, Sano, Sanofi, and Wave Pharmaceuticals

All other authors have no competing interest to declare.

Figures:

Figure 1: Patient flow throughout the study.

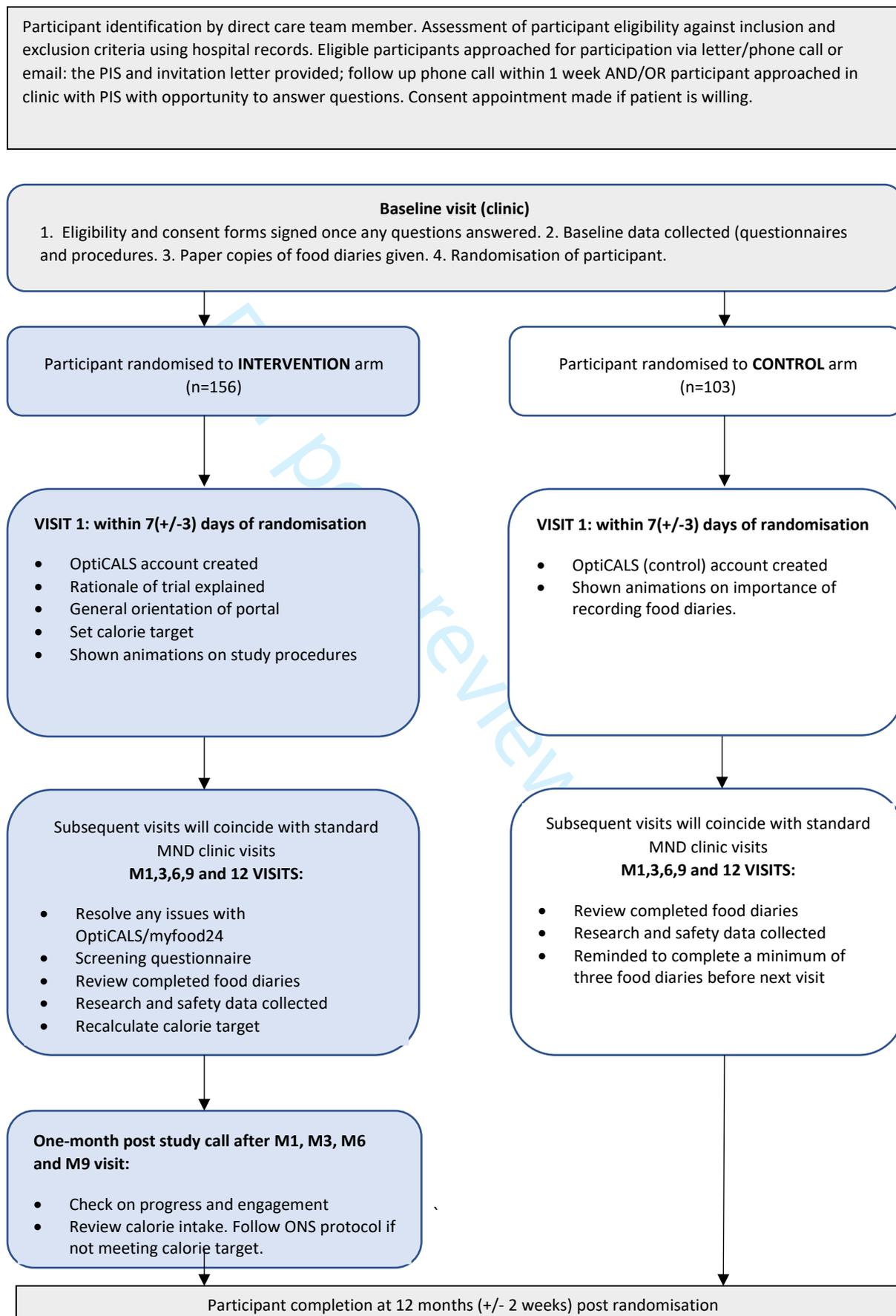
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Figure 1 Participant flow diagram



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