Re:Mission Study Protocol

Version 4 (28/03/2022)

Re:Mission

LBU LEEDS BECKETT UNIVERSITY

STUDY TITLE: A coproduced mixed method evaluation of the NHS England Low-Calorie Diet implementation pilot

SHORT TITLE: Re:Mission – An evaluation of the NHS Low Calorie Diet Programme

RESEARCH REFERENCE NUMBERS:

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FUNDING:

This study has been funded by NIHR HS&DR, with additional funding provided by Leeds Beckett University to fund two PhD studentships to work alongside the programme.

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Funder(s)	NIHR HS&DR
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Committees	- NIHR independent project oversight committee Chair: Professor Peter Bower, Manchester University - Re:Mission PPI group Chair: Ken Clare, Obesity UK - Informal project steering group Chair: Louisa Ells

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES

The Re:Mission project independent oversight group's role:

To provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The main features of the group are:

- To provide advice, through its Chair, to the Project Funder, the Project Sponsor, the Chief Investigator, the Host Institution and the Contractor on all appropriate aspects of the project.

- To concentrate on progress of the project, adherence to the protocol, participant safety (where appropriate) and the consideration of new information of relevance to the research question.

- To ensure the rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society.

- To ensure appropriate ethical and other approvals are obtained in line with the project plan

- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments.

- To provide advice to the investigators on all aspects of the project.

The Re:Mission PPI group's (seven socio-demographically diverse members with a lived experience of obesity and or type 2 diabetes) role is to:

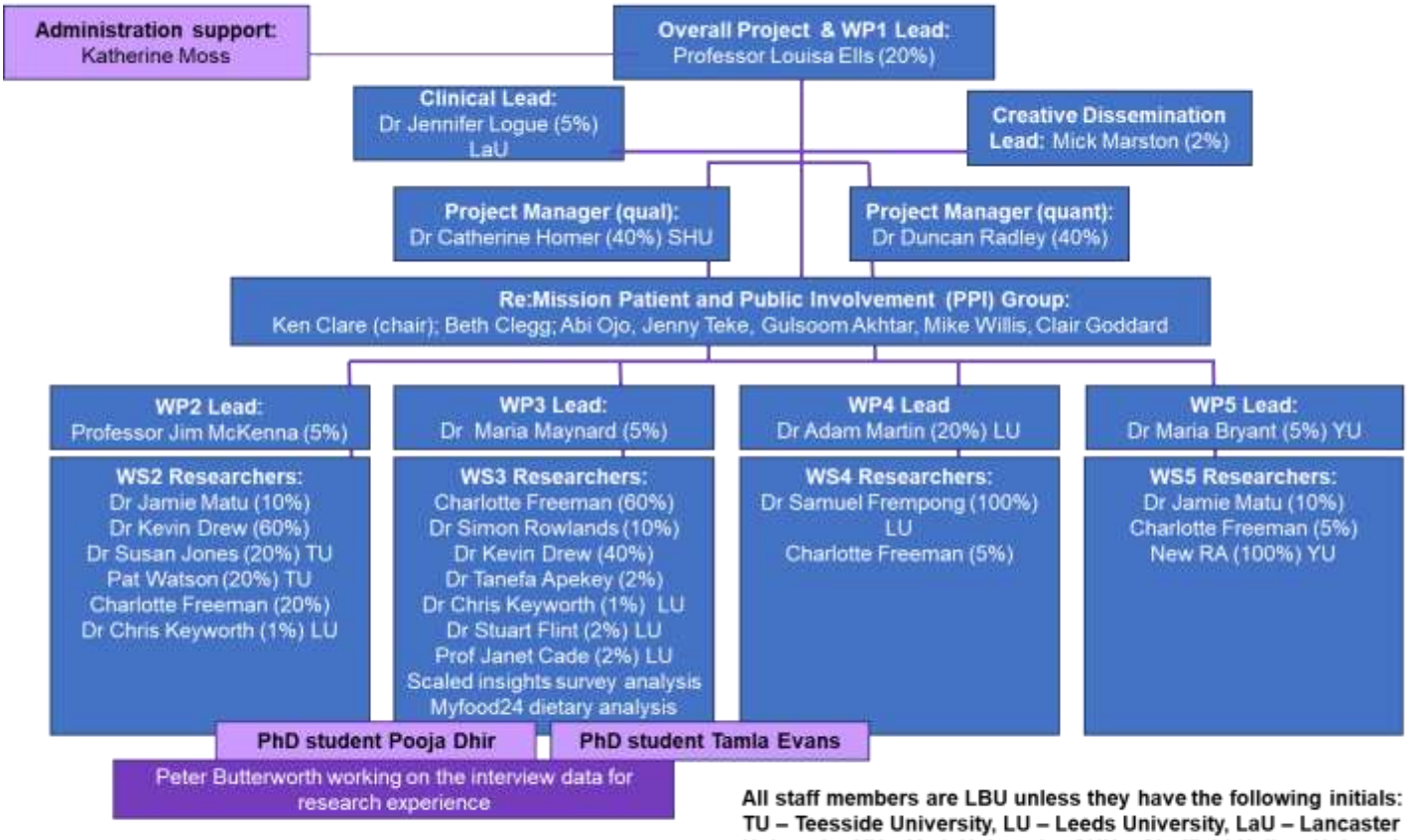
- Co-develop the study protocol
- Co-design the study website and content
- Co-develop all patient facing materials (surveys, interview schedules, Participant Information Sheet)
- Support participant interviews and follow ups
- Co-produce lay summaries, podcasts and blogs
- Work with the creative design team on the patient films, illustrated journals, and talking heads.
- Co-present findings at local, national and international meetings and conferences
- Co-author all study documentation.

The Re:Mission project informal steering group's role:

To provide informal advice and support on the project management and delivery.

The Re:Mission project team:

The Re:Mission project team and their corresponding responsibilities are shown on the project organisational chart below:



All staff members are LBU unless they have the following initials: TU – Teesside University, LU – Leeds University, LaU – Lancaster University, YU – York University, SHU – Sheffield Hallam University

SWAP sub-study WP Lead:
Dr Sarah Kingsbury

SWAP Researchers:
Prof Chris Walton
Prof Thozhukat Sathyapalan
Professor Phillip Conaghan
Dr Jordan Marwood
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SUMMARY OF RESEARCH:

Background: Obesity and Type 2 Diabetes (T2D) are both prevalent non-communicable diseases in the UK, which can significantly impact people's health and wellbeing whilst leading to significant costs to the NHS, and wider economy. Evidence from systematic reviews and recent clinical trials have shown that for some people living with or at risk of obesity and T2D, a Low Calorie Diet delivered through a total diet replacement (TDR) programme can lead to significant weight loss, support remission of T2D and reduce cardiovascular risk factors. The NHS long term plan therefore made a commitment to test an NHS Low Calorie Diet (achieved via a TDR programme) for people living with, or at risk of, obesity and T2D. NHS England (NHSE) have identified 10 pilot sites to test the NHS Low Calorie Diet programme, delivered using one of three different behaviour change support models: one to one, group or digital[1]. As NHSE will collect and analyse quantitative process and impact data, an additional qualitative and economic evaluation (including cost analysis and long-term cost effectiveness modelling) is required to provide a comprehensive mixed method evaluation, underpinned by a realist evaluation to determine what works, for whom, in what context, and why.

Project aim: To deliver a coproduced, comprehensive qualitative and economic evaluation of the NHS Low Calorie Diet pilot, that will be integrated with the NHSE quantitative analyses, to provide an enhanced understanding of the long-term cost-effectiveness of the programme and its implementation, equity, transferability and normalisation across broad and diverse populations.

Research questions and methods: The project brings together a multi-disciplinary team of leading academics from across the North of England, providing expertise in diabetes, obesity, nutrition, physical activity, coproduction, public health, psychology, service evaluation, behaviour change, health economics, implementation and social sciences, to deliver a comprehensive programme of five work packages (WP):

* WP1 Project management, coproduction, patient involvement and dissemination will: 1) facilitate liaison with all key stakeholders, NHSE and the Low Calorie Diet advisory and patient groups: ensuring that patient involvement and coproduction underpins every stage of each work package; 2) provide overarching project management: ensuring timely completion, cohesive working and quality assurance; 3) co-ordinate the interim and final evaluation reports: drawing together the evidence from WP2-5 with NHSE quantitative analyses; 4) deliver a comprehensive programme of dissemination and communication. This will include patient facing illustrative journal-style summaries, infographics, project website, social media feeds, lay summaries, short films, conference presentations, reports and journal articles.

* WP2 Service delivery and fidelity will use a combination of documentary review, session observations and semi-structured interviews with NHS support staff, and focus groups with providers to answer the following research questions (RQ): RQ1 What are the theoretical principles, behaviour change components, content and mode of delivery of the programme, and how do these vary across sites and providers?; RQ2 To what extent does the staff training delivered by each provider address behaviour change theory and content, and how does this vary across sites and providers?; RQ3 To what extent is the delivery of the NHS Low Calorie Diet delivered with fidelity to the specification as set out by NHSE?; RQ4 What are provider and NHS support staff experiences of the service, and what do they perceive to be the key barriers and facilitators to effective delivery, integration and normalisation into routine care?

* WP3 Patient experience and inequalities, will be underpinned by a pluralistic approach, undertaken using cross-sectional and longitudinal patient surveys, interviews and visually represented patient journeys using adapted photovoice methodology. These findings will be aligned to, and integrated with quantitative process and outcome data from NHSE, to answer the following RQs: RQ5 To what extent is the content of the NHS Low Calorie Diet understood and applied by patients?; RQ6 Do socio-demographic characteristics (such as sex, socio-economic status and ethnicity) influence access, uptake, compliance and success on the NHS Low Calorie Diet, and does this vary across the different (one to one, group or digital) behaviour change delivery models?; RQ7 What aspects of the service work and do not work, for whom, in what context and

[1] Although during COVID-19 restrictions all services are being delivered remotely

why?; RQ8 If effective, how can the service be improved in the future, to enhance patient experience and ensure any inequities are addressed?

* WP4 Economic evaluation will use patient-level simulation modelling to estimate the long-term cost-effectiveness of each NHS Low Calorie Diet delivery model (in terms of incremental cost per quality adjusted life year (QALY)) when compared to a counterfactual scenario. This will enable comparisons with other demands on healthcare resources and thus support commissioning decisions. This WP will include a micro-costing exercise for each of the three delivery models, to address: RQ9 What are the costs of delivering the NHS Low Calorie Diet programme from an NHSE perspective and how do they (i) differ across the different delivery models and (ii) compare to estimates provided in the DPOPLET and DiRECT trials?; RQ10 What are the costs of the NHS Low Calorie Diet programme to participants, and how do they differ by delivery model and patient-level characteristics? These cost estimates will be used along with the patient-level demographic and clinical information collected over 12-months by NHSE as inputs in the patient-level simulation model to answer RQ11: What is the long-term cost-effectiveness of the NHS Low Calorie Diet (in terms of incremental cost per QALY) when compared to a counterfactual scenario, and how does this vary by delivery model and patient characteristics? We will also replicate the methods used in DROPLET and DiRECT trials, but using the cost and short-term outcome data collected in this study and by NHSE, to enable further comparison with the cost-effectiveness estimates of those previous trials, to answer RQ12: How does the cost and (short-term) outcome data collected in this study affect the estimates of cost-effectiveness in previous trials?

* WP5 Transferability assessment will employ a theoretical model for the assessment of transferability and normalisation of health interventions, that will incorporate the findings from WP 2-4 with wider evidence to address RQ13: What are the core elements of the intervention that are required to achieve impact, RQ14: What elements can be adapted to suit local context and RQ15: What are the policy implications for wide-spread adoption of the programme?

Anticipated delivery timeframe and impact: The project will be delivered between November 2020 and October 2023 and will inform the national roll out of the programme. It will also address a significant evidence gap in understanding the real-world implementation of a Low Calorie Diet delivered via Total Diet Replacement programmes, which will be shared internationally.

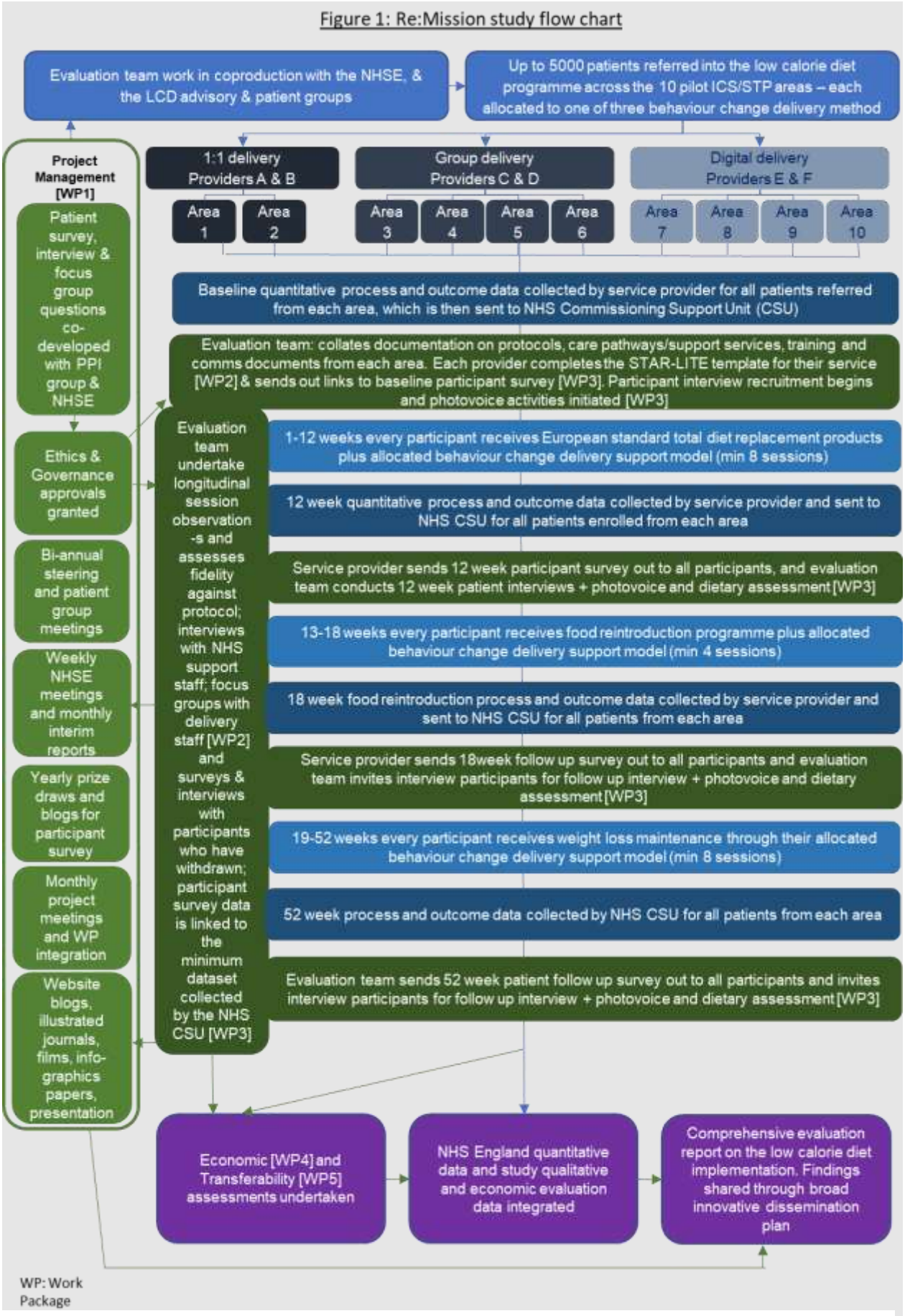
KEYWORDS:

Obesity, Overweight, Type 2 Diabetes, Low Calorie Diet, Total Diet Replacement, Economic evaluation

STUDY FLOW CHART:

The Re:Mission study flow chart is shown in Figure 1 below.

Figure 1: Re:Mission study flow chart



NB the participant survey will also be distributed to the 11 new pilots sites from January 2022.

BACKGROUND

In England, 26% of men and 29% of women live with obesity[1], a chronic relapsing condition that is associated with the development of a number of serious diseases, including: some types of cancers, Type 2 Diabetes (T2D), and liver, muscular-skeletal and cardiovascular diseases. There is a strong association between obesity and T2D, with T2D seven times more likely to occur in adults living with obesity[2]. Development of T2D can lead to an increased risk of cardiovascular disease, blindness, amputation, kidney disease and depression[2]. However, obesity and T2D does not affect all populations equally, with prevalence of both conditions increasing with age and area-level deprivation, and higher amongst people of Black and South Asian ethnicity[2]. It is estimated that 3.8 million adults (≥16 years) have diabetes, and modelled projections indicate that the NHS and wider societal costs associated with obesity and diabetes, will dramatically escalate unless urgent action is taken[3]. The NHS long-term plan[4] therefore pledged to provide targeted support, and access to weight management services in Primary Care for people with a diagnosis of T2D or hypertension and a BMI of ≥27 (adjusted appropriately for ethnicity). This pledge aims to significantly improve health, while reducing health inequalities and associated future costs to the NHS.

Recent systematic reviews[5-9] and clinical trials[10-13] show that for some people living with, or at risk of obesity and T2D, a very low calorie diet or Low Calorie Diet achieved by TDR, can lead to clinically significant weight loss, support remission of T2D, improve quality of life, and reduce cardiovascular risk factors. Based on evidence from the two recent UK trials (Droplet and DiRECT)[11, 12], a commitment was made in the NHS Long-Term Plan[4], to pilot an NHS Low Calorie Diet programme delivered through TDR and behaviour change support, for people living with obesity and T2D. It is therefore important to assess the real-world implementation of the trial intervention. This is particularly important as the two trials informing the NHS programme had some limitations, including: a lack of dietary intake data, insufficient ethnic diversity, and the assessment of just two providers (Counterweight and Cambridge Weight Plan) and one behaviour change support model (one-to-one).

The use of realist methodology can help to provide research-informed theories as to why some people may have 'successful' outcomes and others do not. Policy makers, commissioners and clinicians can use this to inform decision making, for example, by targeting those for whom the intervention works, or by putting in place mechanisms to increase success for those where it might otherwise fail by providing alternative and more suitable support. The concept of realist evaluation has been summarised as: ‘what works for whom in what circumstances and in what respects, and how?’, and is assessed using context, mechanism, and outcome pattern configurations [23].

Qualitative research, especially when combined with quantitative data, can provide important insights into understanding why programmes work or do not work for different populations, however, there remains a lack of published qualitative evidence on TDR Low Calorie Diet programmes. The only recent qualitative studies were undertaken in the US[14], and as part of the UK trials[15, 16], and identified: a need for research outside of trial settings, and the importance of palatable TDR products, physical activity, social support and good coaching to achieve success.

Any new Low Calorie Diet programme being delivered in routine NHS care will require an economic evaluation. One short-term cost-effectiveness analysis of Low Calorie Diet TDR (the DiRECT trial)[17] reported T2D remission in a third of patients at 1 year, at an incremental cost of £2,564 (2017 prices) per case, which the authors concluded was highly likely to be cost-effective. Another long-term economic evaluation of a Low Calorie Diet TDR programme (the DROPLET trial)[18] estimated an overall incremental cost-effectiveness ratio (ICER) ranging from £3,203 to £12,955 (depending on the extent to which weight loss is regained 5 years after the intervention), which is well below the NICE cost-effectiveness threshold. However, only 15% of participants in that study had T2DM and a limitation of the economic model was that it did not account for the possibility of T2DM remission. The study also showed Low Calorie Diet TDR to be more cost-effective in older adults and those with a higher BMI.

NHSE have procured two providers per delivery model, four providers in total, who are delivering 12 weeks TDR, followed by six weeks food reintroduction and then 34 weeks weight loss maintenance support, delivered through one of three behaviour change delivery models (one to one, group or digital). [2]Therefore, a robust evaluation of this pilot is required to generate comprehensive insights into the implementation of this programme within routine clinical care. This evaluation will assess associated patient and health care costs; patient experience; inequity in uptake and compliance, and differential effects particularly within high risk groups (Black and South Asian populations, and those of low socio-economic status); the impact and acceptability of different behaviour change models, and the transferability of the model to support wider adoption and policy change.

RATIONALE:

This study is required to address: 1) the increased national urgency to tackle obesity and diabetes given the higher morbidity and mortality associated with COVID-19 infection observed in patients living with these conditions[19]; and 2) the need to evaluate the national pilot of the Low Calorie Diet programme.

The Low Calorie Diet programme is a significant NHS investment, based on wider international evidence, and outcomes from the two recent UK trials[11, 12]. However, translating controlled clinical trials into routine NHS delivery remains a significant challenge. To optimise the transfer of successful components of interventions into routine practice, it is imperative to undertake a rigorous programme of independent evaluation that provides clear feedback on how and why the programme was, and wasn't implemented, who it did and did not work for, and why. Realist evaluation and Normalisation Process Theory (NPT) are complementary methodological approaches that can help to answer these questions. The evaluation will help develop and refine the programme using quantitative outcome analyses alongside qualitative insights from patients across broader and more diverse communities than those participating in trials, and will also explore wider mechanisms of action such as overlooked elements of self-management, that may supplement and/or undermine 'trial only' effects.

The evaluation team will provide an extensive qualitative programme of study to explore the impact of population characteristics, context and variability in delivery, through patient, provider and NHS insights, alongside an economic evaluation of implementation across the three different delivery models. Employing a patient-centred, coproduction approach is fundamental to the proposed evaluation. Our evaluation team will work in coproduction with NHSE and the Low Calorie Diet advisory group to ensure the approach aligns with primary care and clinical governance requirements, and strengthens and supplements insights from the quantitative analysis of the NHSE minimum dataset. The team also has strong patient representation through an active patient advisory group who will be involved in every stage of the project development and evaluation, to ensure compliance with the eight principles of patient-centred care[20]. Deploying this pragmatic, rigorous evaluation programme will ensure that, before any national roll-out is considered, health inequalities, implementation costs, and further service improvements are fully investigated.

THEORETICAL FRAMEWORK

We will undertake a comprehensive coproduced[21][3] evaluation programme, informed by the MRC guidance on process evaluation of complex interventions[22].

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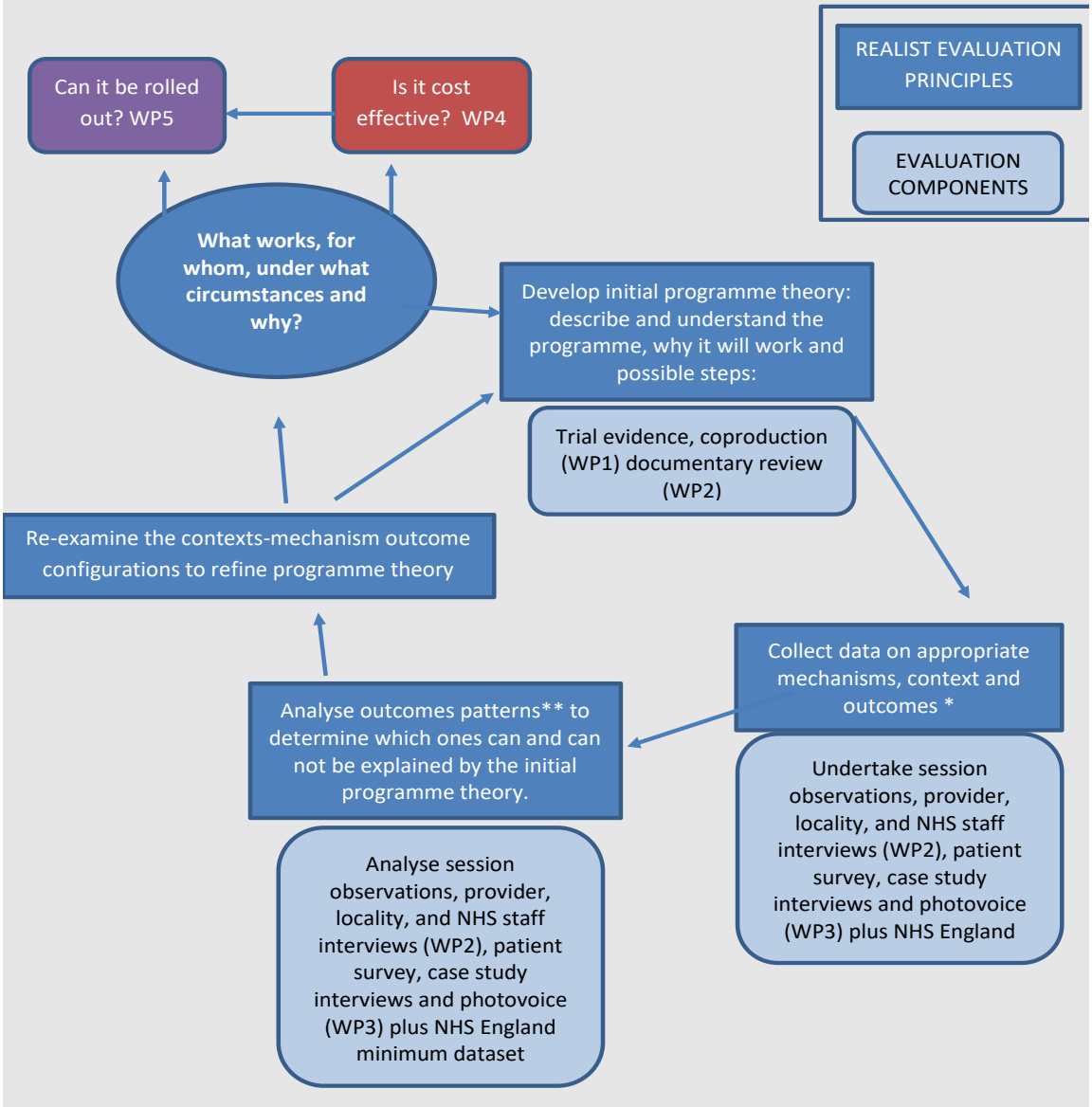
[2] NB Due to current COVID-19 restrictions the one to one and group delivery models are being delivered remotely, any patients who start with remote delivery will continue with this mode of delivery throughout their 1 year treatment, a return to face to face provision will only be reconsidered when it is deemed safe to do so.

[3] Academics, policy makers, practitioners and patients sharing information and decision making to produce academically rigorous research that has real world impact and direct patient benefit.

The Re:Mission study was constructed using the RE-AIM checklist[23] for study planning, and is underpinned by a realist evaluation informed approach, in order to understand what works, for whom, in what respects, to what extent, in what contexts, and how[24] (an illustration of this is provided in Figure 2). We also draw on behaviour change theories[25, 26], normalisation process theory[27], social science and transferability framework for implementation assessment[28]. The relevant EQUATOR network[29] reporting guidelines (COREQ, StARI and CHEERS) will also be applied to qualitative, implementation and economic components respectively.

Figure 2: An illustration of how the Re:Mission study is underpinned by realist-informed approach



** Mechanism – the process of how subjects interpret and act upon the intervention; Context – the features of the condition in which programmes are introduced that are relevant to the operation of the programme mechanisms (the 'for who' and 'in what circumstances').*

*** Outcome patterns - the intended and unintended consequences of programme, e.g. implementation, impact, socio-demographic, temporal outcome, personal attitude, and geographical and biological variations*

RESEARCH AIM AND OBJECTIVES:

Aim:

To deliver a coproduced, comprehensive qualitative and economic evaluation of the NHS Low Calorie Diet pilot, that will be integrated with the NHSE quantitative analyses, to provide an enhanced understanding of the long term cost effectiveness of the programme, and its implementation, equity and transferability across broad and diverse populations.

Objectives are to: (associated Work Package-WP)

1. Assess different provider's experiences of the programme, including any barriers and facilitators to implementation across the different populations. *(WP2)*

2. Assess the experiences and attitudes of NHS staff involved in mobilising the programme across each pilot area and referring and supporting patients on the programme, and their opinions on the management of the programme implementation. *(WP2)*

3. Assess patients' experiences of the programme: including patients with a range of socio-demographics (e.g. socio-economic status, ethnicity, sex, start BMI), and with differing engagement experiences (referred but did not attend, adhered to, or dropped out of the programme) within each of the different delivery models, to gain insight into what worked, and what did not, for whom and why, and how the programme could be improved in the future. *(WP3)*

4. Estimate the long-term cost-effectiveness of each NHS Low Calorie Diet delivery model (in terms of incremental cost per QALY) when compared to a counterfactual scenario, including how this varies by delivery model, to enable comparisons with other demands on healthcare resources and thus support commissioning decisions. *(WP4)*

5. Assess national roll out of the NHS Low Calorie Diet through a transferability and policy impact assessment. (WP5)

6. Integrate findings from WP2-5 with the quantitative analyses conducted by NHSE to: a) examine whether the outcomes of the DROPLET and DiRECT trials can be replicated within a larger and more diverse population, and with different providers and behaviour change delivery models; b) examine how the results of our analysis could impact on the published cost-effectiveness estimates of the DiRECT trial and support future commissioning; c) provide a comprehensive understanding of the programme implementation and impact by socio-demographics, delivery model and locality: examining patterns and trends to inform future service development and commissioning; d) determine the transferability and policy impact of the programme. *(WP1)*

STUDY DESIGN

The Re:Mission study will follow a structured evaluation plan delivered across five interlinked work packages (WP), that will be undertaken in collaboration with NHSE to address the aim and objectives stated above. Each WP is described in detail below:

Work package 1: Project management, coproduction, patient involvement & dissemination

The aim of this work package is to coordinate the coproduction and patient engagement activities, and provide oversight for, and integrate evidence from, the remaining work packages: ensuring the project is delivered within the agreed time, specification and budget. Louisa Ells will lead this WP, with support from project managers: Catherine Homer [qualitative, PPI lead] and Duncan Radley [quantitative and WP integration lead], who both have extensive experience managing projects coproduced with academic and local ICS/STPs; researcher Jamie Matu; clinical oversight from Jennifer Logue; steering group support; NIHR

oversight group governance and PPI group advice led by Ken Clare. This WP will be the main link between the research programme, NHSE and pilot sites, to enable a co-ordinated flexible approach that will allow the other WPs to respond and adapt at pace to meet any change in plans that may result from COVID-19 or other changes to the system. This WP will also play a critical role in the integration of the quantitative (NHSE) findings with the qualitative and economic evaluation data (WP2-5). This will be facilitated through: regular informal with NHSE and formal biannual review meetings with the formal Low Calorie Diet advisory group; coproduced update reports, and a formal programme of integration of data for the NHSE and WP2-5 outputs, to inform the development of the final comprehensive mixed method evaluation report (objective 6).

The final component of this WP is to deliver a comprehensive programme of dissemination and communication. This will include regular interim reports, the final project report, a patient facing interactive illustrated journal-style summary, infographics, a project website, social media feeds, lay summaries, short films, conference presentations and journal articles. Mick Marston will oversee all creative outputs to ensure we maximise reach, engagement and impact through design innovation and creative media.

Work package 2: Service delivery and fidelity

Rationale: The NHS Low Calorie Diet programme specification is based on the protocols from two underpinning trials[11, 12]. To test whether the outcomes of these trials can be replicated within larger more diverse populations it is important that the NHS Low Calorie Diet pilot is delivered with fidelity to the programme specification. This is important because the existing trials were based on a single provider and used only one behaviour change delivery model (one to one support). As the NHS Low Calorie Diet will be trialling the use of different providers, and two additional behaviour change delivery models (group and digital support), an evaluation of treatment fidelity across different providers and delivery models is essential.

Overview of methods: This work package will use a combination of documentary review, session observations, interviews with NHS support staff, and provider focus groups to answer RQs: 1-4.

The methods will be framed using the Health Behaviour Change Consortium NIH-BCC fidelity domains [30] (with a-c addressed in WP2 and d-e addressed in WP3):

(a) Study design – is the intervention congruent with relevant theory and best practice?
(b) Training - have practitioners been properly trained to deliver the intervention?
(c) Delivery – has the intervention been delivered as designed?
(d) Receipt – do patients understand the intervention and perform key skills during delivery?
(e) Enactment – do patients perform relevant skills in real life setting?

Research questions WP 2.1 – Study design:

- What are the theoretical principles, behaviour change components, content and mode of delivery of the programme, and how do these vary across sites and providers? [RQ1]

Methods:

Documentary review: We will collect information on wider support services (e.g. local care pathways, services linked to the NHS Low Calorie Diet programme, local Low Calorie Diet training programmes, incentivisation schemes and communications packages, as well as other locally available weight management and diabetes services) and the impact of COVID-19 (e.g. adaptation plans and impacts on wider support services) from each pilot site locality lead (who will be identified by NHSE). We will also collect the NHS Low Calorie Diet service specifications, training manuals, session content, and marketing materials used by each service provider (four providers have been commissioned – with two different providers for each delivery model). We will also ask the provider from each pilot area to complete the standardised reporting of lifestyle weight management interventions to aid evaluation (STAR-LITE) template[31] (which has been adapted to include additional questions to assess the impact of COVID-19 on service delivery, record resource use and unit costs for the economic evaluation, capture digital and remote delivery implications, and strategies used to

mitigate against digital inequalities). The STAR-LITE template will be completed every year by each service provider, in order to capture any year on year changes to service provision. The STAR-LITE survey will be made available electronically via Qualtrics surveys, and will facilitate the standardised reporting of intervention referral, delivery, components, and costs which will be used to 1) support a primary analysis of key intervention features (including behaviour change content, underpinning theory and delivery) across providers, and 2) evaluate adherence to the national programme specification.

Analysis: The output from the STAR-LITE survey and documents collated will be analysed using the documentary review methodology informed by Bowen[32], and will support WP4 and 5, and help inform the initial programme theory.

Research questions WP 2.2 – Training and delivery:

- To what extent does the staff training delivered by each provider apply behaviour change theory and content, and how does this vary across sites and providers? [RQ2]
- To what extent is the NHS Low Calorie Diet delivered with fidelity to the specification as set out by NHSE? [RQ3]
- What are provider and NHS support staff experiences of the service, and what do they perceive to be the key barriers and facilitators to effective delivery, integration and normalisation into routine care? [RQ4]

Methods:

Behaviour change coding: Each providers' training manuals will be coded against Behaviour Change Technique taxonomy (v1)[33], and behaviour change theory using Michie & Prestwich's Theory Coding Scheme[34], aligning the methodology with that used for the evaluation of the National Diabetes Prevention Programme[35, 36]. This will be undertaken in duplicate, and used to assess the extent to which training coheres to the guiding behaviour change theory and content, and how this varies across providers.

Face to face session observations (currently delivered remotely): We will work with each service provider delivering one to one and group programmes to purposively select two delivery streams to observe from start to finish. Two providers are delivering the one to one, and two providers are delivering the group programmes. As there are 21 active sessions in both the one to one and groups sessions, this will result in a total of 168 observations (providing consent is gained from the staff lead and participants before each session). This will provide a longitudinal insight into delivery across different populations and delivery models. Descriptive non-participatory observations[37] will involve detailed field note taking to assess the behaviour of the delivery staff and participant interactions, during a routine programme delivery session. Observations will be conducted remotely by two experienced qualitative researchers who have experience of session observations and have been trained in coding Behaviour Change Techniques.

Analysis: Field notes (but not audio recordings) will be taken, entered into NVivo and used as part of the data. Fidelity will then be assessed by comparing observations to a fidelity checklist that will be developed from the behaviour change coding, formal service specification and service provider training manual/session content and STAR-LITE responses.

Digital session observations: As the active components of the digital programme are delivered almost entirely via digital media, digital service providers (n=2) collect data on the amount, frequency, duration and usage of the programme. We will therefore ask providers to share this data, alongside access to the programme content, in order to assess fidelity and behaviour change techniques used. We anticipate collecting the following data (in line with the methodology used for the National Diabetes Prevention Programme evaluation protocol https://fundingawards.nihr.ac.uk/award/16/48/07):

• Page views (with reference to behaviour change technique content mapped out by prior work)

• Number, time and date stamps of pages above

• Links clicked, data inputted and downloaded (i.e. to ascertain whether data has been inputted, e.g. a food diary entry, or whether a user has clicked through to use another component of the intervention, e.g. a live chat with health coach). NB this is assess usage data not personal content.

We will work with providers to ensure an opt-out consent process is in place for sharing usage data by: 1) reviewing existing terms and conditions and consent statements that service users complete when registering to take part in the digital Low Calorie Diet programme, and 2) revising consent statements where necessary in conjunction with the provider. Once an agreed opt-out consent process is in place, we will ask providers to identify a cohort of service users which will be followed for the duration of the programme (12 months). We expect this cohort to be identified as all new registrants with the digital programme for one month for each of the 2 providers. We will ensure that the data transferred to Leeds Beckett University from the providers is anonymised and does not contain any personally identifiable data. Providers will be specifically requested to undertake the following:

• Remove any personally identifiable data (name, contact details, date of birth, medical records, IP address)
• Remove any address details leaving only the first 3 letters of the postcode, which will allow us to assess the geographical spread of the usage data we obtain
• Review any free-text entries from service-users that risk sharing personally identifiable data
• Data quality assurance

We will request that providers encrypt the data files using an AES256 compliant encryption mechanism such as 7-zip. It will then be sent to Leeds Beckett University via the secure encrypted, password protected transfer system ZendTo.

Data files will be stored on the high security (NHS IG toolkit compliant server provided by Leeds Beckett University IT). We will request providers transfer data to us on a monthly basis using this process.

Analysis: We plan to use the AMUsED (Analyzing and Measuring Usage and Engagement Data) framework for evaluating the digital interventions[38]. This framework comprises three stages: 1) familiarisation with the intervention and its relationship with the captured data, 2) identification of meaningful measures of usage and specifying research questions to guide systematic analyses of usage data, and 3) preparation of datasheets and consideration of available analytical methods with which to examine the data. We will identify core BCTs (e.g. goal setting, action planning, self-monitoring, feedback, reviewing goals, problem solving and others mentioned in the intervention specification). We will code whether the BCT is present in the intervention (yes/no) and we will code whether users engaged with that specific BCT (yes/no). We will also report specific BCTs and key intervention features which were (1) offered to users, and (2) which users effectively engaged in, as will be conducted in the face to face session observations.

Service provider focus groups: Following ethical approval service providers will be invited to contribute to a focus group. We will aim to recruit a convenience sample of 13 focus groups with between 6-8 participants per group [39] (NB given the different delivery models, and some providers covering more than one pilot site, these focus groups will be organised to capture insights from key frontline staff members across the different service provider and delivery areas). Focus groups (which will be held virtually using video conferencing) will provide insight into providers experiences, and any shared barriers, facilitators and redundancies regarding implementation across different pilot areas, populations, and delivery models (including the impact of COVID-19, and any problems encountered with the referral process).

NHS support staff interviews: We will interview a convenience sample (n=10, one from each pilot area) of the NHS locality staff (i.e. those involved in mobilising the programme). We will aim to interview the locality lead within each pilot site during the first and second year of the programme, to examine how mobilisation, referral mechanisms, communications, training and incentivisation was initiated and developed during the roll out (total interviews n=20). We will also interview a purposive sample (n=20) of NHS staff responsible for referring and supporting patients on the programme, in order to capture insights from GP practices that have experienced referral challenges and successes within each of the pilot areas. All NHS staff interviews will be

conducted within 30-60 minutes and be undertaken one-to-one over a telephone or video call. These interviews will assess experiences and views of the programme from NHS support staff perspectives, including their insights on which patients may be excluded from care (i.e. do not engage with the health care system), which patients receive a conversation about the programme but decline a referral, the local management of patient referrals, staff training, patient centred care, the impact of COVID-19 and any additional indirect costs associated with the programme. We have costed in gift vouchers to help incentivise participation within NHS referral staff.

Analysis: All interviews and focus groups will be guided by a topic schedule informed by the research questions, patient group insights, and the mechanisms, context and outcomes defined by the realist approach and normalisation process theory (NPT). NPT comprises of four main concepts: coherence, cognitive participation, collective action and reflexive monitoring, and seeks to illuminate the processes by which staff normalise a new practice [27, 40, 41]. Using NPT will inform the staff interview/focus group question guides. As with the realist approach, NPT can be used across the life cycle of a project to guide and frame core issues. Thus, both approaches will be used at the initial stages of the project to offer direction and clarity to lines of questioning and will also provide a framework for data analysis.

All interviews and focus groups will be conducted remotely and digitally audio-recorded, and transcribed verbatim with consent of each participant. Each transcript will be checked for accuracy by the researcher who conducted the focus group or interview. NVivo software will be used to aid the data organisation and analyses. Two researchers will independently review a sample of transcripts to formulate codes. Codes will be inductively sorted into potential themes and relevant data extracts collated within identified themes[42, 43]. Thematic networks will be constructed to facilitate the structuring, description and interpretation of the themes[44, 45]. Within themes, case-ordered matrices (from interviews and focus groups) will be constructed according to variables of interest. This case-ordering will enable examination of differences across cases, between delivery modes, and/or different stakeholder groups[45]. Themes will then be built into an explanatory model to demonstrate how various factors might influence successful implementation of the intervention[45].

Work package 3: Patient experience and inequities

Rationale: The experiences of patients eligible for the NHS Low Calorie Diet programme, as well as those delivering it (WP2) are critical to its success. However, previous research has demonstrated that socio-demographic factors can impact upon a patients' experience of living with T2D[46] and can influence Low Calorie Diet success[47]. The NHS Low Calorie Diet programme is based on evidence from two UK trials[11, 12], providing data on patient groups that were less diverse than the general population eligible for the NHSE Low Calorie Diet in England. It is therefore imperative that this evaluation comprehensively understands the experiences of patients sampled from diverse socio-demographic backgrounds and provides insight into any socio-demographic variation in programme uptake, compliance, adherence and success across the three different delivery models. This component of the evaluation is critical in ensuring: 1) the programme addresses the health inequalities that are prevalent across England[48], in particular the inequalities in obesity and diabetes prevalence relating to ethnic group and socio-economic status; and 2) providers are fulfilling their legal obligation to provide equality of opportunity across all protected characteristics[49]).

Overview of methods: This WP will use a combination of complementary stages, underpinned by a pluralistic approach, which include cross sectional and longitudinal participant surveys, with in-depth insight provided by cross sectional and longitudinal interviews using visually represented participant journeys gained through adapted photovoice methods. A longitudinal approach is deemed critical given the chronic relapsing nature of obesity, and the difficulties in long term weight loss maintenance[50]. These findings will be integrated with the quantitative process and outcome data from NHSE, to help examine the context-mechanism-outcome configurations and answer the following research questions.

Research questions WP3.1 - Patient receipt and enactment

- To what extent is the content of the NHS Low Calorie Diet understood and carried out by patients? [RQ5]

Research questions WP3.2 - Patient experiences across socio-demographics and delivery models

- Do socio-demographic characteristics (such as socio-economic status, sex, ethnicity, start BMI, duration of diabetes) influence access, uptake, compliance and success on the NHS Low Calorie Diet programme, and does this vary across the different (one to one, group or digital) behaviour change delivery models? [RQ6]
- What aspects of the service work and do not work, for whom, in what context, and why? [RQ8]
- If effective, how can the service be improved in the future, to enhance patient experience and ensure any inequities are addressed? [RQ9]

Stage 1: Programme wide cross sectional and longitudinal patient survey.
A short (~20minute) participant survey will be developed for each stage of the programme (baseline, end of TDR, end of food reintroduction, end of maintenance and withdrawal). These surveys will be co-developed with end users, drawing together the realist evaluation and NPT approaches to collect a qualitative overview of patient understanding (coherence, cognitive participation), enactment (collective action) and experiences of the programme (reflexive monitoring), in addition to supplementary quantitative data (not currently collected by the NHS minimum dataset, but required to support WP4 & WP5) which will: 1) help understand influencers of uptake, withdrawal, retention and compliance, and how these may vary by socio-demographic factors and delivery model; 2) provide an overview of participant experience and expectations. The survey will be co-developed and tested with our PPI group and current NHS Low Calorie Diet service users to ensure it is acceptable to service users, will provide data that will be useful to participants, and gives rise to participant insights that will further enhance interpretation of the staff interviews (WP2) and the NHSE quantitative data. In order to align with the Diabetes Prevention Programme evaluation, tier 2 weight management minimum dataset and PPI group recommendations, the survey includes a wellbeing assessments (WEMWS[51] and EQ-5D[52]), emotional eating[53], binge eating[54] and activity assessment (Sport England single item question[4]). This data will then be anonymously linked (via a unique referral ID) to the sociodemographic, process and clinical outcomes data collected by NHSE as part of the Low Calorie Diet minimum dataset. The qualitative (free text) questions will explore non-clinical patient centred outcomes, cost, barriers, facilitators, additional weight control practices, the impact of COVID-19 and service improvements. The survey will be available via a secure encrypted online survey[5]. Participants will be asked to provide contact details (phone or email address) in a separate survey (not linked to the participant survey) if they wish to take part in the prize draw and/or would be interested in receiving information about other research opportunities within the study. Data will also be collected cross sectionally for any participants who do not wish, or are unable to complete, the survey at every time point.

Following receipt of ethical approval, we will ask each service provider to send the Participant Information Sheet (PIS) (complete with their unique referral ID) which includes a link to the survey and freephone number to complete the survey over the phone, at the following time points:

- Baseline survey – to be completed between the initial assessment and the first week of the TDR phase.
- End of TDR survey – to be completed at during the last week of the TDR phase and first week of the food reintroduction phase.
- End of food reintroduction survey – to be completed during the last week of the food reintroduction phase and first week of the maintenance phase.
- Maintenance phase – to be completed during the last two weeks of the maintenance phase.
- Withdrawal survey – to be sent to all participants at the point of withdrawal.

[4] PowerPoint Presentation (sportengland.org)
[5] Security Statement // Qualtrics

A freephone number will be established for patients who would rather complete the survey verbally or in another language, to enable participation irrespective of literacy, language, visual ability or internet access (call handlers (with assistance of a translator where required) will complete the online survey on behalf of the participant). We will work with the PPI group to develop a short film about the survey to help raise awareness and survey completion. The PIS and supporting links and phone number, will also be available for participants to access via the Re:Mission study website (www.remission.study). A prize draw of 12x£50 gift vouchers will be made available to incentivise participation, with a prize draw organised and publicised by the study PPI group (4x prize draws per study year). We anticipate an initial survey response rate of around 30% (~1,500 of the 5,000 anticipated patients) based on an uptake of 33.1% observed in the most recent GP patient survey[55]). NB the participant survey will also be distributed to the additional 11 pilot sites that will operationalised from January 2022, which will expand the available recruitment pool.

Analysis: Descriptive and where appropriate inferential statistics will be used to assess any numerical and categorical data in either Excel or SPSS, and free text responses will be synthesised and assessed for emerging themes using Scaled Insights Behavioural Artificial Intelligence software.

Stage 2: Case study: In-depth patient insights.

Of the participants who express an interest in taking part in this stage of the research (either via the study website, participant survey, or recruited by the service provider), we will undertake maximum variation sampling[56], to gain a range of different perspectives by recruiting people from a variety of backgrounds and experiences from across the three delivery models. This form of sampling is designed to explore multiple facets of a problem and investigate issues holistically[56]. Sampled patients will be invited to take part in a 60 minute one to one telephone interview, undertaken at the end of each phase of the programme (12,18 and 52 weeks), replicating the longitudinal qualitative approach undertaken as part of the Counterbalance study[57] and Homer[58]. The purpose of the interviews is to provide in-depth insights into what works, for whom, in what context and why (collecting patient data to assess the mechanism, context and outcomes of the programme). We anticipate recruiting approximately 66 participants – a minimum of six participants who did not start or withdrew from the programme, and at least 30 participants (10 from each delivery model) who start the programme and will be followed up over time. When recruiting six participants who did not start or withdrew from the programme we will aim to sample equally to three groups: those discharged before starting total diet replacement, those discharged during total diet replacement, and those discharged after completing total diet replacement. We will aim to over sample in anticipation of some drop out. The interviews from participants who do not complete the longitudinal interviews will be assessed cross sectionally, additional cross sectional interviews may also be undertaken to explore any key emerging themes in more detail. The interviews will be undertaken using a semi-structured interview guide informed by the realist approach, research questions, photovoice materials (where used) and co-production process (to ensure data enriches the NHSE data) and insights from the survey responses. It is anticipated that the interviews will develop insight into patient expectations and experience of the service, and where appropriate: the reason for not engaging, unexpected or unintended outcomes, what was liked most and least about the service, interaction with other services, confidence in implementing the contents, greatest challenges and successes, views on how the service was delivered, impact of the service on the wider family and social networks, resultant lifestyle changes and achievements, and further explore the context such as the impact of cultural differences, the effect of family and social networks and / or the place of food in the daily lives of participants. The interviews will be supported by our socio-demographically diverse PPI group, who will also be trained in undertaking interviews, so participants can opt to be interviewed by a trained PPI member alongside the study researcher, in recognition of the benefits of having community members as researchers. Prior to each interview participants will also be invited to undertake a 24hr dietary review (using myfood24), either with the researcher after completing the interview or independently beforehand, to track more detailed dietary changes that may occur during the programme. Gift vouchers will be offered to incentivise participation, and translators will be made available for any participants who wish to undertake an interview in another language.

Analysis: The longitudinal interviews will be analysed using the same methodology as for the NHS staff interviews in WP2. The individual dietary data will be auto-analysed within myfood24 and downloaded into Excel for group level analysis.

Stage 3: Longitudinal digitally captured patient journeys.
To try and capture the widest possible range of patient voices, engage participants who may not otherwise participate in an interview only approach, and enrich the interview data, we also propose the use of additional data capture through adapted photovoice methodology. This approach has been successful in the longitudinal follow up of bariatric surgery patients[58] conducted by project manager Homer. Photovoice is a participative research approach used in a community context, where participants take photographs to illustrate their own journey. The technique and approach[59] has also previously been used successfully in bariatric patients[60], Black, Asian and Minority Ethnic groups[61] and underserved[62] communities. Modified photovoice methods will be used alongside interviews to gain a more detailed and in depth understanding of the participants lives and experience of their Low Calorie Diet journey. Prior to each interview, participants will be provided with a 'task' sheet which mirrors the interview schedule in providing prompts of the types of photographs (or short voice or film clips) that participants are asked to take. The task sheets will also include safety guidance to protect participants, and details about consent required before taking pictures of other people. The task sheets and interview schedules have been coproduced with the patient group. Participation in the photovoice element will be entirely voluntary so not to act as a barrier to potential participants who would like to be involved in the study, but do not wish to undertake the photovoice tasks. The photovoice materials will be shared by the participants at the start of the interviews, at this point participants will be asked to talk through the meaning of the photographs, voice clips or film. Any areas of the interview schedule not covered through these descriptions will be covered by asking follow-up questions.

Analysis: The photovoice materials will be conducted alongside the analysis of the interview transcripts and all the data will be stored on NVivo for analysis.

To facilitate the photovoice activity, each longitudinal interview participant (minimum n=30) will be provided with a tablet computer, and then asked if they could capture their journey through photos (and if they wish they can also record short film or voice clips). Participants will own any material they produce and will be asked if they would like to select material to share with the research team prior to their interview, which will help guide the interview process (as described above). Participants will also be asked if they would like to share any of their creative materials to allow the research team to share the images for project reporting and providing a visual insight into the lives of people undertaking the Low Calorie Diet programme. They will also be provided with the opportunity to work with the patient group and media staff at Leeds Beckett University to produce a short 10-15 minute film documenting the patient journey should they wish to. Providing participants with tablets will also provide an opportunity for them to track their dietary intake using (myfood24[63], integrated with access to a novel database of popular multi-ethnic foods developed by Apekey), to examine the impact of more detailed dietary changes over time. Every participant who completes all the longitudinal interviews will be entitled to keep their tablet at the end of the study.

Work package 4: Economic evaluation

Rationale: Economic analyses have recently been conducted alongside two randomised controlled clinical trials of TDR programmes in the UK (the DiRECT and DROPLET trials) and these have informed the design of the NHS Low Calorie Diet programme:

- The within-trial analysis of the DiRECT trial, which compared participants assigned the Counterweight-Plus programme of TDR with participants in a usual care control group, measured healthcare costs, intervention costs and net remission of T2D over two years.[17, 64] Net remission at two years was 32.3%, at an incremental cost of £1,907 per case. A longer-term cost effectiveness analysis,[64] using a three state Markov model (remission, diabetes, death), projected incremental HRQOL gains of 0.06 QALYs and cost savings of £1,337 per person over a lifetime and estimated that the programme would be cost-neutral after six years. The authors noted the rarity of a new

medical treatment for a major chronic disease being both health improving and cost saving, a finding which was robust to various sensitivity analyses, including assessing more conservative assumptions about relapse in T2D over time.

- A long-term economic evaluation involving DROPLET trial data and a multistate life table model estimated an incremental cost-effectiveness ratio (ICER) ranging from £3,203 to £12,955 per QALY (depending on the degree to which weight loss is regained 5 years after the intervention) for a TDR programme delivered via the Cambridge Weight Plan.[65] The study also showed the programme to be more cost-effective in older adults and those with a higher BMI. However, in the DROPLET trial, only 15% of participants had T2D and a limitation of the economic model was that it did not account for the possibility of T2DM remission.

The Re:Mission study economic evaluation will assess the real-world implementation of the NHS Low Calorie Diet programme, delivered through TDR and behaviour change support for people living with obesity and T2D. The intervention will be delivered be across ten pilot sites by four different providers and involve 12 weeks of TDR followed by six weeks food reintroduction and then 34 weeks weight loss maintenance support. The TDR would be delivered through one of three behaviour change delivery models (one to one, group or digital), although due to Covid-19 restrictions, all services are currently being delivered remotely.

WP4 will build on the findings of the economic evaluations of the DiRECT and DROPLET by:

- Assessing the performance of the programme within routine clinical care, rather than in a clinical trial setting
- Assessing differential costs and effects of using different providers and different methods of delivery
- Including larger sample sizes that are more representative of the populations who would be referred to the NHS Low Calorie Diet programme (including ethnic minority groups)
- Exploring differential effects, particularly amongst those at higher risk of T2D and obesity, including within Black and South Asian populations and people with lower socio-economic status
- Including an exploratory assessment of costs incurred by patients themselves (including how these vary by patient-level characteristics), which might impact on programme compliance
- Using an individual-level microsimulation model to assess the long-term cost-effectiveness of the programme when compared to routine care.

Overview of methods:
We will undertake a multi-stage economic evaluation to address the following research questions:

Research questions: WP4.1 - intervention delivery and patient out of pocket cost analyses

- What are the costs of delivering the NHS Low Calorie Diet programme from an NHSE perspective and how do they: (i) differ across the different delivery models and (ii) compare to estimates provided in the DROPLET and DiRECT trials? [RQ9] (method A – intervention delivery cost analysis)
- What are the costs of the NHS Low Calorie Diet programme to participants, and how do they differ by delivery model and patient-level characteristics? [RQ10] (method B – Patient cost analysis)

Research question WP4.2 - long-term cost-utility (cost per QALY) analysis

- What is the long-term cost-effectiveness of the NHS Low Calorie Diet (in terms of incremental cost per QALY) when compared to a counterfactual scenario, and how does this vary by delivery model and patient characteristics? [RQ11] (method C- Patient-level simulation modelling to estimate the long-term cost-effectiveness.

Research question WP4.3 economic comparison with previous trials

- How does the cost and short-term outcome data collected in this study affect the estimates of cost-effectiveness in previous trials? [RQ12] (method D Economic analysis using methods used in the DROPLET and DiRECT trials)

Method (A) Intervention delivery cost analysis (RQ9)

The incremental cost of delivering the intervention when compared to routine care will be assessed for the three different delivery models during the three distinct delivery stages (weeks 1-12, 13-18 and 19-52) of the programme. A bottom-up, micro-costing approach will be used following best practice guidance [66-68].

Data collection will take place as fully integrated components of the semi-structured interviews, focus groups and electronic questionnaire (STAR-LITE) conducted with NHS staff and providers (see WP2 of the main Re:Mission study protocol). In addition to the existing cost questions in STAR-LITE that elicit a free text response, further questions will be designed to elicit details about specific resources used and (where not adequately captured in national databases) their unit costs. Unit costs elicited in this study will be cross-checked with appropriate external sources (e.g. sellers and suppliers of relevant products, national healthcare databases [69, 70] such as PSSRU - Personal Social Services Research Unit data) and published cost analyses of comparable interventions.

The specific resource items to be included in the questionnaire are based on items identified in the DiRECT trial cost analysis[17], other published cost analyses of comparable interventions[71] and through discussions with NHSE. They include (but are not limited to) components of intervention materials, practitioner and patient meetings, and extra patient consultations.

Possible differences between the initial costs of delivering a new programme and the costs of delivering a more established service at scale in the longer term will be discussed in the interviews and focus groups to determine the potential role of learning economies and economies of scale in reducing future delivery costs. Distinctions will also be made in the analysis between fixed costs (e.g. setting up, developing and training staff in delivery of the intervention) and variable costs (e.g. staff time in delivering the intervention, including inviting participants, promoting the intervention, TDR products, etc.). The cost per participant (£) will be reported for the three different delivery models, including how this varies between groups of participants (e.g. by sex, ethnicity, socio-economic status, and site or area), and adjusted to a common baseline year using an appropriate inflation index. The impact of any COVID-19 related adaptations (e.g. provision of remote monitoring equipment) will also be examined to assess the economic impact of COVID-19 programme adaptations.

Method B: Patient cost analysis (RQ10).
An exploratory analysis of patient out-of-pocket costs will be conducted to identify resource use and costs incurred by patients enrolled on the programme, including any differences that may be attributed to different patient characteristics and different delivery models. Resource use questions will be designed for inclusion in the longitudinal patient questionnaires and interviews conducted as part of the study (See WP3 of the main Re:Mission study protocol). The specific resource use items to be included will be determined through discussion with NHSE and our patient group, but will likely focus on travel to appointments, time off work, and any intervention-related materials and resources not reimbursed by the healthcare system such as physical activity sessions and healthy food purchases. A free text question in the questionnaire and a semi-structured interview question (WP3) may also bring to light further issues related to out-of-pocket expenses.

Method C: Patient-level simulation modelling to estimate the long-term cost-effectiveness of the Low Calorie Diet programme compared to a counterfactual scenario (RQ11).

The long-term economic modelling analysis will estimate the healthcare costs and QALYs associated with the LCD when compared to a counterfactual scenario where participants did not receive the Low Calorie Diet. This will be conducted using the UKPDS outcomes model version 2 (UKPDS-OM2), an open-access patient-level simulation model[72].

Inputs to the model will be the patient-level clinical and sociodemographic data collected at baseline and over Inputs to the model will be the patient-level clinical and sociodemographic data collected by NHSE in the minimum dataset, including BMI, blood pressure, HbA1c, other health conditions, sex and ethnicity. To estimate the long-term costs and benefits of the LCD programme, this will include the data collected at all

timepoints between baseline and 12 months. To estimate the long-term costs and benefits associated with the counterfactual scenario in which participants did not receive the LCD programme, the model will be run separately using only the data collected at baseline as inputs.

Dependent on the nature and extent of missing data in the minimum dataset, imputation will be used in our base case analysis so that missing model input data can be replaced with plausible substitutes. Different approaches may be taken to missing data at baseline and follow-up, and on the BMI outcomes compared to covariates, for example. Assuming that data were missing at random (MAR), a predictive mean-matching approach would likely be used incorporating person-level and site-level baseline values. However, final decisions on the approach to imputation will be made after examination of the dataset and in line with guidance published alongside the UKPDS-OM2; the imputation will done in collaboration with NHSE in order to ensure consistency with the approach taken in the NHSE quantitative analyses.

Outputs of the model will be year by year predictions of future clinical outcomes, healthcare treatment costs and QALYs at the patient-level based on the clinical and sociodemographic input data described above. These will be reported separately for each of the delivery models and for the counterfactual scenario. For the counterfactual scenario, the outputs of the model would be reported after baseline, whereas for the three different intervention delivery models, they would be reported after 12 months.

The UKPDS model estimates these outputs using risk equations that were derived originally from data collected over 30 years from UK participants with newly diagnosed T2D in the United Kingdom Prospective Diabetes Study, including patients whose T2D subsequently went into remission (i.e. with HbA1c values below 6.5% for at least 12 months). These risk equations were substantially updated in 2013 and more recently for use in present day policy evaluation and validated against contemporary patient-level data.[73] The model incorporates a complex array of T2D complications, including those related to MI, stroke and cardiovascular diseases. Hence the model is well suited to our principal focus on T2D-related outcomes and on patients with newly diagnosed T2D. Nevertheless, the model does not include the effect of other changes in clinical or health measures that are not related to diabetes complications, but which might be expected to be affected by the NHSE LCD (e.g. BMI). These can be incorporated into the model by making changes to the model inputs for costs and QALYs, and we will pursue this in sensitivity analyses, dependent on the quality of available data in the literature and in consultation with NHSE.

The model outputs (year by year healthcare costs and QALYs) will be incorporated into a cost utility analysis along with the intervention costs calculated in RQ9 above. The analysis will be done on an intention-to-treat basis, i.e. including all participants who registered at baseline regardless of whether they completed treatment, however a complete case analysis (excluding participants who dropped out) will be conducted as a sensitivity analysis. In addition to reporting differences in cost-effectiveness for the three delivery models (when compared to 'routine care'), appropriate methods will be used to assess patient-level heterogeneity in the programme's cost-effectiveness including (but not limited to) by ethnic group and severity of obesity. Following NICE guidelines, costs and QALYs will be discounted at 3.5% per annum (for values post 12 months) and 1.5% in a sensitivity analysis (reflecting recommendations for evaluating preventive programmes)[74]. Decision uncertainty will be illustrated with a scatter plot of incremental cost and QALY pairs and a cost-effectiveness acceptability curve (CEAC).

The impact on cost-effectiveness of various important assumptions will be examined in detail. These may include exploration of the following:

- Different scenarios of (A) weight gain and (B) diabetes relapse after remission. This will be done after 12 months for participants who complete the intervention and, separately, after baseline for participants who drop out of the study and/or do not complete the intervention. The scenarios will draw on published literature (e.g., for obesity: [75, 76], and for diabetes relapse after remission). Example scenarios for weight include one in which patients return to baseline level (and 1kg below baseline level) in a linear fashion over a five-year period, as was assumed in the DROPLET economic analysis.

- Alternative approaches to modelling our 'routine care' scenario. In our base case, the UKPDS outcomes risk equations will be used, i.e. in this scenario patients would be left to propagate through the long-term model. Alternative approaches could be based on data and strategies adopted in comparable studies, e.g. trials with a 'routine care' arm.

These sensitivity analyses will be determined in collaboration with NHSE. We are also currently pursuing the possibility of collecting additional data on outcomes (including weight change and T2D remission) by following-up a sample of participants in our study beyond 12 months.

Method D: Economic analysis using methods used in the DROPLET and DiRECT trials (RQ12)
For the DiRECT trial, we will compare the breakdown of costs of the intervention and calculate a cost per case of T2DM remission after 12 months using data collected in RQ9 and RQ11. For the DROPLET trial, we will compare the costs of the intervention and use the PRIMEtime-Cost-Effectiveness obesity model to conduct a cost-utility analysis of the TDR intervention over a lifetime. The purpose of these analyses is to further strengthen the evidence base for commissioners by: assessing the extent to which the existing findings of two trial-based studies are applicable in a real-world setting; and to provide a comparison with the cost and effectiveness estimates we calculated using the NHSE data and UKPDS-OM2.

Work package 5: Transferability assessment

Rationale: Implementation science has highlighted the importance of context in the success or failure of health care innovations. To support evidence informed commissioning and decision making, it is necessary to assess whether the outcome of the programme is transferrable to a national context. This work package will explore the context surrounding wider implementation of the NHS Low Calorie Diet, both in terms of its transferability and its potential to sit within national policy.

Research question WP5.1: What are the core elements of the intervention that are required to achieve impact? [RQ13] What elements can be adapted to suit local context? [RQ14] What are the policy implications for wide-spread adoption of the programme? [RQ15]

We propose to apply the theoretical model for the assessment of transferability of health interventions, developed by Schloemer[28]. This framework will incorporate the findings from WP 2-4 (which will run concurrently with this WP), with wider evidence, to inform consideration of the core elements of key functions of an intervention, and then estimate which parts are, or are not, transferable (or need to be adapted). The conditional criteria will be based on the Population-Intervention-Environment-Transfer Model of Transferability (PIET-T) conceptual model, in which the population ((P) characteristics, perceptions and attitudes)), intervention ((I) description, relevance, feasibility, adaptations)), environment ((E) policy, health care system), and the transfer of the intervention ((T) communication, expectations, training, sustainability), are considered as key factors which represent the transferability of the intervention from its primary context (i.e. within the pilot sites) to the target context (national roll-out). This considers the conditions of the primary context (the original evaluation) and how well it would transfer to a target. This process will require both information from both the primary and target contexts, and will therefore use multiple approaches which will include:

- A population review from national databases to describe the population characteristics of the target context.
- Document review of the intervention and related policy in both the primary and target context, from WP2 and wider policy documents (e.g. legislation in health care provision, finance, resources, accessibility).
- Qualitative data from WP2&3 on perceptions, feasibility, adaptations and normalisation requirements..
- A rapid review of evidence of Low Calorie Diet within the target population to identify core elements of the programme and to support decision making in target contexts (including findings from NHSE evaluation).

- A short Qualtrics survey to non-pilot areas to capture transfer methods (e.g. goals, structure, management, expectations, relationship building, information exchange, support and need for training).

Hosting two national workshops with commissioners, policy makers, service providers and patients to explore transferability using data gathered from this WP (comparing and contrasting the primary and target contexts) to get a better understanding of the steps needed to ensure optimal transferability

SWAP sub-study Work package

An additional sub-study was funded through the NIHR-SWAP programme in March 2022, to further examine the impact of the NHS Low Calorie Diet programme in patients living with multiple long-term conditions: obesity, T2D and Osteoarthritis. Full details of this sub-study work package can be found in Annex 1.

DISSEMINATION PLANS:

Our dissemination plans, which have been developed with our PPI group, are as follows:

- Short regular (biannual) update reports to all stakeholders including NHSE and the Low Calorie Diet advisory group, to ensure that emerging findings influence service delivery. These reports will all have a plain English summary and will be supported by podcasts and/or blogs for patients and the public.
- Presentations at local, national and international seminars and conferences (all co-presented by the research team and PPI group members).
- A study website – www.remission.study.
- At least four open access peer reviewed journal publications.
- A series of short talking head films to illustrate patient experience and evaluation learning.
- The final study report, which will be supported by summary infographics.
- An illustrated journal-style summary of the final report for patients and the public.
- A 10-15 min film about the patient journey.
- End of year blogs and prize draw updates provided by our PPI group.
- Guidance to support the wider roll-out of the programme based on evidence of transferability.

ETHICAL APPROVALS:

Ethical and governance approvals will be gained before any data collection commences.

PROTOCOL REVISION TRACKING:

Any amendments to this document will be documented in Table 1:

Table 1: Protocol revision tracking.

Protocol version number	Date of amendment	Amendment made	Reason for amendment
V2	21/10/2021	Minor change to project team	Health Psychologist Cristiana Duarte left her post at Leeds University and has been replaced.

		Protocol inserted into Re:Mission study design template. Expansion to the WP4 protocol, following comments from the Low Calorie Diet advisory group. Further detail on the session observation work in WP2 has been added: the addition of new digital observation methodology, and minor changes to the selection of the session observations (from a random sample of session observations to following two full patient journeys per service provider). Cross sectional survey and interviews have been added to WP3, following input from the coproduction process.	To incorporate study branding. Request to expand WP4 methodology was made by the Low Calorie Diet advisory group – who made some suggested amends and requested further methodological detail. Following discussion with the DIPLOMA team who led the NDPP evaluation, we have aligned our methodology so we can draw learning across the two programmes. The digital observation methodology was added as the original methodology was not compatible with the delivery of the digital programme. To acknowledge that not all participants may not wish or be able to, complete all 4 participant surveys. We have also proposed to oversample for the longitudinal interviews to compensate for potential drop out, and will also conduct a small sample of cross sectional interviews where there is a need to further examine key emerging themes.
V3	07/03/2022	*P13 methodology was* 'informed by Bowen'	Correction for clarity.

		P14 convenience sample of 13 (not 11) *P17 Stage 2: Case study: In-depth patient insights. We added that participants can be* recruited by the service provider.	Correction for clarity. This is to reflect the need to accommodate targeted recruitment in the event of the survey and website participants not populating our sampling framework.
V4	28/03/2022	P2, 3, 23 and Annex 1 additional information provided on the SWAP funded sub-study examining impact in patient with Multiple Long Term Conditions.	To provide details on the personnel and methods undertaken as part of the SWAP funded sub study.

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ANNEX 1: Re:Mission SWAP Sub-Study Work Package

SUB STUDY TITLE: Examining the impact of the NHS Low Calorie Diet programme on patients with multimorbidity (obesity, type 2 diabetes and osteoarthritis of the hip or knee)

SHORT TITLE: Re:Mission – SWAP sub-study

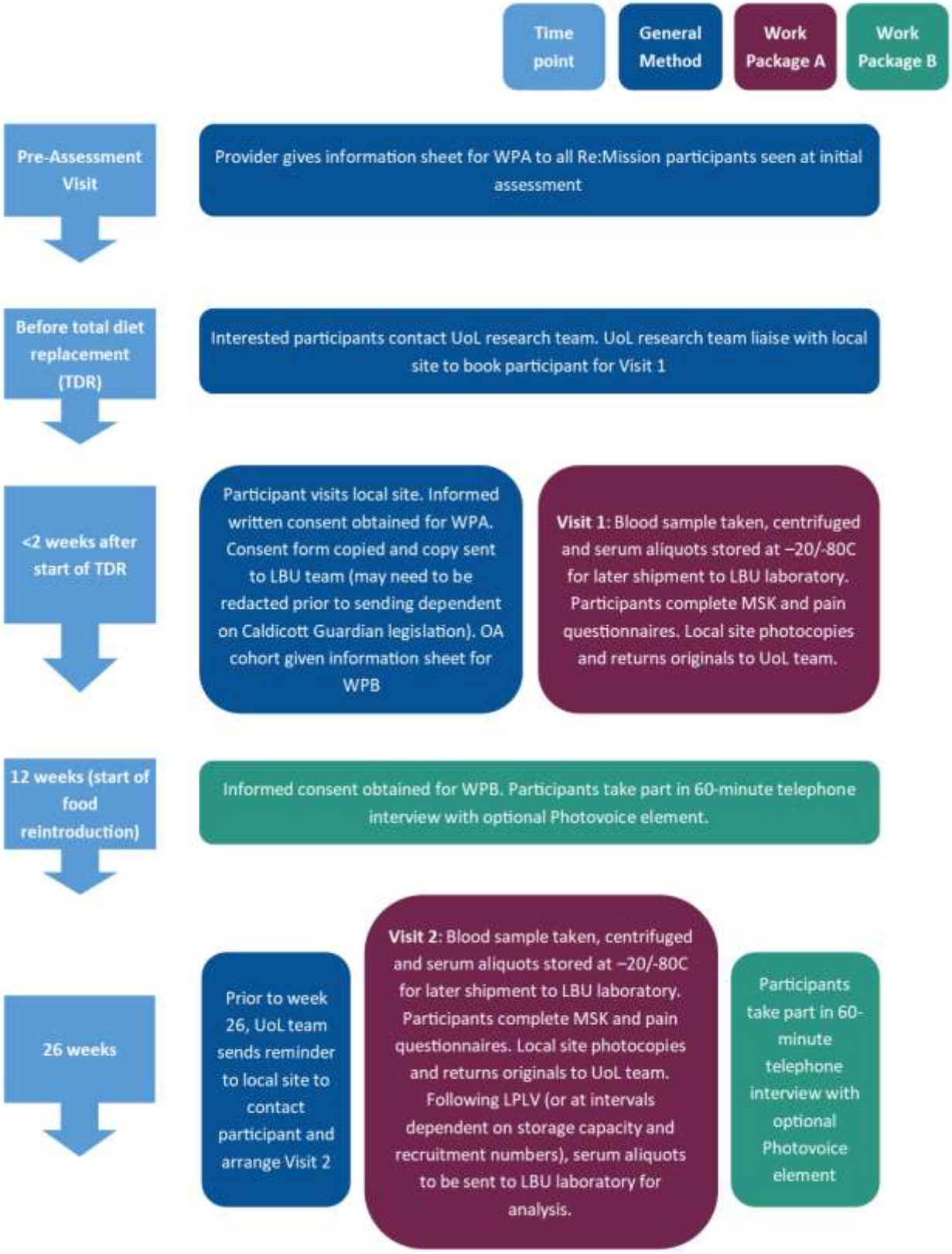
RESEARCH REFERENCE NUMBERS (SWAP SUB STUDY):

Health Research Authority approval: IRAS project ID; REC refence: [pending]

FUNDING:

This study has been funded by NIHR HS&DR SWAP funding.

STUDY FLOW CHART:



A1.0 Context

Joint pain, osteoarthritis (OA), obesity, and type 2 diabetes (T2D), are common diseases that frequently co-exist as Multiple Long Terms Conditions (MLTC)[1]. Many patients taking part in the NHS Low Calorie Diet (LCD) programme will have co-existing obesity, T2D and OA. Our patient advisory group is concerned about the impact of co-existing OA and pain, on LCD patient experience and success. This concern is further substantiated by existing research evidence that suggests: 1) a bidirectional relationship between weight and pain that may impact weight loss[2, 3]; 2) that systemic inflammation, found in obesity and diabetes, may be involved in the development and progression of OA pain[4, 5]. This study presents a unique opportunity to further understand the impact of OA pain on patient experience and inflammatory biomarkers, that will provide critical understanding as to how best to tailor programme support for this patient group.

A1.1 Rationale

Although previous trials have examined the role of LCD programmes delivered through total diet replacement products for OA[6], obesity[7] and T2D[8] none have examined the impact on lived experience and underlying inflammatory mechanisms, specifically in patients with all three conditions. There is currently a gap in terms of the most appropriate support for patients with obesity, T2D and OA as MLTC.

A number of pathological drivers have been postulated to cause OA pain, including local factors (such as cartilage loss and local inflammation) and systemic factors, but these relationships remain unclear. This study will enable us to examine the lived experience, joint symptoms and systemic inflammatory profile of a cohort of patients with obesity and T2D with and without co-existing OA. The findings will provide new insights into the impact of the LCD programme in patients with co-existing OA, and whether the current programme can be tailored to enhance support and success within this patient group.

A2.0 Research Aims and Objectives

Aim:

To collect additional qualitative data and clinical biomarkers to understand the impact of LCD in patients with MLTC: obesity, T2D and painful OA of the hip or knee.

Objectives:

1. To undertake ten additional longitudinal interviews, using novel adapted photovoice methodology to explore the lived experience of the LCD programme in patients with co-existing OA, to explore how this may impact on their ability to participate in the programme and whether additional support needs are required.
2. To assess IL-6 and hs-CRP in LCD patients with and without OA to determine the impact of the programme on underlying inflammatory pathways.
3. Use learning from this study to inform practice and research:
    a. Develop additional support for LCD patients with MLTC if required.
    b. Inform the development of personalised approaches to diabetes management

A3.0 Study Design

This study will be a sub study of the main Re:Mission study evaluation, that will use a mixed methods approach to provide new data that will further our understanding of the relationship between hs-CRP and joint pain, underpinning targeted therapy and providing new treatment options for this well-defined subset of patients with OA. The study will therefore provide outcomes that will directly inform other pain and inflammatory research; inform the care of patients with T2D and obesity, and further inform the NHS LCD evaluation.

This work will be undertaken in two work packages, to answer the following research questions:

- What are the lived experiences of Low Calorie Diet programme participants who have co-existing OA pain?
- What is the relationship between success of the Low Calorie Diet programme and inflammatory biomarkers?
- Can the management of participants on the Low Calorie Diet programme with pre-existing OA pain, be improved?

A4.0 Methods

A4.1 Work Package A: Quantitative research

In this work package we will examine the impact of joint pain in people taking part in the NHS Low Calorie Diet programme

A4.1.1 Target population

100 patients with and 100 patients without OA of the hip or knee from the NHS LCD programme cohort.

Participants will be allocated to the OA or Non-OA cohort using the following screening question: Has your GP ever referred you to see a specialist [physio, orthopaedic, rheumatology] about pain in your hip or knee, or have you been told you have OA of the hip or knee? Participants who answer yes to either question and have not undergone a hip or knee replacement in their OA hip/s and/or knee/s (i.e. have at least one native hip or knee affected by OA), will be enrolled into the 'OA cohort'. Participants who answer no to both questions will be enrolled into the 'Non-OA cohort'.

A4.1.2 Eligibility criteria

Inclusion criteria

(a) Age 18 years or over

(b) Ability to provide informed consent

(c) Referral into NHS Low Calorie Diet programme.

OA participants only:

(a) At least one native hip or knee affected by OA

Exclusion criteria

(a) Any physical or mental condition or disorder, which, in the opinion of the investigator, may affect participation in the study.

A4.1.3 Recruitment

Potential participants will be provided with a copy of the Participant Information Sheet (PIS) by the Service Provider at their pre-assessment visit. The PIS will provide detailed information about the rationale, design and personal implications of the study, as well as contact details of the central study team. Patients will be invited to call the team if they have any questions or concerns about the study, or if they would like to register their interest in taking part. Once a participant has confirmed their interest in the study, the central research team will then liaise with the local research site to organise the first study visit.

A4.1.4 Informed consent

In all instances, potential participants will be given as long as they need, ideally at least 24 hours, to consider participation and will be given the opportunity to discuss the study with their family and healthcare professionals before being invited to give consent to participate in the study.

Assenting participants will then be formally assessed for eligibility by the PI or authorised delegate as listed on the trial specific delegation log and invited to provide informed, written consent. The right of the patient to refuse consent without giving reasons will be respected. A copy of the consent will be given to the participant, and one filed in the Study Files. The written consent will be taken by the PI or authorised delegate, who has signed / dated the staff authorisation / delegation log.

A4.1.4.1 Participants who withdraw consent

Participants are free to withdraw from the study at any time for any reason without prejudicing any further treatment and with no obligation to give the reason for withdrawal.

In the case of a participant withdrawal, data collected up until the point of withdrawal will be retained for the full archive period in line with the Data Protection Act 2018. Samples and data collected from samples cannot be withdrawn once they have been used.

A4.1.4.2 Managing/replacing participants who withdraw early

Participants who withdraw from the study early will not be replaced.

A4.1.5 Methods of assessment

A4.1.5.1 Participant Reported Outcomes

Participants will be asked to complete three additional questionnaires at the baseline and 6 month visits:

(a) Knee injury and Osteoarthritis Outcome Score (KOOS) and / or Hip disability and Osteoarthritis Outcome Score (HOOS)

These questionnaires assess the participant's opinion of their knee/hip. Questions are asked regarding knee/hip symptoms, pain, function in daily living and function in sports and recreational activities. Each question is assigned a score from 0-4. Total scores can range from 0 (most extreme symptoms) to 100 (no symptoms). Participants will complete one or both dependent on whether they have knee OA, hip OA, or both.

(b) Adapted Nordic questionnaire (Kuorinka et al., 1987)

A standardised questionnaire designed to answer the following question: "Do musculoskeletal troubles occur in a given population, and if so, in what parts of the body are they localised?" The questionnaire includes a shaded manikin highlighting regions of the body and asks the participant to indicate which regions they experience trouble (ache, pain or discomfort). For the purposes of this study, the questionnaire has been adapted to determine if the pain is new onset post-COVID-19 and to rate the overall (average) severity of the pain in the past week on a 0-10 numerical rating scale (NRS), where 0 is no pain and 10 is pain as bad as it can be.

(c) Musculoskeletal Health Questionnaire

The Musculoskeletal Health Questionnaire MSK-HQ is a short questionnaire that allows people with musculoskeletal conditions (such as arthritis or back pain) to report their symptoms and quality of life in a standardised way. It contains 14 questions scored on a 5 point scale from 'not at all' to 'very severe', with an additional question about physical activity levels in the last week.

A4.1.5.2 Biological samples

A maximum of 9 mls of blood will be taken at each study visit to enable measurement of inflammatory biomarkers, including hsCRP and IL-6.

The blood will be drawn into 1 x 9ml clot tube. For further information on sample collection and processing, seethe latest version of the Biological Sample Collection Form.

As part of the biological sub study personal details will be removed from all research blood samples after separation into the component parts and before testing, samples will be identifiable by subject identification number only. It will be possible to link the study and laboratory databases through this unique number so that long-term disease outcomes and predictors of response to future treatments can be examined. Biological samples will be stored at recruitment sites and the LBU Laboratory for the duration of the study with explicit consent for the samples to be stored beyond the duration of the study for future research. Any samples that are not used at the end of this study will be transferred to an HTA-approved Research Tissue Repository

once the project specific approval expires and will be used in future studies within this research remit. Aliquots of these biologic materials may be shared for research purposes only with national and international academic and industrial collaborators worldwide. The samples will be fully anonymised of patient identifiers before transportation.

Contextual data may also be included in any submissions. Access to such non-identifiable data will be reviewed for appropriateness before release. The transport of samples will be via IATA certified staff, logged and registered via a database and sent in a clinical fashion via independent internal transport.

A4.1.5.3 Data Linkage

We will ask patients for their permission to link their data to the LCD minimum dataset via their unique referral ID, so the inflammatory data can be linked to the LCD clinical data.

A4.1.6 Study procedures by visit

Summary schedule of study assessments

STUDY VISIT	**Pre-baseline**	**Visit 1** **Baseline***	**Visit 2** **6 month follow-up** **(+/- 4 weeks)**
Study information provided to potential participants in clinic	X		
Informed consent		X	
Inclusion / Exclusion		X	
Participant questionnaires		X	X
Biological sample		X	X

**As close to commencement of the LCD programme as possible*

^To coincide with completion of the food re-introduction phase

A4.1.7 Data handling

A4.1.7.1 CRF completion

The research team is responsible for prompt reporting of accurate, complete, and legible data in the case report forms (CRFs) and in all required reports. Any change or correction to the CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted. Completed CRFs should be photocopied, the copy stored locally and the original posted to the central research team.

Completed CRFs to be posted to:

Osteoarthritis Clinical Trials, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA

A4.1.7.2. Database entry and reconciliation

Case report forms will be entered into an electronic database. Computerised data cleaning checks will be used in addition to manual review to check for discrepancies and ensure the consistency of the data. Regular backups of the electronic data will be performed.

A4.1.7.3. Screening and enrolment logs

Subject's enrolment will be recorded in the Subject Enrolment Log.

The Investigator will keep a list containing all subjects enrolled into the study. This list remains with the Investigator and is used for unambiguous identification of each subject. The list contains the subject identification number, full name, date informed consent signed, date of screening/baseline visit, and the hospital number or NHS number, if applicable.

A4.1.7.4. Archiving and data retention

Study data and documents will be retained for 5 years following the completion of the study. Arrangements for confidential destruction will then be made. No records/study documentation/data may be destroyed without first obtaining written permission from the Sponsor.

Essential documents include (this list is not exhaustive):

- Signed informed consent documents for all subjects.
- Subject identification code list, screening log (if applicable) and enrolment log.
- Record of all communications between the Investigator, the REC and the Sponsor.
- Composition of the REC, and the Sponsor (or other applicable statement as described in section 11.5).
- List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of case report forms and documentation of corrections for all subjects.
- All other source documents (subject medical records, hospital records, laboratory records, etc.).
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial).

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

A4.1.7.5. Study suspension, termination and completion

Suspension or termination of the study may occur at any time for any reason, following discussion between the Investigator and the Sponsor. Upon study completion, the Investigator will provide the Sponsor with final reports and summaries as required by regulations, and will be responsible for completing a premature end of study report to the Research Ethics Committee (REC) within 15 days.

A4.1.8 Data evaluation

A4.1.8.1. Responsibilities

Data analysis will be conducted by members of the study team. A full statistical analysis plan will be written before any analyses are undertaken.

A4.1.8.2. General statistical considerations

This will be an exploratory study using observational data. The data will be analysed using a suitable statistical package such as SPSS or Stata.

In general, summary statistics will be presented as [n (number of available measurements), arithmetic mean, standard deviation, median, minimum, and maximum] for quantitative variables and absolute and relative frequency tables for qualitative data. Data will also be displayed graphically.

A4.1.8.3. Planned analyses

In general, the analyses will consist of descriptive presentations of the data, but formal statistical comparisons will be carried out where appropriate. A statistical analysis plan will be completed before the start of the data analysis.

Firstly, general summary statistics, mainly descriptive will be presented and summarised appropriately depending on the distribution of each variable for example means and medians, or percentages and proportions within each cohort. This will provide estimates of the prevalence of systemic inflammation (as measured by hsCRP, IL6) in the different cohorts. Data will also be displayed graphically by means of distribution plots where appropriate to aid visualisation. Non-interval scaled data (PROs) will undergo Rasch analysis (see below) prior to descriptive analyses and parametric testing. Associations between different variables within each cohort will be assessed using Pearson correlation coefficients and scatter plots. Logistic regression analyses will be performed to determine if case status (symptom reporting) is related to inflammatory biomarker levels. Where appropriate, adjustments for multiple comparisons will be considered e.g. Bonferroni correction.

It is anticipated that patient-reported outcomes (PROs) included in this study will undergo parametric statistical testing, however most of these are ordinal and would not satisfy assumptions for parametric analyses in their raw form. Rasch analysis can support this process by providing a transformation of an ordinal score into a linear, interval-level variable, given fit of data to Rasch model expectations. The various PROs collected in the different cohorts will be transformed to interval scaling by assessing fit to the Rasch measurement model in RUMM 2030 software. This process formally tests that the data meet minimum requirements for measurement then allows transformation from ordinal to interval linear scaling facilitating parametric analysis.

A4.1.8.4. Determination of sample size

This represents a cohort study therefore no formal sample size / power calculations have been carried out, however we anticipate that approximately 200 patients will be included in the study, 100 participants with hip or knee OA and 100 participants without hip or knee OA.

A4.1.9 Safety issues

As this study is an observational study with no intervention, the only AE's or SAE's recorded will be those directly related to the study visits.

A4.1.9.1 Defining adverse events (AEs)

An **adverse event** (AE) is any untoward medical occurrence in a study participant which does not necessarily have a causal relationship with study procedures. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease experienced whilst participating in the study, regardless of its causal relationship to the study visits. As this is an observational study with no intervention, the only AE's to be collected will be those directly related to study visits.

A4.1.9.2 Defining serious adverse events (SAEs)

A **serious adverse event** (SAE) is an adverse event which is defined as serious, i.e. that it:

- Results in death. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the participant's final research clinic appointment must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such.
- Is life-threatening.
    - Requires inpatient (overnight) hospitalization or prolongation of an existing hospitalization.
    - Results in a persistent or significant disability or incapacity.
    - Results in a congenital anomaly or birth defect.
    - Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require

medical or surgical intervention to prevent one of the outcomes listed in this definition.

- Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the Investigator requires reporting.

As this is an observational study with no intervention, the only SAE's to be collected will be those directly related to study visits. Causality and expectedness will be assessed by the PI or duly authorised clinician as listed on the trial specific delegation log.

A4.1.9.3 Urgent safety measures

If the research team becomes aware of information affecting the risk/benefit balance of the trial they may take immediate action to ensure participant safety. Urgent safety measures deemed necessary must be reported immediately by telephone to the main REC for the trial and must be followed within three days by notice in writing setting out the reasons for the urgent safety measures and the plan for further action. The REC co-ordinator will acknowledge within 30 days.

A4.1.9.4 Serious breaches of protocol

A **serious breach** is a breach which is likely to effect to a significant degree either:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Serious breaches of GCP and the trial protocol will be reported to governance-ethics@leeds.ac.uk within 24 hours (same day, except weekends) from the time the research team becomes aware of the incident.

A4.1.9.5 Annual reports

An annual report describing the general progress and any relevant safety data related to the trial must be submitted to the main REC and the Sponsor on the anniversary of the REC approval being granted. The appropriate form for non-CTIMPs is available from the HRA website.

The Chief Investigator (CI) must review and sign / date the report.

A4.2 Work Package B: Qualitative research

For this work package we will extend the number of longitudinal adapted photovoice interviews to a further ten patients living with obesity, T2D and OA, recruited from the 100 OA patients selected through work package A. This is an extension to the existing main evaluation within the Re:Mission study (IRAS project ID

294667; REC refence: 21/WM/0136) – see methodology described in the main protocol, with the only difference being collection of the last interview at 6 rather than 12 months, in order to fit data collection time frames with the completion of the funded evaluation.

A5.0 STUDY MANAGEMENT, ADMINISTRATION, ETHICS AND REGULATORY REQUIREMENTS

A5.1 Good clinical practice (GCP)

This clinical trial will be run in accordance with the Principles of ICH GCP and the UK Policy Framework for Health and Social Care Research.

A5.2 Delegation of Investigator duties

The PI will maintains overall responsibility for ensuring that all persons assisting with the study are adequately qualified and informed about the protocol, any amendments to the protocol, the study procedures, and their trial-related duties and functions.

The PI will maintain a delegation log of sub-investigators and other appropriately qualified persons to whom he or she has delegated trial-related duties.

A5.3 Adherence to protocol

During the course of the study, there should be no deviations from the protocol. In medical emergencies, the PI or delegate may use his/her medical judgment and may remove a study participant from immediate hazard before notifying the Sponsor and the REC in writing regarding the type of emergency and the course of action taken.

A5.4 Subject information and informed consent

Before being enrolled in the study, subjects must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An informed consent document (Participant Information Sheet) that includes both information about the study and the consent form will be prepared and given to the subject ideally at least 24 hours prior to the screening visit. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. Where possible, the document must be translated (by an independent interpreter) into a language understandable to the subject and must specify who informed the subject.

At visit 1, participants will be given the opportunity to ask questions and the nature and objectives of the study will be explained. The PI or duly authorised delegate is responsible for the informed consent discussions.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

The original signed consent document will be retained in the study files. Other copies of the consent form are required:

- One copy will be given to the participant.

Consent is an ongoing process and will be reassessed at each study visit.

No trial specific procedures will be conducted until valid consent has been obtained.

A5.5 Subject confidentiality

Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to anyone outside the clinical care team. The subjects will be informed that representatives of the Sponsor, REC or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence.

All information collected during the course of the trial will be kept strictly confidential, and information will be held securely both on paper and electronically.

The study team will comply with all aspects of the UK General Data Protection Regulation.

The Principle Investigator at each site will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

A5.5 Monitoring and audit

The Sponsor reserves the right to audit any site involved in the trial and authorisation for this is given via the study contract or agreement, the PI should allow direct access to trial documentation for the purpose of an audit.

A5.6 Study management

A5.6.1 Definition of source data

Source documents are original records in which raw data are first recorded. For the purposes of this study, the case report form will be the source document for all study data. Source documents should be kept in a secure, limited access area.

A5.7 Approval of clinical study protocol and amendments

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the REC, HRA and the Sponsor with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met, including approval of the study by the NHS, the Sponsor Research and Development department, the REC and HRA.

Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised, thus all protocol amendments and administrative changes must first be discussed with and approved by the Sponsor before being submitted to the REC and/or HRA, in accordance with legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised.

The Investigator must keep a record of all communication with the REC, HRA and the Sponsor.

A5.7.1 Protocol amendments

Requests for any amendments to the study must be sent to the Sponsor by the Chief Investigator. The Sponsor will determine whether said amendments are substantial or non-substantial prior to their submission to the appropriate bodies for approval. Participants should be re-consented to the study if the amendments affect the information they have received, patient safety, or if the change alters the type or quality of the data collected for the study. Participants should only be re-consented **after** an amendment has been fully approved.

A5.7.2 Ongoing information for Research Ethics Committee

Unless otherwise instructed by the REC and the Sponsor, the Investigator must submit to the REC and the Sponsor:

- Information on serious adverse events that are unexpected and related to study procedures (RUSAEs) from the Investigator's site, within 15 calendar days of the research team becoming aware of them.
- Expedited safety reports, as soon as possible.
- Annual reports on the progress of the study.
- Declaration of End of Study form.

A5.8 Trial oversight

Oversight of the study will be conducted by the Trial Management Committee. Amongst its members will include the CI and Project Managers. Meetings will occur regularly.