RE:MISSION STUDY PROTOCOL

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:

NIHR reference: **NIHR132075**

Research registry reference: **researchregistry6614**

Leeds Beckett University LREC reference for WP2 (excl NHS interviews): **80438**

Health Research Authority approval for WP2 NHS interviews and WP3 pending.

FUNDING:

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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

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES

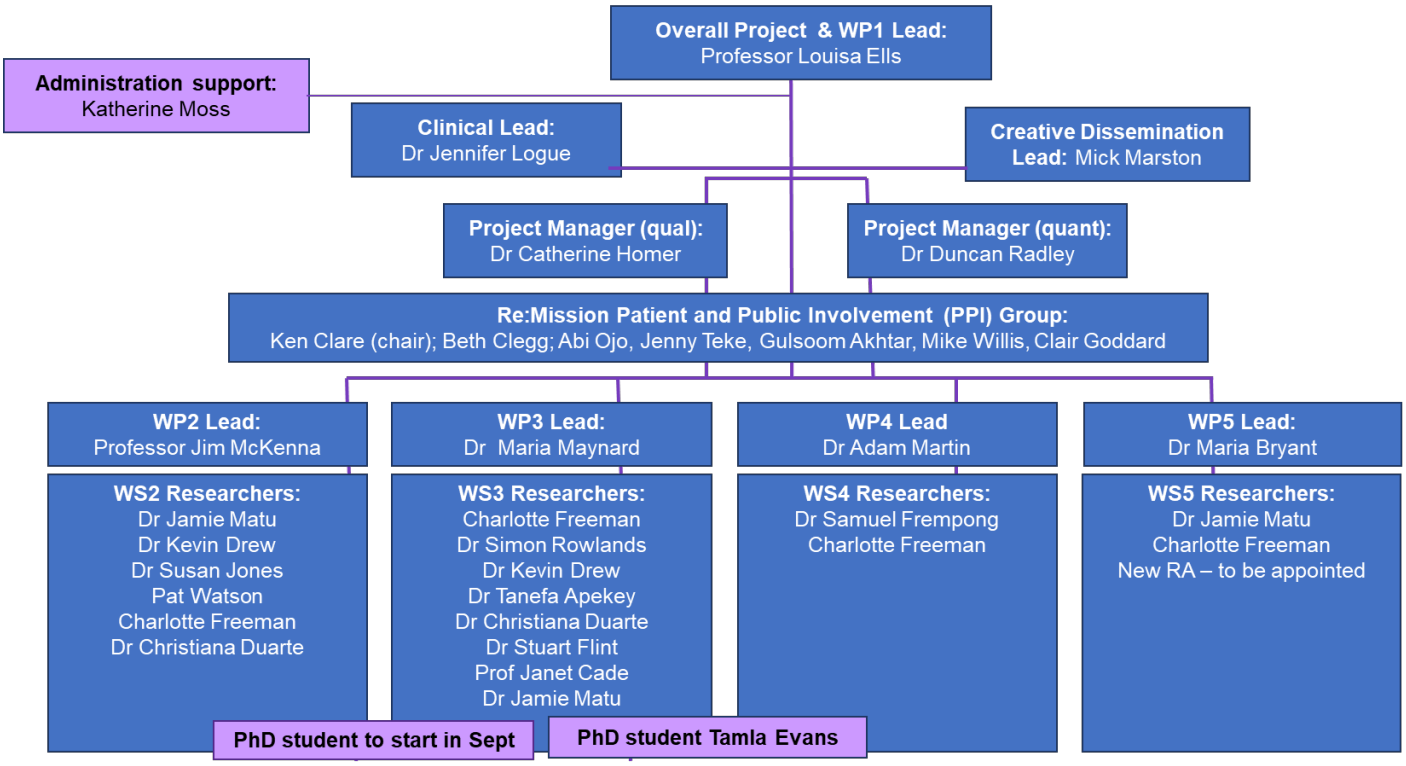
The Re:Mission project independent oversight group's role:
To provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health 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:


Overall Project & WP1 Lead:
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Clinical Lead:
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Creative Dissemination Lead: Mick Marston
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Dr Christiana Duarte
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Charlotte Freeman
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Dr Kevin Drew
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Dr Christiana Duarte
Dr Stuart Flint
Prof Janet Cade
Dr Jamie Matu
WS4 Researchers:
Dr Samuel Frempong
Charlotte Freeman
WS5 Researchers:
Dr Jamie Matu
Charlotte Freeman
New RA – to be appointed
PhD student to start in Sept
PhD student Tamla Evans

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 longitudinal patient surveys, interviews and visually represented patient journeys using adapted photovoice

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

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 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 cost per quality adjusted life year (QALY). 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 recent Low Calorie Diet trials?; RQ10 What are the costs of the NHS Low Calorie Diet programme to participants, and how do they differ by delivery model and socio-demographics? 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 cost per QALY and how does this vary by delivery model and patient characteristics? We will also replicate the methods used in recent Low Calorie Diet 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 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 TDR programmes, which will be shared internationally.

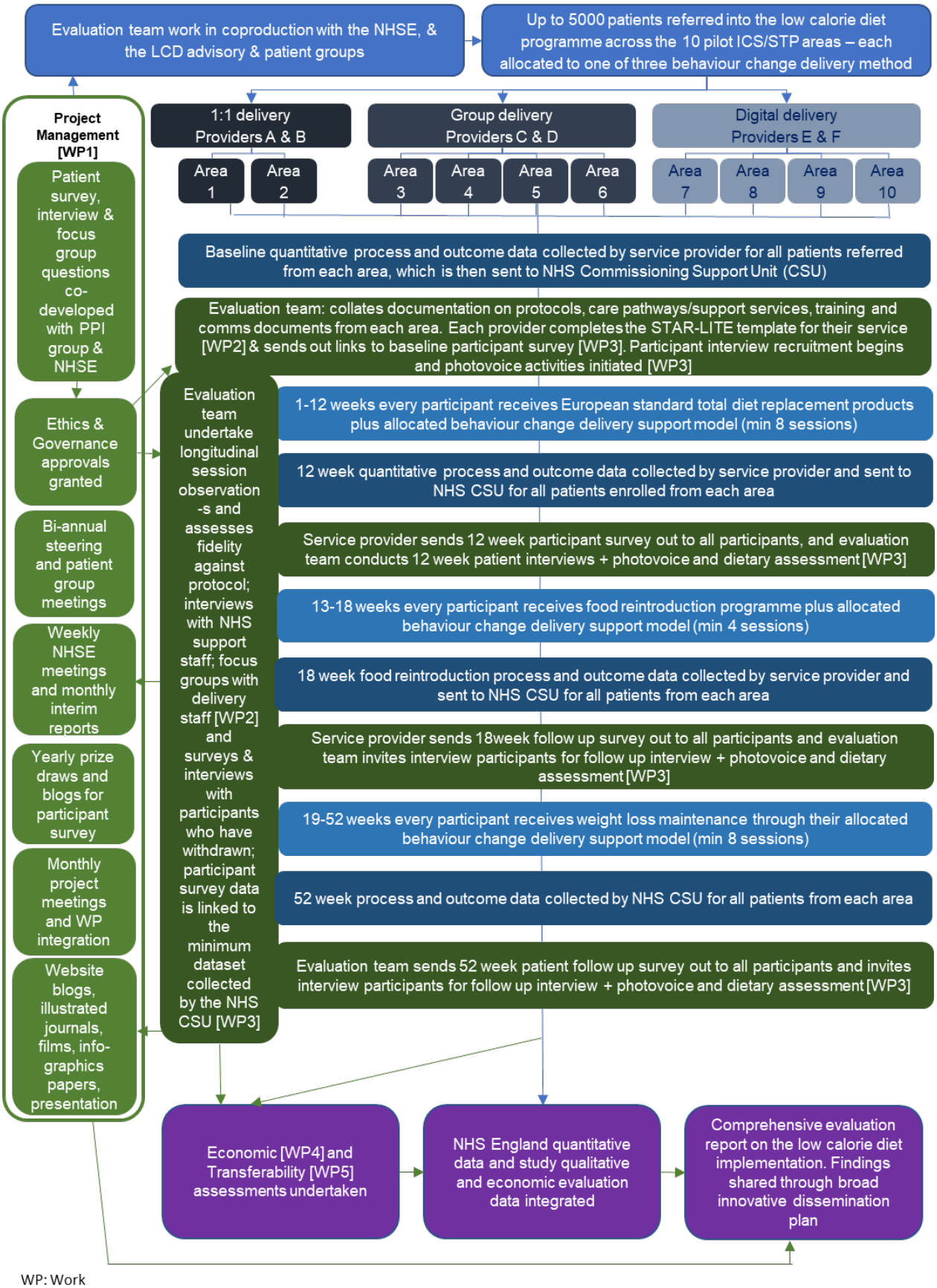
KEYWORDS:

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



WP: Work Package

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.

[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.

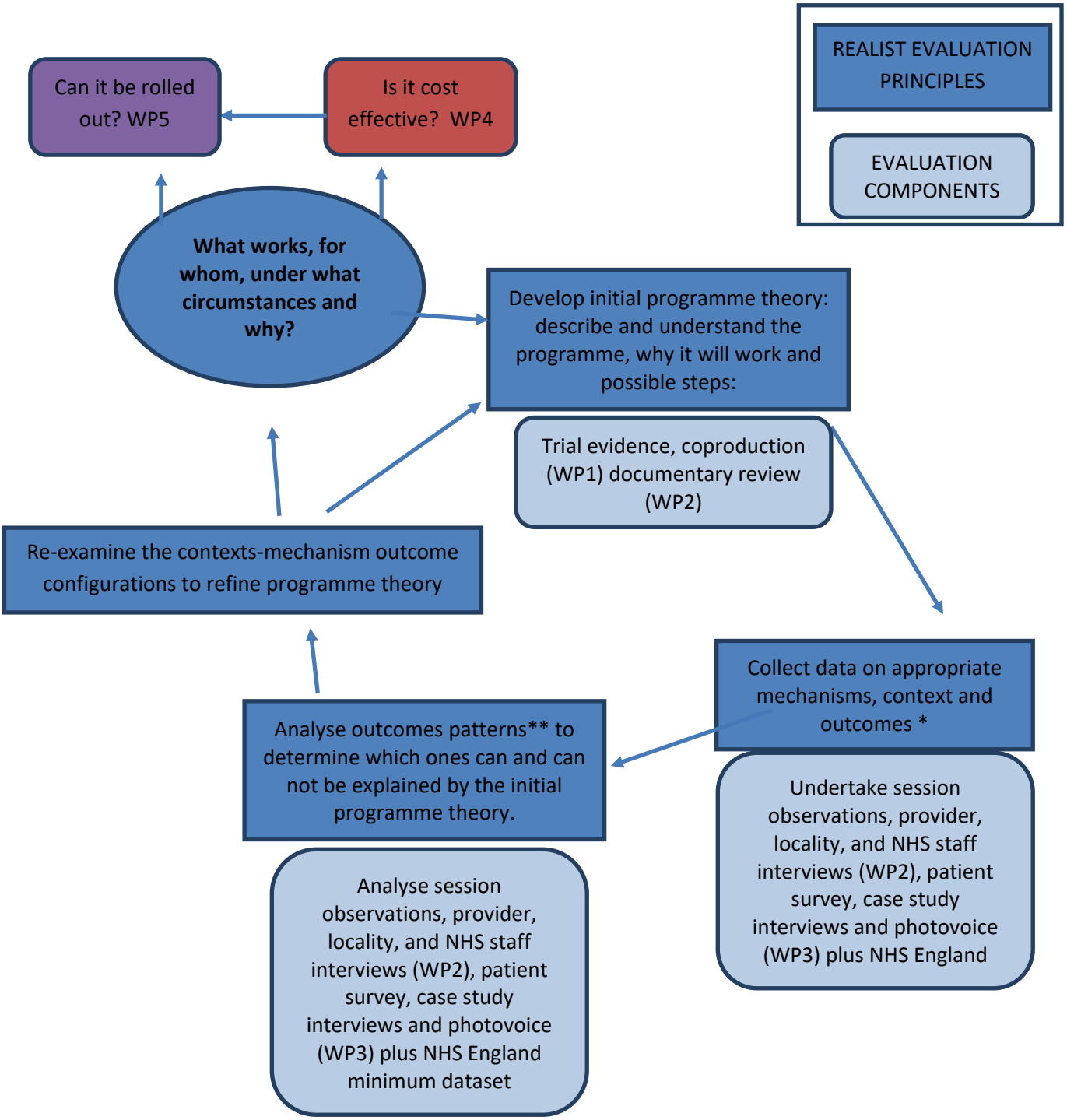
THEORETICAL FRAMEWORK

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

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.

[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.

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 cost per quality adjusted life year (QALY), including undertaking a cost analysis of each of the delivery models 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 developed 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 (undertaken by Tamla Evans, Cristiana Duarte, Stuart Flint, Jim McKenna). Each providers' training manuals will be coded against the behaviour change theory and content identified in the STAR-LITE template. This will assess the extent to which training coheres to the guiding behaviour change theory and content, and how this varies across providers.

Session observations (undertaken by Charlotte Freeman, Susan Jones, Pat Watson, Kevin Drew, Catherine Homer): We will work with NHSE to purposively select delivery sessions to observe (once consent is gained from staff lead and participants) during each phase of the programme (TDR, food reintroduction and maintenance) within each pilot area. We aim to undertake approximately 90 observations in total, to capture nine sessions (three in each of the delivery phases) across the 10 pilot areas. This will provide a longitudinal insight into delivery across different populations and delivery models. Descriptive non-participatory observations[33] 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.

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.

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 10 focus groups (one from each pilot area) with

between 6-8 participants per group [34]. 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 support staff (i.e. those involved in mobilising the programme). We will 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 last for no more than 30minutes 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 will seek support from NHSE to recruit locality leads and the locality leads to sample and recruit relevant referral staff. We will also work with the NIHR Clinical Research Networks to help facilitate recruitment, and have costed in gift vouchers to help incentivise participation within NHS support and 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, 35, 36]. 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[37, 38]. Thematic networks will be constructed to facilitate the structuring, description and interpretation of the themes[39, 40]. 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[40]. Themes will then be built into an explanatory model to demonstrate how various factors might influence successful implementation of the intervention[40].

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[41] and can influence Low Calorie Diet success[42]. 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[43], 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[44]).

Overview of methods: This WP will use a combination of complementary stages, underpinned by a pluralistic approach, which include longitudinal participant surveys, with in-depth insight provided by longitudinal interviews and visually represented participant journeys using 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[45]. 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 longitudinal patient survey. A short (~20minute) participant survey has been for each stage of the programme (baseline, end of TDR, end of food reintroduction, end of maintenance and withdrawal). These surveys were co-developed with the PPI group, Diabetes UK, NHSE, service users and providers, 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 has been 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[46] and EQ-5D[47]), emotional eating[48], binge eating[49] and activity assessment (Sport England single item question[4]). This data will then be

[4] PowerPoint Presentation (sportengland.org)

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 collected. 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.

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.

A freephone number is 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 have worked 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[50]).

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 or participant survey), we will undertake maximum variation sampling[51], 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[51]. 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 52weeks), replicating the longitudinal qualitative approach undertaken as part of the Counterbalance study[52] and Homer[53]. 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 36 participants – 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. The interviews will be undertaken using a semi-structured interview guide informed by the realist approach, research questions, photovoice

[5] Security Statement // Qualtrics

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 non-enrolment, 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. At the end of each interview participants will also be invited to undertake a 24hr dietary review (using myfood24), either with the researcher or independently 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[53] 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[54] has also previously been used successfully in bariatric patients[55], Black, Asian and Minority Ethnic groups[56] and underserved[57] 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 (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[58], 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: Two previous trial-based economic evaluations have demonstrated that the Low Calorie Diet approach is cost-effective in a UK-based primary care setting. However, the first involved only a within-trial analysis with a short time horizon (one-year) that did not assess QALYs[17]. Although the second study did estimate QALYs with a time horizon of a lifetime (using multistate lifetable modelling), most trial participants did not have T2DM and the model did not assess the impact of T2DM remission[18]. Furthermore, neither study examined the role of different delivery models and were both conducted under trial conditions with sample sizes that were relatively small and not representative of the populations who would be referred to the NHS Low Calorie Diet programme. Given the potential scale of investment that would be necessary if the programme were offered to patients with, or at risk of obesity and T2DM nationwide, it is necessary to conduct a long-term economic evaluation of alternative delivery models involving a large sample of real-world data on the relevant target population, and any associated participant costs that may impact programme compliance.

Overview of methods:
We will undertake a three-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]
- What are the costs of the NHS Low Calorie Diet programme to participants, and how do they differ by delivery model and socio-demographics? [RQ10]

Research questions 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 cost per QALY and how does this vary by delivery model and patient characteristics? [RQ11]

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]

Stage 1: Cost analysis 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 [59-61]. 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 as part of WP2. 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. The specific resource items to be included in the questionnaire will be identified in the DIRECT trial cost analysis[17], other published cost analyses of comparable interventions[62] and through discussions with NHSE. They will include (but not limited to) components of intervention materials, practitioner and patient meetings, and extra patient consultations.

Unit costs elicited in WP2 will be cross-checked with appropriate external sources, e.g. sellers and suppliers of relevant products, national healthcare databases [63, 64] (e.g. PSSRU - Personal Social Services Research Unit data) and published cost analyses of comparable interventions. 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. We will also examine the impact of any COVID-19 related adaptations (e.g. provision of remote monitoring equipment) to examine the economic impact of COVID-19 programme adaptations.

An exploratory analysis of patient out-of-pocket costs will also be conducted to identify resource use and costs incurred by patients enrolled on the programme, including any differences that may be attributed to different delivery models. Resource use questions will be designed for inclusion in the longitudinal patient questionnaires and interviews conducted in WP3. The specific resource use items to be included will be determined through discussion with NHSE and our patient group, but will likely include 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 (for example some bariatric surgery patients report hair dressing costs that occur as a result of hair loss).

Stage 2: Long-term cost-utility analysis. The long-term economic modelling analysis will be conducted using the UKPDS outcomes model version 2 (UKPDS-OM2), an open-access patient-level simulation model[65].

Inputs to the model will be the patient-level clinical and sociodemographic data collected at baseline and over 12 months by NHSE in the minimum dataset, including BMI, blood pressure, HbA1c, other health conditions, sex and ethnicity. 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 in collaboration with NHSE, after examination of the dataset and in line with guidance published alongside the UKPDS-OM2.

Outputs of the model will be year by year predictions of future clinical outcomes, healthcare treatment costs and QALYs at the patient-level for each of the delivery models and a ‘routine care’ scenario. The model estimates from these outputs (including those related to cardiovascular complications) will use risk equations that are derived from data collected over 30 years from UK participants with T2DM in the United Kingdom Prospective Diabetes Study. For the ‘routine care’ scenario the outputs would be estimated after baseline, and for the three different intervention delivery models, they would be estimated after 12 months.

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 *Stage 1* 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)[66]. 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, including exploration of:

- Different scenarios of weight gain (i.) after 12 months for participants who complete the intervention and (separately) (ii.) after baseline for participants who drop out of the study and/or do not complete the intervention. This will draw on published literature[67], (including an update to a meta-analysis of studies of long-term weight outcomes following a weight management programme[68]). Scenarios will include returning to baseline level (and 1kg below baseline level) in a linear fashion over a five year period (as assumed in the DROPLET economic analysis[18]). The scenarios will be determined in collaboration with NHSE and we are eager to explore the possibility of collecting additional data on weight change by following-up a sample of participants beyond 12 months.
- 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 will be based on data and strategies adopted in comparable studies, e.g. trials with a 'routine care' arm, and through discussion with NHSE.

Stage 3: Replication of the DIRECT and DROPLET trial methodologies and comparison of results. 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 Stage 1 and Stage 2. 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.

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

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1. NHS Digital, *Statistics on Obesity, Physical Activity and Diet, England, 2020*. 2020.
2. Gatineau M, et al., *Adult obesity and type 2 diabete*. 2014, Public Health England: London.
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