Protocol

The 'DR-EAM' study – (Type 2) Diabetes weight Reduction - Evaluation of App coaching Model

Contents

1. Background

Type 2 diabetes (T2DM) affects 4.1 million people in the UK and consumes >10% of the NHS budget (Diabetes UK). Recently, the DiRECT study (Lean, 2017) demonstrated that a 12-month face-to-face Low Calorie Diet programme achieved an average 10kg weight-loss, 10mmol/mol HbA1c reductions, 50% medication reductions, and T2DM-remission (defined as blood-glucose levels <48mmol/mol and off all diabetes-related medications) in 46% of participants, driving significant participant benefits. This builds on a wide literature of Low Calorie Diet programmes achieving significant weight loss and medication reductions in people with T2DM.

If these clinical outcomes could be achieved at scale in the UK, the potential savings for the NHS from reductions in T2DM complications and medication costs are very significant. However, face-to-face T2DM Low Calorie Diet programmes such as Counterweight Plus used in DiRECT are hard to scale due to challenges of accessibility, capacity and cost. We need new, scalable Low Calorie Diet interventions and a digital-enabled behaviour change intervention (DBCI) could achieve this.

In this project, we aim to evaluate the clinical outcome benefits and NHS return on investment of an existing Digital Behaviour Change Intervention (DBCI) based on the published literature of Low Calorie Diets in T2DM called Oviva Diabetes 800 compared to usual NHS care. We will recruit 250 NHS participants from GP practices across South West London and Buckinghamshire.

This project has been funded by Innovate UK (part of UK Research & Innovation, https://www.ukri.org/). The trial will be undertaken by Oviva, working in partnership with University of Westminster and Insight Health Improvement who will evaluate clinical and financial impacts respectively.

2. Methodology

This is a single-arm real-world evaluation with a matched control group from comparable GP practices.

2.1 Population

250 participants with T2DM from GP practices across South West London CCG and Buckinghamshire NHS.

2.2 Inclusion and Exclusion criteria

Inclusion Criteria

- Minimum age of 18 years
- Maximum age of 65 years
- Male or female
- Minimum BMI of 27kg/m^2 (adjusted to 25kg/m^2 in people of South Asian or Chinese origin)
- BMI <45kg/m^2
- T2DM diagnosed at any time
- HbA1c eligibility, most recent value, which must be within 12 months:
    - HbA1c ≥ 43 mmol/mol if on oral diabetes medication or GLP-1
    - HBA1c <108 mmol/mol
    - If HbA1c 90-108 mmol/mol, the value must be within 3 months of referral
- On, or about to start, a second-line diabetes-related oral medication or GLP-1 (metformin is first-line)
- Access to blood glucose monitoring equipment if on a sulphonylurea prior to referral
- Ability to speak, read and receive care in English
- Access to and willing to use an iOS or Android smartphone for the duration of the intervention

Exclusion Criteria

- T2DM either diet-controlled alone, or on metformin alone
- Current insulin use

- Pregnant or breastfeeding or considering pregnancy during next 6 months
- Significant physical comorbidities:
    - Active cancer
    - Myocardial infarction or stroke within previous 6 months
    - Severe heart failure defined as equivalent to the New York Heart Association grade 3 (NYHA)
    - Recent eGFR <30 mls/min/1.73 m2
    - Active live disease (except for NAFLD), or a history of hepatoma, or <6 months of onset of acute hepatitis
    - Severe angina, cardiac arrhythmia including atrial fibrillation or prolonged QT syndrome
- Active substance use disorder / eating disorder
- Porphyria
- Weight loss >5% body weight within last 6 months or on current weight management programme or had/awaiting bariatric surgery (unless willing to come off waiting list)
- Health professional assessment that the person is unable to understand or meet the demands of the treatment programme and/or monitoring requirements, which may include Learning disabilities
- Taking monoamine-oxidase inhibitor medication
- Taking warfarin
- Taking varenicline (smoking cessation medication)
- Unstable retinopathy or lack of retinal screening in the last year
- Active/investigation for gastric or duodenal ulcers
- People currently participating in another clinical trial

2.3 Recruitment

Recruitment will be carried out by NHS GP Practices across South West London CCG and Buckinghamshire. South London Clinical Research Network and Thames Valley Clinical Network will support recruitment.

People will be invited to participate in the study via their GP practice. Eligible participants will be sent a text message or letter giving details of the programme and evaluation. A link to an electronic Participant Information Sheet (PIS) will be provided alongside the text, and a printed PIS will be included alongside programme details if a letter is sent. If they are interested in participating, they will contact their GP who will then create a referral to Oviva. The initial call with Oviva will explain the programme and the evaluation, and the participant will be signposted again to the PIS. Once the PIS has been read, understood and agreed, participants will sign an electronic consent form if they are happy to consent to their data being used in the evaluation. If people do not give consent for their data to be included within the evaluation they will still have the opportunity to access the Diabetes 800 programme.

2.4 Consent

Participants will initially give consent verbally over the phone to a Patient Pathway Co-ordinator at Oviva. They will then be sent a consent form in electronic form. Written consent will be taken in electronic format and documented.

Following a GP referral into the study, participants will be sent a link to the PIS. Participants will receive a phone call from a Patient Pathway Co-ordinator (PPC) from Oviva who will share details of the Diabetes-800 programme and the evaluation. The PPC will ask participants for verbal consent to participate in the evaluation and then participants will be sent an online consent form where they will check boxes to confirm that they have read the PIS, had any questions about the evaluation answered, and confirm that they are happy for their data to be included in the evaluation. Once consent has been given, it is then recorded in the electronic medical record which will also be date stamped.

2.5 Baseline evaluation

Baseline measures will be taken from primary care records. A venous HbA1c and blood pressure measurement will be requested to be completed by the GP at baseline if one is not available from the last 3 months. GP time and costs are compensated within the trial. Age, gender, ethnicity, height, lipid markers and current medications can be collected from the referral form. A baseline questionnaire will be sent to participants before they start the programme to capture baseline activity levels and EQ5D score. In addition, the participants will be asked why they chose or did not choose to take part.

2.6 The intervention

This study is an evaluation of a clinical programme called Diabetes-800 designed by Oviva.

Diabetes-800 is a digital, remote behaviour change intervention, which provides personal 1 to 1 support and expert advice delivered either over the phone or via the Oviva App. . The programme is 12 months in duration inclusive of a 12 week low-calorie diet (approximately 800 calories per day), a four week food reintroduction phase and nine months of behaviour change support from a registered dietitian, with additional support from a diabetes specialist nurse where required.

During the low-calorie diet, participants will be following a TDR or Total Diet Replacement; they will consume four meal replacement products per day and no food or calorie-containing drinks. In the food reintroduction phase, participants will move back onto food consumption, but will increase their calorie intake each week as directed by their dietitian. In the maintenance phase you will be supported to

maintain weight loss or achieve further weight loss if goal weight has not been reached.

As part of the programme, participants will be given access to the Oviva app where they can log their meals, thoughts, feelings, activity levels and they will be able to communicate with their dietitian through the app. If participants cannot or do not want to access the app, they will be supported with regular phone calls from the dietitian.

This study will evaluate the effectiveness of this intervention combined with IoT GSM-connected BodyTrace weight scale and Bluetooth-connect Fitbit Inspire physical activity tracker with added linked patient-engagement ML-algorithms and will compare to a matched dataset for those subject to usual care, with data collected at 6, 12 and 24 months. The clinical outcomes will be evaluated using simple statistical tests such as paired t-tests as this is a simple within-group non-randomised design.

The study will also involve an economic evaluation of the Diabetes-800 programme compared to the matched control group accessing usual care. The impact of Diabetes-800 on NHS costs will be estimated, and extrapolated over a 5-year time period, relative to usual care. Biomedical variables and prescribing data for the intervention group during the 2-year study period will be analysed, and compared with equivalent data from a control dataset of non-participating patients with type 2 diabetes in South London. This control dataset will be used to represent usual care.

Trajectories for prescribing and for biomedical variables such as HbA1c, weight, blood pressure and cholesterol for years 3-5 will be estimated for the intervention group and for usual care based on evidence from the clinical literature.

2.7 Outcomes

This project will examine process and clinical outcomes.

2.7.1 Process outcomes

Programme uptake, retention and completion rates

Uptake will be measured by:
1) The number of people who take up an invitation to participate as a proportion of total number of people invited who meet eligibility criteria
2) The number of people who attend the start of Oviva Diabetes 800 as a proportion of total number of people who agree to participate

Completion and retention will be measured by:

1) The total number of people who complete (take part in at least 60% of sessions) the programme as a proportion of the total number of people who start

2.7.2 Clinical outcomes

Primary outcomes: Weight and blood glucose (HbA1c)
Secondary outcomes: Changes in blood pressure, lipids, physical activity, quality of life, participant experience surveys, and diabetes and blood pressure medications.

Methods:

- Weight by the BodyTrace weight scale
- HbA1c by venous sample
- Blood pressure by British and Irish Hypertension Society validated monitors
- Lipids by venous sample
- Physical activity by the Fitbit device
- Quality of life by EQ-5D
- Participant experience, including the NHS Friends & Family Test by standardised survey

Table 1: Outcome measures and protocol for capture

	Screening/ Baseline	3 months	6 months	9 months	12 months	24 months
Age	x					
Gender	x					
Weight	x	x	x	x	x	x
Height	x					
BMI	x				x	x
Ethnicity	x					
When T2DM diagnosed	x					
Medications: active medications including name, dose, frequency and date started (focus on diabetes, blood pressure, cholesterol related)	x				x	x
HbA1c	x (within 3 months of referral)		x		x	x
Total cholesterol	x				x	x

HDL	x				x	x
LDC	x				x	x
Triglycerides	x				x	x
Systolic and diastolic blood pressure	x (within 3 months of referral)				x	x
Question on why did they take part	x					
Question on why did they did not take part	x					
Physical activity (average daily step count per week)	x	x	x	x	x	x
EQ-5D	x		x		x	x
NHS Friends & Family Test					x	
Structured participant feedback survey					x	

2.8 Return on Investment

The impact of Diabetes-800 on NHS costs will be estimated, and extrapolated over a 5-year time period, relative to usual care. Biomedical variables and prescribing data for the intervention group during the 2-year study period will be analysed, and compared with equivalent data from a control dataset of non-participating patients with type 2 diabetes in South London. This control dataset will be used to represent usual care.

Trajectories for prescribing and for biomedical variables such as HbA1c, weight, blood pressure and cholesterol for years 3-5 will be estimated for the intervention group and for usual care based on evidence from the clinical literature.

Costs will be estimated for routine care, medications, and complications. These pathways will be costed using published data sources such as PSSRU Unit Costs of Health and Social Care.

Costs for medications will be estimated using the NHS Electronic Drug Tariff. Costs for complications will be derived from recent published diabetes models such as the health economics model produced for NICE guidance NG28, supplemented with

evidence from published studies where necessary.[1]

The rate of complications for the intervention group and for usual care will be estimated using the risk equations from the UK Prospective Diabetes Study (UKPDS) Outcomes Model (OM2). This is a computer simulation model produced by Oxford University, based on patient-level data from the United Kingdom Prospective Diabetes Study. The UKPDS Outcomes Model has been widely used in research, clinical and commercial applications in the UK and internationally. The model uses a range of input variables including sex, ethnicity, weight, height and biomedical characteristics such as HbA1c, HDL and LDL cholesterol and systolic blood pressure to project rates of complications in a given patient group.[2]

2.9 Data Extraction

Oviva will store all outcome measures in its secure electronic medical record system, collating all information captured through delivery and from primary care in a final evaluation table.

North East London Commissioning Support Unit will provide the matched control dataset from comparable GP practices in South West London.

Data will be validated for errors before sharing securely with evaluators.

The University of Westminster will receive a single CSV file with anonymised participant level data via NHSmail's secure feature. The recipient address for the University of Westminster will be confirmed by Oviva's Operations Manager before sending.

Insight Health Improvement will receive a single CSV file with anonymised participant level data from Oviva via NHSmail's secure feature. The recipient address for Insight Health Improvement will be confirmed by Oviva's Operations Manager before sending.

Insight Health Improvement will also receive a single CSV file with anonymised participant level data from North East London Commissioning Support unit for the matched control dataset. The recipient address for Insight Health Improvement will be confirmed by the CSU responsible individual before sending.

3. Withdrawal criteria

The safety of the study participants takes priority. Any significant adverse event (as assessed by the researchers) will halt the study and the ethics committee and sponsor will be informed as per standard protocol. All adverse events will be recorded and investigators will review each adverse event as it arises. In addition,

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[1] https://www.nice.org.uk/guidance/ng28/evidence/appendix-f-full-health-economics-report-pdf-2185320355

[2] https://www.dtu.ox.ac.uk/outcomesmodel/

participants will be free to withdraw at any time and are not required to give a reason.

Adverse events

Adverse Event (AE): Any untoward medical occurrence in a participant or clinical study subject.

Serious Adverse Event (SAE): Any untoward and unexpected medical occurrence that:

- results in death
- is life- threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- requires hospitalisation, or prolongation of existing in participants' hospitalisation.
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Reporting of AE and SAEs

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Non-serious AEs

All such events, whether expected or not, should be recorded.

SEAs

An SAE form should be completed and faxed to the Chief Investigator within 24 h. However, relapse, death and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the xxxx Research Ethics Committee where in the opinion of the Chief Investigator the event was:

- ‘related’, i.e. resulted from the administration of any of the research procedures; and
- ‘unexpected’, i.e. an event that is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the

Chief Investigator becoming aware of the event, using the NRES SAE form.

Local investigators should report any SAEs to the sponsor and their Local Research Ethics Committee and/ or Research and Development Office.

4. Regulatory issues

Ethics approval
This study (IRAS ID 269780) has received ethical approval from the Yorkshire & The Humber - Bradford Leeds Research Ethics Committee committee on 3rd December 2020.

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In such cases, the participants remain within the study for the purposes of follow-up and data analyses. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment.

Confidentiality
The Chief Investigator will preserve the confidentiality of participants in the study and is registered under the Data Protection Act.

5. Data Handling

All participant data will be stored in Oviva's secure electronic medical record system. Oviva has secure data handling systems and processes, is NHS Digital Data Security & Protection Toolkit 2019-20 compliant, has Cyber Essential Plus Certification, and the Oviva app has been certified by NHS Digital through the Digital Assessment process.

The evaluators will be required to adhere to Oviva's standards through a Data Processing Agreement.

Matched control data will be managed by North East London Commissioning Support Unit, an organisation which holds large NHS datasets and has robust Information Management systems.

Indemnity

University of Westminster holds negligent harm and non-negligent harm insurance policies, which apply to this study.

Sponsor
University of Westminster will act as the main sponsor for this study.

Funding
This research project is funded by Innovate UK.

Audits and inspections
The study may be subject to inspection and audit by University of Westminster under their remit as sponsor and other regulatory bodies to ensure adherence to GCP.

Publication policy

The findings of the research will be published in an open-access, peer-reviewed journal. In addition we will be collaborating with participant groups and professional groups to disseminate the findings via multiple media channels such as participant association publications, print and broadcast media.