Study Title: Testing the effectiveness of a low carbohydrate diet with remote support for patients with type 2 diabetes in primary care, on weight and glycaemic control: a randomised controlled trial

Internal Reference Number / Short title: REmote SUpport for Low-Carbohydrate Treatment of type 2 diabetes: the RESULT trial

Ethics Ref: 21/WM/0101

IRAS Project ID: 295974

Date and Version No: V 2.0 16/07/21

Chief Investigator: Professor Paul Aveyard
Nuffield Department of Primary Care Health Sciences, University of Oxford; Radcliffe Observatory Quarter, Woodstock Road, Oxford
NIHR Oxford Biomedical Research Centre

Paul.aveyard@phc.ox.ac.uk

Investigators: Dr Elizabeth Morris

Nuffield Department of Primary Care Health Sciences, University of Oxford; NIHR Oxford Biomedical Research Centre

Professor Susan Jebb
Nuffield Department of Primary Care Health Sciences, University of Oxford; NIHR Oxford Biomedical Research Centre

Sponsor: University of Oxford

Funder: This work is supported by the NIHR Biomedical Research Centre, Oxford, and the Wellcome Trust Clinical Doctoral Research Fellowship (EM).

Chief Investigator Signature:

All the investigators declare that they have no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. KEY CONTACTS 6
2. LAY SUMMARY 6
3. SYNOPSIS 7
4. ABBREVIATIONS 9
5. BACKGROUND AND RATIONALE 10
6. OBJECTIVES AND OUTCOME MEASURES 11
7. STUDY DESIGN 13
8. PARTICIPANT IDENTIFICATION 13
8.1. Study Participants 13
8.2. Inclusion Criteria 13
8.3. Exclusion Criteria 14
9. PROTOCOL PROCEDURES 14
9.1. Recruitment 14
9.2. Screening and Eligibility Assessment ..... **Error! Bookmark not defined.**
9.3. Informed Consent 15
9.4. Baseline Assessments 15
9.5. Randomisation and blinding 16
9.6. Description of study intervention and comparator 16
9.6.1. Intervention group 16
9.6.2. Control group 17
9.7. Subsequent Visits 17
9.8. Sample Handling 18
9.9. Early Discontinuation/Withdrawal of Participants 18
9.10. Definition of End of Study 19
10. SAFETY REPORTING 19
11. STATISTICS AND ANALYSIS 19
11.1. Description of the Statistical Methods 20
11.2. Sample Size Determination 20
11.3. The Level of Statistical Significance 20
12. DATA MANAGEMENT 20
12.1. Access to Data 20

12.2. Data Recording and Record Keeping 20
13. QUALITY ASSURANCE PROCEDURES 22
14. PROTOCOL DEVIATIONS 22
15. SERIOUS BREACHES 22
16. ETHICAL AND REGULATORY CONSIDERATIONS 23
16.1. Declaration of Helsinki 23
16.2. Guidelines for Good Clinical Practice 23
16.3. Approvals 23
16.4. Reporting 23
16.5. Transparency in Research 23
16.6. Participant Confidentiality 23
16.7. Expenses and Benefits 24
17. FINANCE AND INSURANCE 24
17.1. Funding 24
17.2. Insurance 24
17.3. Contractual arrangements 24
18. PUBLICATION POLICY 24
19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY 25
19. REFERENCES 25
20. APPENDIX A: STUDY FLOW CHART 26
21. APPENDIX B: SCHEDULE OF STUDY PROCEDURES 27
22. APPENDIX C: AMENDMENT HISTORY 28

1. KEY CONTACTS

Chief Investigator	Professor Paul Aveyard Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford NIHR Oxford Biomedical Research Centre paul.aveyard@phc.ox.ac.uk
Sponsor	University of Oxford
Funder(s)	This work is supported by the NIHR Biomedical Research Centre, Oxford, and the Wellcome Trust Clinical Doctoral Research Fellowship (EM).
Committees	Trial Management Group: Dr Elizabeth Morris, Professor Paul Aveyard, Professor Susan Jebb, Dr Jadine Scragg, Dr Michaela Noreik Trial Steering Committee: Professor Jonathan Pinkney, jonathan.pinkney@plymouth.ac.uk (chair of the TSC), Dr Bethany Shinkins, B.Shinkins@leeds.ac.uk, Dr Amelia Hollywood, A.Hollywood@reading.ac.uk, Mr Derek Jerome, dclj2001@yahoo.co.uk

2. LAY SUMMARY

The standard for diabetes management is changing. What was previously thought to be a lifelong progressive condition to be managed primarily with increasing doses of medications, may instead be put into remission (achieving normal or near-normal blood glucose levels without medications) if treated with intensive weight loss support. However, the majority of patients with type 2 diabetes still rely on general dietary advice from primary care professionals. While there is considerable uncertainty regarding the optimal diet composition for people with type 2 diabetes, there is a growing interest from patients, practitioners and the general public in using real-food, low carbohydrate diets to achieve weight loss, improved glycaemic control and even disease remission. A recent small-scale study demonstrated that it was possible, and effective in the short-term, for practice nurses in primary care to support patients with type 2 diabetes to adopt a real-food, low-carbohydrate weight loss diet. However the patients and healthcare professionals who took part in this study were keen to know whether digital interventions and app-based

support could be an alternative way to achieve the same results, with the potential for more frequent support without increasing the demand on the primary care workforce. This study aims to investigate whether an app-based low-carbohydrate intervention with remote behavioural support is effective at improving glycaemia, weight, and other markers of cardiometabolic risk, for people with type 2 diabetes in primary care.

3. SYNOPSIS

Study Title	Testing the effectiveness of low carbohydrate diet with remote support for patients with type 2 diabetes in primary care, on weight and glycaemic control: a randomised controlled trial		
Internal ref. no. / short title	Low Carb App		
Study registration	Clinicaltrials.gov: NCT04916314		
Sponsor	University of Oxford		
Funder	NIHR Oxford Biomedical Research Centre (BRC) Wellcome Trust		
Study Design	Individually randomised controlled trial		
Study Participants	Adult men and women with type 2 diabetes and BMI ≥27kg/m^2 (30 if recorded as white ethnicity)		
Sample Size	100 (50 intervention, 50 control)		
Planned Study Period	01/08/2021 – 01/10/2023 Per participant: 12 months		
Planned Recruitment period	01/08/2021-31/12/2021		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To determine the effectiveness of an app-based programme offering support for a low energy, low carbohydrate diet on glycaemia, compared with usual care in people with type 2 diabetes	Change in participants' HbA1c from baseline to 3 months and baseline to 1 year (co-primary outcomes)	Baseline, 3 months, 1 year
Secondary	• To determine the effect of an app-based programme offering support for a low energy, low carbohydrate diet on remission of type 2	Number of participants meeting consensus definition for remission from	1 year

	diabetes compared with usual care	type 2 diabetes at 1 year	
	• To determine the effect (Short- and longer-term) of an app-based support programme for dietary change in type 2 diabetes on weight, compared with usual care	Change in participants' weight from baseline to 3 months and baseline to 1 year	Baseline, 3 months, 1 year
	• To determine the effect of an app-based programme offering support for a low energy, low carbohydrate diet on other markers of cardiometabolic risk, compared to usual care	Change in participants': - Blood pressure (systolic and diastolic) -Lipid profile (total-, HDL- and LDL-cholesterol, triglycerides) -Liver function (Bilirubin, ALT, ALP, Albumin)	Baseline, 3 months, 1 year Baseline, 3 months, 1 year
	• To determine the effect of an app-based programme offering support for a low energy, low carbohydrate diet on diabetes related distress and quality of life	Change in participants' PAID score and EQ5D Interviews with participants	3 months
Process Measures	• To examine engagement with the programme	• Data will be collected on measures of engagement with the three main components of the programme ("Learn", "Track", and "Support"), via the app programme, and change in dietary	Baseline, 3 months, 12 months

	• To examine the demographic profile of participants • To explore participants' experience of using the app-based support	intake patterns (via Intake24 24 hour dietary recall questionnaire) • Data (age, gender, ethnicity, level of education, deprivation index, dietary preference) will be collected via questionnaire • Interviews with participants	Baseline 3 months
Intervention(s)	"SecondNature" App: remote support for a low-carbohydrate dietary intervention for weight loss		
Comparator	Usual care		

4. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
FBC	Full Blood Count
GCP	Good Clinical Practice
GP	General Practitioner
HbA1c	Glycosylated Haemoglobin A1c
HRA	Health Research Authority
ICF	Informed Consent Form
IG	Information Governance
LFTs	Liver Function Tests (Bilirubin, ALT (Alanine aminotransferase), AST (Aspartarte aminotransferase), ALP (Alkaline Phosphatase), Albumin)
NHS	National Health Service
RES	Research Ethics Service
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department

REC	Research Ethics Committee
SOP	Standard Operating Procedure
T2DM	Type 2 diabetes mellitus

5. BACKGROUND AND RATIONALE

There are an estimated 4 million people living with type 2 diabetes (T2D) in the UK, with numbers expected to rise to 5 million by 2025 (1). Globally, almost 15% of all deaths are attributable to diabetes in the 20-79 years age group, with 47% of those deaths occurring in people under 60 years of age(1). Currently, 10% of the NHS annual budget is spent on diabetes (around £10 billion).

But the paradigm for T2D management is changing.(2) What was previously thought to be a lifelong progressive condition to be managed primarily with escalating doses of medications, may instead be put into remission if treated with intensive weight loss support(3). However, the majority of patients with type 2 diabetes still rely on general dietary advice from primary care professionals. There is considerable uncertainty regarding the optimal diet composition for people with T2D, but there is a growing interest from patients and practitioners in using real-food, low carbohydrate diets to achieve weight loss, improved glycaemic control and even disease remission.

In our previous DIAMOND study, a randomised controlled feasibility trial (n=33), we demonstrated that it was feasible and acceptable for practice nurses to support patients with T2D to adopt a real food, low-energy, low-carbohydrate weight loss diet in primary care. On average, participants in the intervention group achieved clinically significant improvements in weight and HbA1c in the short-term (12 weeks)(4). Recruitment was from April-October 2018; Participant follow up appointments were from August 2018-February 2019. Participants received no further formal support or intervention after the 12 week period.

After study completion, healthcare professionals and participants in qualitative interviews expressed an interest in whether the programme could be expanded to include app-based or other remote support. Patients were keen to consider increased levels and modes of support, and the potential for a synchronous “community” of participants to support each other, while practitioners were concerned about adequate workforce capacity and time constraints of delivering increased contacts within primary care.

With increasing interest in remote monitoring and digital support options during the Covid19 pandemic, as well as the NHS Long Term Plan’s focus on development and support of digital interventions, this question has become increasingly relevant. Many programmes aiming to support weight loss and improvement in control of T2D – or even disease remission – are based on evidence from trials of programmes with in-person support. However, when it comes to wider commissioning or roll-out in routine care, such programmes are often expanded to include digital delivery of the interventions (such as in the National Diabetes Prevention Programme, and Diabetes Remission Total Diet Replacement Pilot), sometimes without clear randomised controlled trial evidence that digital versions of the programmes will have similar effectiveness.

There is a growing support from observational evidence to suggest that remote support via a digital platform can positively affect the weight and glycaemia of patients with type 2 diabetes who engage with these interventions. One such platform offering remote behavioural and dietary support for people with type 2 diabetes provides a three-month remote behavioural change programme with mentoring from a registered dietitian or nutritionist (health coach), encouraging adoption of a low energy, low-carbohydrate diet, peer group support, structured education articles and activity tracking technology. These elements are accessed via a smartphone or web-based application; each participant additionally receives an instructional handbook, and recipe book (+/-wireless weighing and activity tracking technology). A service evaluation of 190 participants referred as part of routine care from January to July 2018 found that 75% of patients (n=144) started the programme, and 65.3% (94) of these submitted weight readings after 12 months. Of these, 60% achieved over 5% total body weight loss, and 28.7% achieved over 10% body weight loss; the average total 12 month weight change was -7.8kg (+/- 8.6kg). 28.5% of participating patients attended for a blood test with their GP after 12 months as part of routine care; in those with available HbA1c data, there was a statistically significant change in HbA1c compared to baseline (mean -10.4mmol/mol, SD +/- 8.6mmol/mol)(5). An earlier larger cohort of 896 patients who completed a similar programme (3 months of "core" support, plus ongoing access to sustainable advice and encouragement of weekly engagement) over a 1 year period, comprising both self-funded clients and those referred by their GP free of charge, found a significant change in mean weight of -7.12kg (SD 6.37kg) at 6 months and -6.14kg (SD 9.97 kg) at 12 months compared to baseline measures(6). While the weight and glycaemic changes reported appear promising, and clinically significant, these observational studies have several key limitations (including the generalisability of the patient population (a selected group of people with high intrinsic motivation to take part, often in locally limited geographical areas); observational design and lack of a control or comparator group; and significant loss to follow up and absence of follow up data, without the ability to determine why) that preclude drawing reliable conclusions as to the programme's performance and effectiveness.

Therefore, the aim of this study is to test in a randomised controlled trial whether a low energy, low carbohydrate diet delivered via remote support is effective at improving glycaemia, weight, and other markers of cardiometabolic risk, for people with type 2 diabetes in primary care.

Understanding changes in clinical outcome measures and participant behaviours could inform future programmes to support people with type 2 diabetes in primary care.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**

Primary Objective To determine the effectiveness of an app-based programme offering support for a low energy, low carbohydrate diet on glycaemia, compared with usual care in people with type 2 diabetes	Change in participants' HbA1c from baseline to 3 months and baseline to 1 year (co-primary outcomes)	Baseline, 3 months, 1 year
Secondary Objectives • To determine the effect of an app-based programme offering support for a low energy, low carbohydrate diet on remission of type 2 diabetes compared with usual care	Number of participants meeting consensus definition for remission from type 2 diabetes at 1 year	1 year
• To determine the effect (Short- and longer-term) of an app-based support programme for dietary change in type 2 diabetes on weight, compared with usual care	Change in participants' weight from baseline to 3 months and baseline to 1 year	Baseline, 3 months, 1 year
• To determine the effect of an app-based programme offering support for a low energy, low carbohydrate diet on other markers of cardiometabolic risk, compared to usual care	Change in participants': - Blood pressure (systolic and diastolic) -Lipid profile (total-, HDL- and LDL-cholesterol, triglycerides) -Liver function (Bilirubin, ALT, ALP, Albumin)	Baseline, 3 months, 1 year
• To determine the effect on diabetes related distress and quality of life	Change in participants' PAID score and EQ5D,	Baseline, 3 months, 1 year
Process Measures To examine engagement with the programme	Data will be collected on measures of engagement with the three main components of the programme ("Learn", "Track", and "Support"), via the app programme, and change in dietary intake	Baseline, 3 months, 12 months

To examine the demographic profile of participants To explore participants' experience of using the app-based support	patterns (via Intake24 24 hour dietary recall questionnaire) Data (age, gender, ethnicity, level of education, deprivation index, dietary preference) will be collected via questionnaire Interviews with participants	Baseline 3 months

7. STUDY DESIGN

This is an individually randomised controlled trial. Participants, recruited via GP practices, will be randomised 1:1 with simple randomisation and no stratification to either the intervention group or control (usual care). They will be enrolled in the study for 1 year, of which the intervention (dietary support via the app) will run for 3 months. Most study procedures will be conducted online or remotely (by telephone) including: screening, eligibility assessment, informed consent, randomisation, engagement with the app-based intervention. Participants will be asked to attend 3 face to face appointments for the research study at their local GP practice for measurements to be taken (weight, blood pressure) and blood tests, at baseline, 3 months and 1 year, and will have 1 additional telephone contact with their GP or practice nurse before starting the intervention. Face to face appointments will be incorporated with routine clinical appointments when possible.

A flow diagram showing the trial design is given in Appendix A

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

One hundred adults with type 2 diabetes and a BMI ≥27kg/m^2 (≥30kg/m^2 if white ethnicity) will be recruited.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 40 years or above.
- Diagnosed with current type 2 diabetes (i.e. not in remission) in the last 6 years
- BMI of ≥27kg/m^2 (≥30kg/m^2 if ethnicity recorded as white)

- Has a smartphone or computer with internet access (and the correct operating system requirements to use the intervention programme)
- Are able to complete the eligibility and baseline assessments online
- Would like to make changes to their diet or lifestyle to improve their diabetes control, lose weight, or improve their general health

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Unable to understand the study materials and interventions
- Currently following a weight loss programme (defined as a structured, prescribed and monitored programme and not a self-directed weight loss attempt)
- Pregnant, breastfeeding, or planning to become pregnant during the course of the study
- History of bariatric surgery, including gastric banding
- Currently using insulin therapy
- Proliferative diabetic retinopathy, or maculopathy.
- Recent myocardial infarction or stroke (<3 months)
- Renal failure (chronic kidney disease stage 4 or 5)
- Current active treatment for cancer (other than skin cancer treated with curative intent by local treatment only)
- Their doctor does not feel they are appropriate to participate for another reason (e.g. active eating disorder diagnosis, significant psychological disturbance)

9. PROTOCOL PROCEDURES

An overview of study procedures is shown in appendix B.

9.1. Recruitment

We aim to recruit 100 participants via their GP practices. Based on a conservative response rate of 10% from similar previous studies, we will approach approximately 1000 eligible individuals from approximately 10 GP practices in England(7). The primary care provider will search their electronic registers for eligible individuals and GPs will screen out those to whom it would be inappropriate to send a letter. The letter from their GP will invite the patient to consider taking part in the study and the patient will be directed to the study website for more information and to access the online Participant Information Sheet. Contact details for the research team will be available for them to contact to discuss the study in more detail and/or ask any questions. Participants wishing to be considered for inclusion in the trial will be directed to the section of the website to complete the initial eligibility assessment. This helps to ensure participants have sufficient IT skills to be able to engage with the intervention.

As part of the initial eligibility assessment participants will be asked to report their height and weight to calculate BMI (these numbers will not be recorded, just whether they meet eligibility criteria or not). If the participant is ineligible a pop-up will explain that they do not meet the eligibility criteria for this study and they will not proceed further and no information will be requested. If they are eligible they will be asked to provide their full name and email via an approved secure platform (the SENTRY programming system, run by the University of Oxford Nuffield Department of Primary Care Health Sciences Clinical Trials Unit, where the information will be stored securely and in compliance with local IG policy) so that the research team can contact them. They will also be asked to create a four-digit access code for the online consent.

9.2. Informed Consent

As detailed above (section 9.2) participants will visit a website to read the Participant Information Sheet online and able to print out if they wish to. The Participant Information and Informed Consent presented to the participants online will detail no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information and have the opportunity to call the research team, their GP or consult other independent parties to ask any questions before they decide whether they will participate in the study. Following their initial eligibility assessment (section 9.1), eligible participants will be sent an email with a link to the online database where consent is taken. They will log in with their full name and access code given previously at the initial eligibility assessment (section 9.1). They will then agree to each statement of the consent form and then sign the consent form by putting their full name and access code. Once consent has been given, participants will click on a link to the electronic data capture system database which will be activated following their consent, to complete the baseline assessment. Participants will be able to download a copy of the consent form to keep for their records.

9.3. Baseline Assessments

All participants will complete a 2 part baseline assessment, firstly online and then at their GP practice.

1. Online:
   Participants will be asked to complete a baseline questionnaire requesting demographic information and their current medication, and the standard questionnaires that will be used in the study (the Problem Areas in Diabetes (PAID) score, the EQ5D (quality of life assessment), and a 24 hour dietary recall questionnaire (“Intake24 dietary assessment tool”, where participants are asked to record all food and drink intake in the last 24 hours). This will also further assess whether people are sufficiently able to complete online trial procedures, and only those who complete the questionnaire will be randomised. Participants will be informed in the Participant Information Sheet that they will only be able to enter the study after completing each individual questionnaire fully in one attempt as the system will not allow them to go back into each

questionnaire to answer the remaining questions later. Overall there are 3 questionnaires for each participant to complete. These should take less than 30 minutes to complete. Patients will be able to fill in the baseline questionnaires and 24 hour dietary recall at any time after completion of the online consent form but before the appointment at their GP practice, as long as they complete each questionnaire in one attempt. Should a participant not complete their questionnaires, reminder emails will be sent at one and two weeks after they received the initial invite to complete the questionnaires.

2. At the GP practice (visit 1)
   Having completed the online assessment, participants will be asked (via message on their screen on completing the assessment, and followed up via email) to book the in-person portions of their baseline assessment at their GP practice for measures which cannot be conducted online. At this appointment (with a nurse or healthcare assistant), their height, weight and blood pressure will be measured and recorded, and a blood sample taken for baseline values (HbA1c, lipid profile, liver function tests). Once their practice confirms they have attended this appointment they will be sent a link to the randomisation system.

9.4. Randomisation and blinding

All eligible participants will be individually randomised to one of two arms: Intervention (12 week, app-based dietary support), or control (usual care; no active additional intervention). The randomisation will be conducted using the Redcap inbuilt randomisation software. This ensures full allocation concealment as information on future allocations is not accessible to the person randomising.

The participants will be aware that they will be randomised to either an app-based support programme or control, therefore no blinding can take place. Due to the nature of the intervention it will not be possible to blind members of the study team to participant allocation. A letter will be provided to the participant's GP to inform them of which group the participant has been allocated to.

9.5. Description of study intervention and comparator

9.5.1. Intervention group

Participants randomised to the intervention group will receive an email informing them they have been assigned to the intervention group, and that their contact information (name and email) has been securely passed to the provider, who will contact them to process the programme onboarding and account creation. They will contact the participant with information how to download and access the app-based intervention. Thereafter, any identifiable information required by the programme provider application will be provided by the participant. The intervention involves diet, activity and behaviour change components. It comprises a three-month remote behavioural change programme with mentoring from a registered dietitian or nutritionist (health coach), peer group support, structured education articles and activity tracking technology. These elements are accessed via a smartphone or web-based application. Each participant will also receive a hard copy of an instructional handbook and a recipe book.

Participants randomised to the intervention group will also receive 1 additional telephone appointment with their GP or practice nurse, towards the start of the 12 week intervention period, to review their current medications and assess any changes to their medication regime may be warranted in view of their anticipated participation in the programme and planned weight loss. We will provide clinicians with current best practice guidelines they may wish to consider but the decisions for individual patients will remain with their clinician.

For participants in the intervention group, data on participant engagement with the app will be received from the company under appropriate agreements. These data will include (as examples) measures of engagement with the three main components of the programme: Learn, Track, and Support. “Learn” interactions are defined as the number of articles read by participants; “Track” interactions are defined as the number of times a participant registered or viewed weight readings; “Support” interactions are defined as the number of messages sent or read in either the private or group chat channels.

9.5.2. Control group

Participants randomised to the control group will receive no additional intervention, and will continue to receive their usual NHS diabetes care from their general practice.

9.6. Subsequent Visits

All Participants will be followed up after 3 months (visit 2) and at 12 months (visit 3).

They will be sent a reminder (initially via email or text, followed up by post and/or telephone call if required) to inform them to expect contact from their GP practice to book study appointments at both 3 and 12 months. These appointments are both study research visits. The appointments will take approximately 15 minutes. At this appointment they will have the same procedures as at their baseline assessment repeated: their weight and blood pressure will be recorded, and blood tests taken (3 sample tubes – for HbA1c, lipid profile and liver function). These visits will be combined with routine clinical care visits where possible. We will explicitly gain consent from participants to be able to extract relevant outcome measure data from their medical records during this time period matching that which would have been collected at the face-to-face appointments (blood results, weight, blood pressure) (which may be used, for example, if a patient is unable to attend their scheduled follow up appointment but has not withdrawn from the study and has attended their practice for relevant measurements in the interim).

They will also be asked to complete the same online questionnaires (PAID score, EQ5D, and 24 hour dietary recall) as they completed at baseline, again at 3 and 12 months, with the addition of specific questions to proactively ascertain any SAEs which may have occurred (and demographic information will not be re-requested as this is not presumed to have changed).

A purposively sampled proportion of participants from the intervention group (aiming to achieve diversity of age, race, and success and engagement with the programme measured by weight/HbA1c outcomes and engagement metrics respectively) will be contacted via telephone for a semi-structured interview to discuss their experience of the intervention, after they complete the 3 month intervention period. Interviews will last approximately 30 minutes. With participants consent this will be audio-recorded.

After 12 weeks the active intervention period will be complete, but participants will retain access to the app interface with stored educational information they have been provided with, and hard copy accompanying information, to refer back to if they wish.

9.7. Sample Handling

Blood samples for 3 sets of tests (HbA1c, liver function, and lipid profile) will be taken at the 3 specified visits, with an approximate maximum total volume of 9ml. All blood samples will be taken, handled, analysed and disposed of according to standard NHS procedures and local practice policy. Blood samples will be taken according to the study schedule outlined in appendix B, in order to estimate changes in glycaemic control and other biomarkers. The samples will be sent to NHS laboratories for analysis and results reported to the GP following standard procedures. These data will subsequently be extracted from participants' medical records onto the participant CRF.

9.8. Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the trial at any time.

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. If a participant decides to withdraw from treatment, we will seek to retain them in the trial for follow-up by explaining the value to the trial of collecting follow up data from all participants by speaking with the participants. However, if the participant wishes to withdraw from follow up we will use their data up to the point that they withdraw unless they request that we do not do so. The reason for withdrawal will be recorded in the electronic case report form (ECRF). Participants that withdraw from the trial will not be replaced. Should a participant wish to withdraw, their information that is held with the provider, will be retained for 10 years following cease of use. This relates to information provided to the intervention provider by the study team and the participant. Cease of use refers to the last login to the online programme by the participant. Each participant can request that their personal information that is retained by the intervention provider is deleted by contacting either the intervention provider or the study team, who will process that request.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)

- Significant protocol deviation
- Clinical decision

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

9.9. Definition of End of Study

The end of study is the point at which the final data is collected -the last 12 month visit of the last participant.

10. SAFETY REPORTING

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening (i.e., an event in which the participant 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 were more severe).
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

10.2. Reporting Procedures for Serious Adverse Events

The duration of the SAE recording period for each participant lasts from their enrolment on to the study, to their completion of the study. Any serious adverse event (SAE) occurring to a participant will be recorded at the time that the research team is made aware of the incident, and reported to the REC that gave a favourable opinion of the study where in the opinion of the clinically qualified Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form, in accordance with HRA process. We will also proactively ascertain for any additional SAEs at the 3 and 12 month outcome data collection timepoints.

11. STATISTICS AND ANALYSIS

The study results will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 statements (8). A full analysis plan will be prepared and finalised before any data analysis.

11.1. Description of the Statistical Methods

The primary statistical analysis of efficacy outcomes will be carried out on the basis of intention-to-treat (ITT). This is, after randomisation, participants will be analysed according to their allocated intervention group irrespective of what intervention they actually receive. We will endeavour to obtain full follow-up data on every participant to allow full ITT analysis, but we will inevitably experience the problem of missing data due to withdrawal, loss to follow up, or non-response to questionnaire items.

We will analyse the primary continuous outcome with a linear model adjusting for baseline value of the relevant variable where relevant. For exploratory analyses, we will use analogous models, but interpret the data in an exploratory manner rather than confirmatory. For binary outcomes (e.g. remission), we will test for a difference in proportions, e.g. using Fischer's exact test.

11.2. Sample Size Determination

Based on previous studies of this intervention(5) and studies in similar populations(3), we estimate an 8-10mmol/mol change in HbA1c at 12 months in the intervention group in those who engage with the programme (SD 8.6mmol/mol), with a 1-2mmol/mol (SD 6mmol/mol) change in the control group. With α and β set at 0.05 this would require approximately 48 participants; however to power for a co-primary outcome would require 72 to 88 participants in total (allowing for variability in estimated effect size). In similar trials of behavioural interventions we would expect retention to follow up of >80%; allowing for the online nature of this trial, and the retention rates of observational studies of this intervention we will aim to recruit 100 participants to allow for cumulative attrition at the intervention sign-up, engagement, and follow up stages.

11.3. The Level of Statistical Significance

The results from the trial will be prepared as comparative summary statistics (difference in proportions or means) with 95% confidence intervals. All the tests will be done at a 5% two-sided significance level.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.2. Data Recording and Record Keeping

The trial is being run with support from the PC-CTU. The data management will be run in accordance with the Trials Unit SOPs, which are fully compliant with Good Clinical Practice (GCP). A trial specific Data Management Plan (DMP) will be developed for the trial outlining in detail the procedures that will be put in place to ensure that high-quality data are produced for statistical analysis.

A unique trial specific number and/or code in any database will identify the participants. All data will be directly entered online by the participant unless followed- up by the research team, using phone calls,

text messages or email. There will be two databases as all information is collected online and therefore identifiable information is also collected. Only the trial team will be able to have access to the databases. Trial data will be kept in compliance with the relevant Sponsor's policy, in particular: the University of Oxford: Data Protection Checklist: https://researchsupport.admin.ox.ac.uk/policy/data/checklist and Practical: Consideration**: https://researchsupport.admin.ox.ac.uk/policy/data/practical**

The data will be stored in Sentry and REDCAP and both are held on University secure servers and the University IT team provide security through Firewalls and backups of the systems are taken daily.

The trial management file and any paper CRFS (if used) will be secured in a locked cabinet in a locked room in the Department of Primary Care Health Sciences.

On completion of the trial and data cleaning, the trial documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for five years. Participants' identifiable information will be destroyed at the end of the trial. Prior to database lock, the Data Manager will undertake a dataset review. The anonymised dataset will be stored on a University secure server with access held by the Senior Data Manager. Procedures in relation to data transfer are documented within the PC-CTU_SOP_DM108 and in accordance with the Information Governance Policy.

The audio recordings of telephone interviews will be stored in password protected files, saved under a file name of participant ID and no other personally identifiable information, on a secure server. The audio recordings will be transcribed by an approved University transcriber with whom appropriate information security and confidentiality agreements are in place. File transfer (of initial audio and then transcriptions) will take place using encrypted files and a University IG approved method of data transfer (Oxfile), with encryption password sent separately and to a different address. Transcriptions will be pseudonymised as soon as is practical, and original audio recordings deleted as soon as the transcriptions have been cross checked and the original audio is no longer required. Pseudonymised transcriptions will then be stored in a file on a secure server.

For those who are assigned to the intervention group, participants' contact information (name and email), with consent, will be passed to Second Nature using a secure, encrypted NHS email. All other identifiable information, which will be provided by the participant to Second Nature, is governed by their privacy policy (available at: secondnature.io/terms). The provider, Second Nature, will retain any information held on an individual for up to 10 years after that individual has ceased use of the System. At that point, the information will be deleted. As covered in section 5 of the providers' privacy policy, participants may request that personal information is deleted at any time. This referral pathway mirrors how this process would work in a real world setting and replicates the current referral pathway to Second Nature. Data on participant engagement with the app will be received from the company under appropriate agreements. These data will include (as examples) measures of engagement with the three main components of the programme: Learn, Track, and Support. "Learn" interactions are defined as the number of articles read by participants; "Track" interactions are defined as the number of times a participant registered or viewed weight readings; "Support" interactions are defined as the number of messages sent or read in either the private or group chat channels. This data will be pseudonymised.

The participant food diaries will be collected using gold standard dietary analysis programme Intake24, a web-based 24 hour dietary recall system. This system is used for the government-run National Diet and Nutrition Survey and is the best available method to collect this data. The Third Party, Intake24, has been assessed by the Information Security team at Oxford University, via a Third Party Security Assessment, to present a low risk for collection of data of this nature and scale, and is on the IG approved list of third

parties, and all necessary agreements will be in place for use of this third party. Participants will be sent a PID-specific link to complete their dietary recall data; this link will be sent by email by the research team (in compliance with all University policies regarding email). Participants will not upload any personal data to this platform, it is solely to capture their dietary intake (i.e. what they had to eat and drink in the preceding 24 hours).

13. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A Trial Management Group (TMG) will provide oversight of all matters relating to participant safety and data quality. The study is not blinded, carries low risk with no rules for early termination and the trial protocol would not be modified based on interim data. Therefore it is felt that it is neither necessary nor appropriate to have a specific Data Monitoring and Ethics Committee in addition to the TMG.

A Trial Steering Committee (TSC) will be formed to provide external oversight of the study and its progress.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

This study involves no identified significant risks to participants. They are primarily consenting to engaging with dietary and behavioural advice which is intended to support them to lose weight and improve their diabetes control and general health. There are known no significant risks of this advice.

Venepuncture for blood samples may cause momentary discomfort. Standard NHS operating procedures as used in routine clinical care will be used for the collection and processing of samples, and all will be carried out by appropriately trained clinicians in the participants' usual GP practice.

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any additional study documentation will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.5. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.6. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the

personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Participants will receive a £20 voucher when they provide data at 12 months follow-up. This is to reimburse participants time and encourage retention for the study, and cover any reasonable travel expenses to the GP surgery (while not requiring processing of financial data or collation of travel receipts on the part of the participants). Participants may benefit from taking part in this study as they may lose weight and some participants will receive free access to a treatment that would usually incur a fee. We will share the results of the trial by making them available on our website.

17. FINANCE AND INSURANCE

17.1. Funding

The study will be funded by through an NIHR Oxford Biomedical Research Centre (BRC) research grant to the Nuffield Department of Primary Care Health Sciences, and the Wellcome Trust Clinical Research Fellowship to EM (CI). The research funding will be administered by the University of Oxford.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The trial results will be published and all who meet the criteria for authorship will be listed as authors. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. The funders will have no role in decisions on publication but authors will acknowledge the funding source.

Other dissemination methods may be used including press releases and social media; the Investigators will be involved in reviewing drafts of such items as well as the relevant media teams.

Participants will be informed of the trial results through an information sheet prepared for a lay audience that will be made available on the department website.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

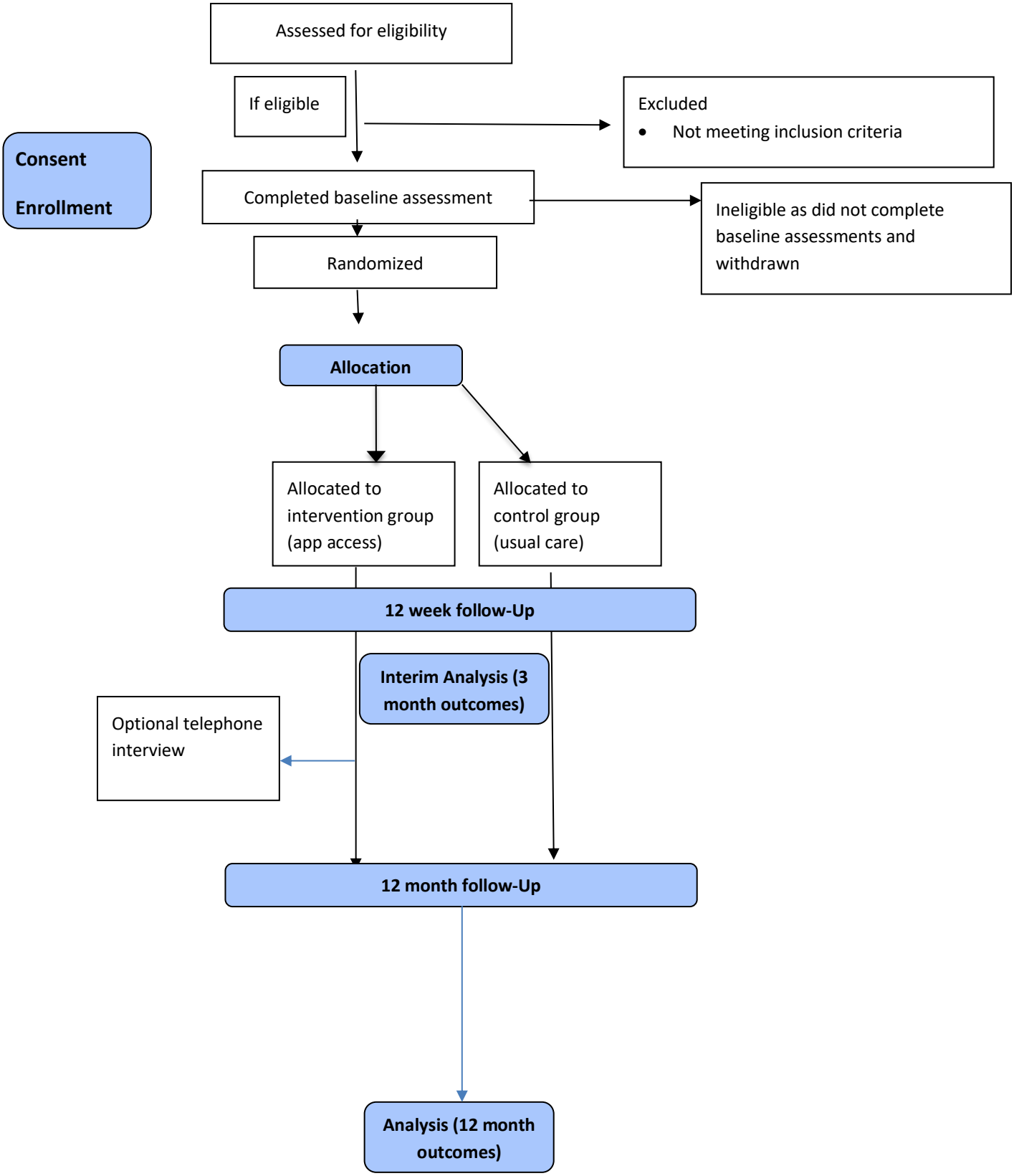
Not applicable

19. REFERENCES

1. DiabetesUK. Facts and Stats. Diabetes UK website, wwwdiabetesorguk. 2015.
2. Morris E, Jebb S, Aveyard P. Type 2 diabetes: treating not managing. The Lancet Diabetes & Endocrinology.
3. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The Lancet. 2018;391(10120):541-51.
4. Morris E, Aveyard P, Dyson P, Noreik M, Bailey C, Fox R, et al. A food-based, low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care: A randomized controlled feasibility trial. Diabetes, Obesity and Metabolism. 2019;n/a(n/a).
5. Kar P, Goward C, Whitman M, Davies M, Willner T, Shaw K. Engagement and effectiveness of digitally enabled behavioural change support for people living with type 2 diabetes. Practical Diabetes. 2020;37(5):167-72.
6. Idris I, Hampton J, Moncrieff F, Whitman M. Effectiveness of a Digital Lifestyle Change Program in Obese and Type 2 Diabetes Populations: Service Evaluation of Real-World Data. JMIR diabetes. 2020;5(1):e15189-e.
7. Jolly K, Lewis A, Beach J, Denley J, Adab P, Deeks JJ, et al. Comparison of range of commercial or primary care led weight reduction programmes with minimal intervention control for weight loss in obesity: Lighten Up randomised controlled trial. 2011;343:d6500.
8. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother. 2010;1(2):100-7.

20. APPENDIX A: STUDY FLOW CHART

Figure 1: CONSORT flow diagram:



21. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Activity/Assessment	Screening	Baseline (Visit 1)	*INTERVENTION	Visit 2	Qualitative interview by phone*	Visit 3	
Months	-1 to 0	0	0-3	3	3-12	12	
Length of assessment	10 mins	30 mins (online)	15 mins (in person)	3 months	30 mins	30 mins	15 mins
Initial eligibility screening	X						
Informed Consent	X						
Weight		x			X		X
Height		x			X		X
Blood pressure		x			X		X
Blood test		x			X		X
Randomisation (if eligible)		x					
Online demographic questionnaire			x				
Online Questionnaires (PAID, EQ5D, 24 hour dietary recall) +/- SAE reporting*			x		X		X
Engagement with app				*X			
****Telephone medication check**				*X			
****Experience of intervention (qualitative interview) by telephone**						*x	

***Can be completed separately to online consent**

****Intervention group only**

22. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	01/06/2021	Jadine Scragg	Section 1 –Typographical clarification Section 3 – Addition of study registration detail and revised study dates Section 9.3 – update to reflect that the baseline questionnaire can be completed at any time point between completion of consent and appointment at GP practice. Section 9.5.1 – update to reflect the referral pathway of patients assigned to the intervention group to the app provider. Section 9.8- clarification of what should happen to patient data in the event of withdrawal

				Section 12.2 – added information to describe how participant data will be stored, transferred and managed