

Study Title: Polycystic ovary syndrome trial (POST): dietary approaches to the management of Polycystic Ovary Syndrome

Short title: POST; Polycystic Ovary Syndrome Trial

Ethics Ref: 25/SC/0210

IRAS Project ID: 331409

Date and Version No: Version 2.0_16September2025

Chief Investigator: Dr Jadine Scragg

Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

Investigators: Professor Susan Jebb, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Dr Sharon Dixon, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Ms Lauren Wheeler, PPI representative, England

Sponsor: University of Oxford
Joint Research Office
1st Floor, Boundary Brook House,
Churchill Drive
Headington
Oxford
OX3 7GB

Funder: National Institute for Health Research – Biomedical Research Centre

Chief Investigator Signature: The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol



Dr Jadine Scragg

Conflicts of Interest Statement

None applicable

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

Contents

1.	KEY CONTACTS.....	6
2.	LAY SUMMARY.....	6
3.	SYNOPSIS	8
4.	ABBREVIATIONS.....	10
5.	BACKGROUND AND RATIONALE.....	11
6.	OBJECTIVES AND OUTCOME MEASURES.....	17
6.1	Primary Objective and Outcome Measures: Progression Criteria.....	17
7.	STUDY DESIGN	21
8.	PARTICIPANT IDENTIFICATION	21
8.1.	Study Participants.....	21
8.2.	Inclusion Criteria.....	21
8.3.	Exclusion Criteria	22
9.	PROTOCOL PROCEDURES	22
9.1.	Screening and Eligibility Assessment.....	22
9.1.	Informed Consent.....	24
9.2.	Randomisation.....	25
9.3.	Blinding and code-breaking.....	25
9.4.	Description of study intervention(s), comparators and study procedures (clinical).....	25
9.4.1.	Dietary Programme	25
9.4.2.	Usual Care Arm	26
9.5.	Baseline Assessments	26
9.6.	Follow-up Visits in both arms	27
9.7.	Sample Handling.....	27
9.8.	Therapeutic visits in intervention arm only.....	28
9.9.	Qualitative interviews in the intervention arm	28
9.10.	Early Discontinuation/Withdrawal of Participants.....	29
9.11.	Definition of End of Study.....	30
10.	SAFETY REPORTING	30
10.1.	Definition of Serious Adverse Events	30
10.2.	Reporting Procedures for Serious Adverse Events.....	31

11.	STATISTICS AND ANALYSIS.....	31
11.1.	Statistical Analysis Plan (SAP)	31
11.2.	Description of the Statistical Methods	31
11.3.	Sample Size Determination	31
11.4.	Analysis populations	31
11.5.	Decision points	32
11.6.	Stopping rules.....	32
11.7.	The Level of Statistical Significance	32
11.8.	Procedure for Accounting for Missing, Unused, and Spurious Data.	32
11.9.	Procedures for Reporting any Deviation(s) from the Original Statistical Plan	32
12.	DATA MANAGEMENT	32
12.1.	Source Data	32
12.2.	Access to Data	32
12.3.	Data Recording and Record Keeping	33
13.	QUALITY ASSURANCE PROCEDURES.....	34
13.1.	Risk assessment.....	34
13.2.	Study monitoring	34
13.3.	Study Committees	34
14.	PROTOCOL DEVIATIONS	34
15.	SERIOUS BREACHES	34
16.	ETHICAL AND REGULATORY CONSIDERATIONS.....	35
16.1.	Declaration of Helsinki.....	35
16.2.	Guidelines for Good Clinical Practice	35
16.3.	Approvals.....	35
16.4.	Other Ethical Considerations.....	35
16.5.	Reporting	35
16.6.	Transparency in Research.....	36
16.7.	Participant Confidentiality.....	36
16.8.	Expenses and Benefits	36
17.	FINANCE AND INSURANCE	36
17.1.	Funding	36
17.2.	Insurance	36
17.3.	Contractual arrangements.....	36
18.	PUBLICATION POLICY.....	37

19.	DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY	
	37	
20.	ARCHIVING.....	37
21.	REFERENCES.....	37
22.	APPENDIX A: STUDY FLOW CHART	41
23.	APPENDIX B: SCHEDULE OF STUDY PROCEDURES.....	42
24.	APPENDIX C: Calculation of confidence intervals for progression criteria and sample size	43
25.	APPENDIX D: Amendment history	43

1. KEY CONTACTS

Chief Investigator	Dr Jadine Scragg Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG Tel: +44(0) 1865 617960 Email: jadine.scragg@phc.ox.ac.uk
Sponsor	Research Governance, Ethics & Assurance University of Oxford Boundary Brook House Churchill Drive Headington Oxford OX3 7GB Tel: +44(0) 1865 289885 Email: rgea.sponsor@admin.ox.ac.uk
Funder(s)	National Institute for Health Research – Biomedical Research Centre

2. LAY SUMMARY

Aim

To assess the feasibility to deliver this intervention (a low energy low carbohydrate food-based diet and support from practice nurses) in primary care (primary outcome) and evaluate its impact on weight change alongside clinical and symptomatic markers of PCOS (secondary).

Background

Primary care records show that about 2% of women aged 15-45 years old have a coded diagnosis of Polycystic ovary syndrome (PCOS), but it is likely considerably underdiagnosed. People with PCOS commonly experience symptoms such as anovulation, menstrual cycle irregularity and hyperandrogenism, and up to 75% women with PCOS have subfertility. Despite its significant impact, PCOS diagnosis and management pose substantial challenges to primary healthcare providers and patients alike. Primary care is typically the first port of call for women who experience problems in their metabolic, menstrual, fertility and reproductive health, including PCOS. However, variability in presenting symptoms, provider confidence, and patient education gaps contribute to delayed interventions, suboptimal patient care, and diminished quality of life. The majority of evidence is derived from studies in specialist care settings and may not be suited to primary care.

We developed this programme using “real food”, supporting patient self-management to reduce the demand on practitioner time so it is realistic for the NHS. We tested this in a feasibility trial for people with type 2 diabetes, which showed we could recruit people with T2D who followed the programme with nurses delivering the programme as intended.

Design and methods

In this trial, we will recruit practices nationally, aiming to include 40 people from approximately 5-7 general practices who are socially representative of the UK population. We will ask practices to write to people with PCOS who are overweight and meet the study criteria. Interested persons will be able to contact the trial team for more details. If the person appears eligible, s/he will see a nurse at the local practice who will confirm eligibility and take informed consent and then measure height, weight, blood pressure, and take a blood test.

We will randomise participants in a 1:1 (intervention: control) ratio, stratifying by general practice. Participants offered the programme will be invited to see the nurse six additional times over 6 months.

At 6 months (post-baseline visit), we will repeat the baseline measures. The main outcome is whether it is feasible to deliver such a dietary intervention in routine primary care for PCOS.

3. SYNOPSIS

Study Title	Polycystic ovary syndrome trial (POST): dietary approaches to the management of Polycystic Ovary Syndrome
Internal ref. no. / short title	POST; Polycystic Ovary Syndrome Trial
Study registration	ISRCTN11396451
Sponsor	RGEA, University of Oxford
Funder	National Institute for Health Research – Biomedical Research centre
Study Design	Randomised controlled trial
Study Participants	Adults (aged 18 to 45 years (inclusive)) with polycystic ovary syndrome and with a BMI of at least 27kg/m ² (≥30kg/m ² if white ethnicity) We will invite health care professionals who deliver the intervention to take part in interviews or discussion groups until we reach information power. We anticipate that a sample of around 15 participants should hold sufficient information power to meet the defined objectives.
Sample Size	40, randomised in a 1:1 ratio (intervention: control) to assess measures of feasibility and acceptability We will invite people to take part in interviews or discussion groups until we reach information power (up to 10).
Planned Study Period	15 months starting 01/08/2025 and ending 31/10/2026
Planned Recruitment period	6 months starting 01/08/2025
Intervention(s)	A low-energy, low-carbohydrate food-base diet providing 800 – 1000 kcal/day with behavioural support from a practice nurse
Comparator	Usual Care for PCOS in primary care

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Feasibility progression criteria		
Willingness to attempt the intervention	Proportion of participants allocated to the intervention arm to attempt the intervention (lower 95%CI)	Nurse documentation at Intervention visit
Patient and practice recruitment	The number of primary care sites and participants to be recruited within the recruitment period	The number of general practices recruited within the 6 month recruitment period will be reported The number of patients recruited within the 6 month

		recruitment period will be reported
Fidelity of intervention delivery	Proportion of sessions where all intervention components are delivered	Evaluation of transcribed consultations against checklist of essential elements; throughout intervention phase.
Availability of data at final follow up (6 months)	Proportion of participants to attend the final follow-up appointment, or to provide relevant data as obtained through medical records	Number of participants attending final study visit or for whom there is available data
Secondary outcomes		
Weight change	The change in weight	The change in weight from the onset of the intervention (baseline) to 6 months after baseline
Blood pressure	Mean change in systolic and diastolic blood pressure	The change in both systolic and diastolic blood pressure between baseline and 6 months
Medication usage	Change in medication usage	Initiation of new medications during the study period or change in existing medications including antihypertensives
HbA1c	Mean change in HbA1c concentration	The change in HbA1c between baseline to 6 months
Cardiovascular risk	Change in QRISK3 score or SMART score	Change in QRISK3 score or SMART score between baseline and 6 months
Type 2 diabetes risk	Change in the risk score for type 2 diabetes	Change in the risk score for type 2 diabetes between baseline and 6 months
Insulin resistance	Change in HOMA-IR score	Change in HOMA-IR score between baseline and 6 months
Modified Ferrimen-Gallwey score	Change in modified Ferrimen-Gallwey score	Change in modified Ferrimen-Gallwey score between baseline and 6 months
Hormonal profile	Change in free androgen index	Change in free androgen index between baseline and 6 months
Health related quality of life	Change across total score of the EQ_5D_5L questionnaire	Change across total score of the EQ_5D_5L questionnaire between baseline and 6 months
Mental wellbeing	Change across WHO-5 score	Change across WHO-5 score between baseline and 6 months
Impact on menstrual periods	Self-assessment of the number of menstrual periods within the past 3 months, the length and the perceived pain and heaviness of their bleed	Change or perceived improvement between baseline and 6-months
Exploratory outcomes		
Proportion of people becoming pregnant	We will report on the proportion of people who become pregnant during the trial period.	Medically confirmed pregnancies documented in medical records will be reported at 6 months

Proportion of people with new diagnoses of type 2 diabetes	We will report on the proportion of people who have new diagnoses of type 2 diabetes during the trial period.	Based on medical records at 3 and 6 months from baseline
The experience of the intervention and the impact of the programme on the participants’ lives and behaviours	Qualitative analysis following semi-structured interviews	Qualitative interviews performed after completion of the intervention.
The experience of healthcare practitioners delivering the intervention	Qualitative analysis following semi-structured interviews and/or focus groups	Qualitative interviews and/or focus groups performed after completion of the intervention.
Process measures		
Percentage of eligible patients of total practice population	Percentage of eligible patients as a proportion of total practice population of patients with PCOS, excluding people with a diagnosis of type 2 diabetes and who are currently prescribed/ have been prescribed oral contraceptive pills in the last 3 months	
Percentage of eligible patients who accept the invitation to participate	Percentage of people who fulfil the recruitment criteria who accept the invitation to participate, based on the proportion of people who are invited by their practice who contact the research team	
Adherence to low-carbohydrate diet	Dietary composition assessed using dietary recall questionnaire after baseline, 3 and 6 months	
Proportion of patients to request the intervention be delivered face-to-face or remotely	Proportion of participants allocated to receive the intervention who choose to receive it delivered face-to-face, remotely (including video consultation or telephone) or a combination of the two. Recorded via a questionnaire at the end of the intervention.	
Arms		
Intervention(s)	A low-energy, low-carbohydrate food-base diet providing 800 – 1000 kcal/day with behavioural support from a practice nurse	
Comparator	Usual Care	

4. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority

ICF	Informed Consent Form
LELC	Low Energy Low Carbohydrate
NHS	National Health Service
OCP	Oral Contraceptive Pill
PI	Principal Investigator
PCOS	Polycystic Ovary Syndrome
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance, University of Oxford
SOP	Standard Operating Procedure
TDR	Total Diet Replacement
VLCD	Very Low Calorie Diet

5. BACKGROUND AND RATIONALE

Primary care records show that about 2% of women aged 15-45 years old have a coded diagnosis of Polycystic ovary syndrome (PCOS), but it is likely considerably underdiagnosed. People with PCOS commonly experience symptoms such as anovulation, menstrual cycle irregularity and hyperandrogenism, and up to 75% women with PCOS have subfertility. Despite its significant impact, PCOS diagnosis and management pose substantial challenges to primary healthcare providers and patients alike. Primary care is typically the first port of call for women who experience problems in their metabolic, menstrual, fertility and reproductive health, including PCOS. However, variability in presenting symptoms, provider confidence, and patient education gaps contribute to delayed interventions, suboptimal patient care, and diminished quality of life. The majority of evidence is derived from studies in specialist care settings and may not be suited to primary care, where patient populations may differ.

Weight loss is likely beneficial for people living with PCOS

It is estimated that 1 in 10 women in the UK are living with polycystic ovary syndrome (PCOS). Approximately 50% of women with PCOS have overweight/obesity ¹ and 65-80% have insulin resistance. Evidence shows that moderate weight loss (3-9%) is associated with improvements in the reproductive and metabolic abnormalities often observed with PCOS ^{2,3}. Our systematic review and meta-analysis of RCTs compared weight loss interventions to usual care or lesser-intense interventions for people living with PCOS. Weight loss interventions were associated with a mean difference in weight change of -3.78kg (-4.61;-2.94); $I^2=78\%$. Our systematic review found that weight loss interventions increased the number of menstruations in people with PCOS to a greater extent than those in the comparator 2.64 [0.65 to 4.63]; $I^2 = 43\%$ ⁴. Only a minority of the included studies reported on symptoms that people with PCOS have identified as important, such as hirsutism and therefore these findings should be interpreted with

caution. None of the included studies were conducted in primary care, despite primary care being the primary setting for PCOS management, at least within the UK. NICE recommends that people with PCOS who are overweight are offered advice to lose weight, but recommends no specific intervention. In general populations advice to lose weight, without support, is largely ineffective and achieves approximately 0.4 kg weight loss over 12 months ⁵.

Low carbohydrate diets for people with PCOS

Previous systematic reviews have compared diets lower in carbohydrates (<45% of total energy intake from carbohydrates) with diets higher in carbohydrates (>45%), and shown improvements in BMI, HOMA-IR and some hormonal markers (total testosterone, follicular stimulating hormone, sex hormone binding globulin and LDL-cholesterol⁶). However, this meta-analysis included only 8 studies and all but one followed participants up for less than four months. Only one study (n=16) followed reported data for longer, 24 weeks. Some of the included studies only had very small absolute differences in carbohydrate consumption, or used hypocaloric diets which makes it challenging to appraise the impact of a low carbohydrate diet, despite promising improvements between arms. Other reviews assessing the impact of dietary composition on the symptoms of PCOS found no significant differences in anthropometric outcomes according to dietary composition, though menstrual regularity was improved following a low glycaemic index based diet compared with advice for healthy eating ⁷.

Given the central role of insulin resistance in the aetiology of PCOS, other interventions for people with T2D may help. Unwin *et al* showed that with advice on a lower carbohydrate diet, without an emphasis energy restriction, patients lost 10kg, with 51% achieving remission from T2D in primary care ⁸. This shows the potential for simple, behavioural and dietary advice within primary care to lead to weight loss and, based on the findings from our systematic review, improvements in PCOS symptoms. Insulin resistance is associated with hyperandrogenism, driving the symptoms of PCOS ⁹. Carbohydrates are the major secretagogues of insulin and diets restricted in carbohydrate have been shown to improve glycaemia and insulin sensitivity in people with PCOS ^{2,10}.

The vast majority of the data available for dietary and behavioural change for people with PCOS has derived from trials embedded in research specific or university settings. Therefore, there is little to no evidence guiding how feasible these sorts of interventions may be when delivered in usual care. In the UK, NHS primary care is where a substantial proportion of management of PCOS is conducted and is also typically the first point of contact for PCOS diagnosis and management. Behavioural, dietary interventions have been successfully delivered by primary care clinicians to patients with type 2 diabetes with good acceptability and feasibility, but it is not clear how this may be adapted to people with PCOS and their usual clinicians ^{8,11}.

Options for people with PCOS

People with PCOS typically have a greater health resource utilisation and associated healthcare costs compared with controls without PCOS ¹². However, there are few resources available for people with PCOS in the NHS. There are no NHS weight management services specifically for people with PCOS, and patients will often opt to pay for private services if they have the means to do so, creating inequities. PCOS is not currently listed as a criterion on for referral to many specialist weight management services within the UK. However, NHS weight management pathways are in place which could be suitable for people with PCOS. PCOS is considered one of the obesity-related conditions which may make people

eligible to be referred for tier 3 weight management support in NHS England, if they have a BMI of >35 kg/m². However, these weight management services are oversubscribed with long waiting lists (typically over 2 years), and in our formative conversations, people with PCOS told us this rarely, if ever, happens. The inclusion criteria is also restrictive, excluding many people who live with PCOS and overweight.

Other treatment options may include the oral contraceptive pill or referral to an endocrinologist who may recommend the prescription of metformin. However, this is rare and does not provide people with support. Specifically, during our formative PPI group conversations, people advocated for primary care to be best situated to provide holistic support for PCOS and weight management. PCOS also can make it difficult to conceive and weight loss in those seeking fertility treatment has been shown to increase natural conceptions. However, support for this is similarly rare.

The intervention

Primary care clinicians cite the lack of evidence-based recommendations as the major challenge when counselling people with PCOS. Promising evidence of effectiveness for people with PCOS is an intervention based on a total diet replacement programme that achieved a mean weight loss of 17% over 12 weeks. These programmes are offered in the NHS for people newly diagnosed with T2D¹³ but are not funded for the treatment of PCOS and were viewed with caution during discussions with a PPI group, as they were not considered to be adaptable for different cultures or suitable for people with childcare responsibilities.

We will combine the low energy prescription associated with a TDR with a low-carbohydrate diet. We developed DIAMOND; a food-based, low-energy, low-carbohydrate intervention with behavioural support from nurses and comprehensive written materials for the patient. It was feasible and acceptable to patients with type 2 diabetes and their clinical care team¹⁴ and is being tested in a trial aiming for diabetes remission with results expected by early 2025. It can be delivered by a range of primary care staff, needing no expertise in nutrition. Patients with PCOS are predominantly treated by non-specialist staff in primary care, and it is anticipated that this intervention can be tailored for people with PCOS.

Compared to people living with T2D, people with PCOS are typically younger and more likely to be in work. We will therefore give people the option to have the intervention delivered remotely and explore interest in this as a process measure.

PPI input

People with PCOS took part in conversations to discuss their experiences of PCOS management within primary care, where they perceived clinicians as 'unable to give specific information'. Most had resorted to seeking information about diet and PCOS online. Many had negative experiences and attendees expressed a preference for support from their GP practice, who they trust to give independent and authoritative advice. They welcomed the possibility of more structured support for weight loss, especially if it was available remotely, explaining that regular face-face appointments can be disruptive. People reported substantial personal expenditure incurred through self-symptom management. One message was clear- the need for support; *"The best thing that happened to me was being diagnosed with diabetes- I actually got help"*.

Impact on patient care

If successful, this intervention could be readily adopted into routine care for people with PCOS. It meets the needs of patients seeking advice, and provides a structured programme for primary care clinicians to offer and may pave the way for people with PCOS to access other NHS weight management interventions. We will work closely with the NHS to discuss implementing the intervention, should it be effective.

Main research questions & aims

To fill this evidence gap, this study aims to investigate the feasibility of delivering a low-carbohydrate, low-energy, food-based dietary intervention in primary care, to patients with PCOS who are overweight. Our intervention draws upon the motivational importance of the relationship between the GP and the patient, but provides almost all technical knowledge through the use of structured materials such as meal plans, thus addressing the uncertainty that health professionals have about nutrition. Likewise, we aim to improve patients' adherence to the programme by providing a structured simple behavioural support programme for staff to use when implementing this programme. We have trialled this intervention in populations with T2D in a feasibility, which passed its progression criteria comfortably and is now being trialled in a trial exploring its effectiveness to achieve remission from T2D ^{11,15}.

The hypothesis is that compared to usual care, an intervention involving targeted health professional advice and goal setting, will help patients understand and adhere to a low-carbohydrate, low-energy diet that will lead to significant reductions in weight and improvements in insulin resistance and subsequent symptoms of PCOS, providing positive reinforcement of the dietary modification. In the longer term, the energy content of the diet can be increased, but adherence to a lower-carbohydrate diet offers the potential for sustained glycaemic control and sustained benefits. Together with a return to a low-energy regimen in the case of weight regain, this dietary strategy provides the foundations for a sustainable long-term approach to the management of this PCOS, which could readily be incorporated into usual primary care.

Specific aims of this research are:

- i. To investigate the feasibility of delivering this behavioural and dietary intervention to a population of patients with PCOS in primary care, and determine whether progression to the development of a full scale randomised controlled trial is indicated.
- ii. To assess achievements against a number of process measures to inform future trial design.
- iii. To investigate the potential physical and biochemical impact of this behavioural and dietary intervention.
- iv. To explore experiences into patients participation and gain an insight into the acceptability of the intervention

Description of the intervention

This behavioural, dietary intervention was originally designed for use in primary care for people living with T2D and their clinicians, with detailed descriptions of the interventions elsewhere^{11,15,16}. In brief, the intervention is comprised of targeted advice from a healthcare professional, with personalised goal setting, combined with written nutritional and dietary information to guide food choices, with structured follow up and reinforcement in follow up sessions. The dietary advice will comprise two essential components: exclusion of carbohydrates from the diet (with the exception of dairy products, pulses and legumes), and energy restriction; with additional support regarding healthy food choices such as

increasing salad and vegetable intake, and choosing leaner meats and fish. Dietary recommendations are provided for people who have dietary restrictions. Specific dietary guidance has been co-developed with patients, to inform the variety of foods recommended, ensuring adaptability to different styles of cuisines.

To design effective complex behavioural interventions, such as those required to facilitate dietary change, comprehensive behavioural analysis and grounding in behaviour change theory are important¹⁷. The Capability, Opportunity, and Motivation- Behavioural model (COM-B)¹⁸, Theory Domains Framework (TDF)¹⁹, and Behaviour Change Wheel (BCW)¹⁸, are validated and well recognised frameworks which can be used to facilitate analysis of targeted behaviours, and determine which intervention functions are most likely to be effective in changing the target behaviour in different contexts. In this study, the aim is to change people's behaviour around food choices and adherence to a diet, assessing feasibility and acceptability to both patients and their clinicians. An analysis of this behaviour, and of the findings of previous qualitative studies in related areas using these validated frameworks, identified key influencing factors to include the TDF domains of knowledge, skills, decision processes and behavioural regulation (psychological capability), social influences and environmental context (social and physical opportunity), and beliefs about capabilities and consequences, optimism, intentions and goals (reflective motivation), as well as reinforcement²⁰⁻²⁵. As such, the intervention strategy has been developed to address and support these.

There are many studies which have assessed the quantitative impacts of weight loss for PCOS, but few, if any, have appraised acceptability^{4,26}. We initially developed this intervention in line with the Transtheoretical Framework of Acceptability (TFA), and have since adapted to be more in line with values, beliefs and experiences of people with PCOS²⁶.

We have shown that the intervention on which this trial is based upon can be delivered with good fidelity and feasibly in primary care for people with type 2 diabetes¹¹. This intervention was identified based on the likely impact on the underlying pathophysiology, such as weight reduction (caloric restriction) and improved insulin resistance (carbohydrate reduction). However, specifically, the DIAMOND intervention, over other interventions based on carbohydrate reduction and caloric restrictions based on core behavioural components which have been highlighted as important in previous qualitative literature of peoples experiences of receiving management for PCOS, such as dedicated appointment time with a primary health care clinician, the provision of evidence-based knowledge, ongoing monitoring and feedback and patient focussed goal setting^{27,28}.

However, people with T2D typically have annual reviews and therefore more routinely engage with healthcare professionals for the management of their health conditions. Therefore it is plausible that further adaption and development is needed, to maximise acceptability to people with PCOS. Patients with PCOS do not typically have routine reviews, unless for other health conditions, which may therefore not address their needs of dedicated time to discuss the management of PCOS. Clinicians may feel less comfortable to discuss behavioural changes and management strategies for PCOS, given it is less routine. Lack of dedicated time and perceived lack of clinician knowledge has a marked impact on patient satisfaction with the management they received for PCOS^{27,29,30}. Therefore, we have continued to adapt this intervention in line with validated frameworks to identify intervention functions which are likely to be effective to enact behavioural change. This includes providing social and physical opportunity, evidence-based information to both clinicians and patients and ongoing monitoring and feedback.

Known and potential risks and benefits

Potential benefits of this intervention include significant weight loss and improvement in symptoms and biomarkers of PCOS. This, in turn may reduce the likelihood of developing T2D, reducing the risks associated with obesity, mediated through improved lipid profile, blood pressure and associated cardiovascular risk profile.

Potential risks of this low-carbohydrate, low-energy approach to dietary intervention for people with PCOS include:

- Risk of hypotension in patients taking antihypertensive medications. Recommendations will be made available to support GPs in their titration of medications according to BP readings (including home BP monitoring) – as forms part of usual clinical care for patients on antihypertensives.
- Risk of constipation. For anyone undertaking an energy-restricted diet of this nature, there is a risk that they may develop constipation. Recognising this, all participants will be warned about the potential to develop constipation, the importance of increasing their fluid intake, how to recognise early signs of constipation, and when to contact their GP for a laxative. In the health professionals training and manual, advice on how and when to prescribe Fybogel to counter constipation will be given.
- Change in INR for patients on warfarin. It is known that changes in dietary patterns can affect patients' INR values (and required warfarin dosing). Patients are routinely advised to inform their warfarin monitoring service of any significant lifestyle or medication changes, which will guide their clinicians in advising on dosing and frequency of blood tests. Patients will be advised to follow this routine advice if they are taking warfarin, and inform their monitoring service that they will be following a low-carb low-calorie diet. They may then be offered an additional INR test at the clinical services' discretion.

Population to be studied and who might be generalised to

Recognising the increasing economic burden of both obesity and PCOS, as well as the cost incurred to both patients and the health service, in morbidity and mortality, the primary population to be studied in this feasibility trial will include: adult patients with PCOS and a BMI of $\geq 27\text{kg/m}^2$ (non-white ethnicity) and $\geq 30\text{kg/m}^2$ (white ethnicity). This subgroup of patients with PCOS also presents both a practical and a potentially beneficial time to engage with patients in their treatment journey. Currently, there are very few, if any, treatment options available to people with PCOS in primary care, beyond specific symptom management, such as OCPs. People with PCOS are often not eligible to be referred to existing weight management services, unless they have other weight-related comorbidities, and therefore it is unclear on how feasible more intensive weight management interventions may be. Therefore, we have specifically designed this intervention and trial for people without other weight-related comorbidities which would otherwise make them eligible for referral to such services. People with PCOS typically report feeling unsupported by their managing clinician, so a clinician's suggestion of added support or for the patient to make significant changes, may represent a valuable "teachable moment" for optimising engagement with behavioural interventions^{31,32}.

Explanation of rationale for assessing feasibility

This study will investigate a dietary and behavioural intervention, to support patients who are overweight with PCOS to reduce their weight and improve their associated symptoms and biomarkers, such as menstrual irregularity, hirsutism and hormonal profiles. A full trial to demonstrate that this intervention works to produce sustained weight loss and improved symptomatic control would need to be large, and therefore expensive. Following the MRC framework for developing complex interventions, before this is justified, we need to ensure that the intervention can be delivered as intended, that it reduces weight and improves symptoms in the short term, and that recruitment and research methods run as planned, through conducting a feasibility study. Additionally, it is important to ascertain whether patients will accept the intervention to which they are randomised, the degree of cross-contamination of trial arms, and the capability of HCPs to deliver an intervention to a population who ordinarily would not be eligible to receive under current NHS guidance.

Therefore, the specific aim of this study is to test the feasibility of this intervention for achieving weight loss and improving symptoms in overweight individuals with PCOS, in primary care.

6. OBJECTIVES AND OUTCOME MEASURES

The aim is to assess the feasibility to deliver this intervention in primary care (primary outcome) and evaluate its impact on weight change alongside clinical and symptomatic markers of PCOS (secondary), embedding qualitative components and process measures to inform whether to progress to a full randomised controlled trial. The objectives are to assess the impact on:

- hormonal profile
- glycaemic control
- cardiovascular risk
- weight
- wellbeing
- symptoms of PCOS; hirsutism and impact on menses

We will also assess equity of programme uptake and in exploratory subgroup analyses, we will assess the impact of the programme by age, socioeconomic status and ethnicity.

6.1 Primary Objective and Outcome Measures: Progression Criteria

The following progression criteria will determine whether to progress to a full trial:

1. That 60% of participants allocated to the intervention arm to attempt the intervention after randomisation
(Evaluated by documentation after intervention visit; assessed as the proportion of patients who agree to start the dietary intervention, as recorded by the nurse delivering the intervention session).
2. Fidelity of intervention delivery: That healthcare professionals conduct the intervention delivery session with at least 60% of essential elements present.
(Evaluated by assessment of audio recorded consultations against a checklist of essential elements).

3. Availability of data at final follow-up. That 60% of participants attend the final follow-up session or provide data
(Documentation of final study visit and/or record of provision of relevant data)
4. Ability to recruit primary care sites and patients within the recruitment time period (6 months)

In determining thresholds for progression criteria, based on previous trials of a similar nature, we expect a drop-out rate of up to 25%, and expect that the first two criteria would achieve 75-80%^{33,34}. Therefore based on a 95% confidence interval around this achievement, progression criteria have been set at 60% for each of these outcomes (calculations detailed in appendix D, based on a sample size of 40 participants, allocated intervention: control group in a 1:1 ratio).

6.2 Secondary Objectives and Outcome Measures

A mixture of quantitative and qualitative methods will be used to assess process measures and effectiveness measures. This feasibility study is not powered to detect statistical differences in efficacy outcomes but will examine the following parameters in order to test trial procedures, process, resources and management, to aid sample size estimates for a future trial, to determine the most appropriate primary outcome measures for a future trial, and to inform further development of the intervention strategy.

Process Measures:

- Percentage of eligible patients as a proportion of total practice population
- Percentage of people who fulfil the recruitment criteria who accept the invitation to participate
- Participant adherence to the protocol: including, change in dietary composition (low-carbohydrate, energy restricted - assessed using dietary recall questionnaires); participants' self-reported concordance with the intervention; availability of data for outcome measures; attendance at follow up sessions; contamination of the control group (i.e., those who choose to follow the principles of the intervention (i.e. follow a low-carbohydrate diet), despite being allocated to the control group). This will be assessed using food frequency questionnaires to establish change in dietary composition (frequency of carbohydrate consumption, energy restriction) of control group participants.
- Proportion of people diagnosed with type 2 diabetes at baseline and throughout the defined study period
- Proportion of people who choose to receive the intervention face-to-face, remote (either video consultation or phone call) or a combination

Effectiveness Measures:

- The change in weight
- Mean change in systolic and diastolic blood pressure
- Change in medication usage
- Mean change in HbA1c concentration
- Change in lipid profile – total cholesterol, HDL, triglycerides, calculated non-HDL cholesterol, and total cholesterol:HDL ratio
- Change in QRISK3 score or SMART score

- Change in the risk score for type 2 diabetes
- Change in fasting glucose, fasting insulin and HOMA-IR score
- Change in modified Ferrimen-Gallwey score
- Change in free androgen index
- Change across total score of the EQ_5D_5L QoL questionnaire
- Change across WHO-5 score
- Self-assessment of the number of menstrual periods within the past 3 months, and the impact on menstrual bleeds

Qualitative Measures:

- Experience of and insight into acceptability of the intervention, for patients and healthcare practitioners.

Summary of Objectives and Outcome measure

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Feasibility progression criteria		
Willingness to attempt the intervention	Proportion of participants allocated to the intervention arm to attempt the intervention (lower 95%CI)	Nurse documentation at Intervention visit
Patient and practice recruitment	The number of primary care sites and participants to be recruited within the recruitment period	The number of general practices recruited within the 6 month recruitment period will be reported The number of patients recruited within the 6 month recruitment period will be reported
Fidelity of intervention delivery	Proportion of sessions where all intervention components are delivered	Evaluation of transcribed consultations against checklist of essential elements; throughout intervention phase.
Availability of data at final follow up (6 months)	Proportion of participants to attend the final follow-up appointment, or to provide relevant data as obtained through medical records	Number of participants attending final study visit or for whom there is available data
Secondary outcomes		
Weight change	The change in weight	The change in weight from the onset of the intervention (baseline) to 6 months after baseline
Blood pressure	Mean change in systolic and diastolic blood pressure	The change in both systolic and diastolic blood pressure between baseline and 6 months
Medication usage	Change in medication usage	Initiation of new medications during the study period or

		change in existing medications including antihypertensives
HbA1c	Mean change in HbA1c concentration	The change in HbA1c between baseline to 6 months
Cardiovascular risk	Change in QRISK3 score or SMART score	Change in QRISK3 score or SMART score between baseline and 6 months
Type 2 diabetes risk	Change in the risk score for type 2 diabetes	Change in the risk score for type 2 diabetes between baseline and 6 months
Insulin resistance	Change in HOMA-IR score	Change in HOMA-IR score between baseline and 6 months
Modified Ferrimen-Gallwey score	Change in modified Ferrimen-Gallwey score	Change in modified Ferrimen-Gallwey score between baseline and 6 months
Hormonal profile	Change in free androgen index	Change in free androgen index between baseline and 6 months
Health related quality of life	Change across total score of the EQ_5D_5L questionnaire	Change across total score of the EQ_5D_5L questionnaire between baseline and 6 months
Mental wellbeing	Change across WHO-5 score	Change across WHO-5 score between baseline and 6 months
Impact on menstrual periods	Self-assessment of the number of menstrual periods within the past 3 months, the length and the perceived pain and heaviness of their bleed	Change or perceived improvement between baseline and 6-months
Exploratory outcomes		
Proportion of people becoming pregnant	We will report on the proportion of people who become pregnant during the trial period.	Medically confirmed pregnancies documented in medical records will be reported at 6 months
Proportion of people with new diagnoses of type 2 diabetes	We will report on the proportion of people who have new diagnoses of type 2 diabetes during the trial period.	Based on medical records at 3 and 6 months from baseline
The experience of the intervention and the impact of the programme on the participants' lives and behaviours	Qualitative analysis following semi-structured interviews	Qualitative interviews performed after completion of the intervention.
The experience of healthcare practitioners delivering the intervention	Qualitative analysis following semi-structured interviews and/or focus groups	Qualitative interviews and/or focus groups performed after completion of the intervention.
Process measures		
Percentage of eligible patients of total practice population	Percentage of eligible patients as a proportion of total practice population of patients with PCOS, excluding people with a diagnosis of type 2 diabetes and who are currently prescribed/ have been prescribed oral contraceptive pills in the last 3 months	

Percentage of eligible patients who accept the invitation to participate	Percentage of people who fulfil the recruitment criteria who accept the invitation to participate, based on the proportion of people who are invited by their practice who contact the research team
Adherence to low-carbohydrate diet	Dietary composition assessed using dietary recall questionnaire after baseline, 3 and 6 months
Proportion of patients to request the intervention be delivered face-to-face or remotely	Proportion of participants allocated to receive the intervention who choose to receive it delivered face-to-face, remotely (including video consultation or telephone) or a combination of the two. Recorded via a questionnaire at the end of the intervention.
Arms	
Intervention(s)	A low-energy, low-carbohydrate food-base diet providing 800 – 1000 kcal/day with behavioural support from a practice nurse
Comparator	Usual Care

7. STUDY DESIGN

This feasibility study will be an individually randomised controlled trial, performed in adult patients with PCOS and a BMI $\geq 30\text{kg/m}^2$ ($\geq 27\text{kg/m}^2$ if non-white). Due to the nature of the intervention, it will not be possible to blind the participants, clinicians delivering the intervention, or some of the study team to the treatment allocation.

Each participant will be enrolled for 6 months from randomisation to final follow up, and will consist of a total of up to 9 visits, where allocated to receive the intervention or 3 visits, where allocated to receive usual care. Data collection will be in the form of participant self-reporting questionnaires (menstrual frequency, wellbeing and quality of life), healthcare professional feedback, and biometric and biochemical measurements (weight, free androgen index, HbA1c, fasting glucose, etc). A flowchart of the project is included in appendix A, and schedule of study in appendix B.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

We are seeking to enrol 40 adult participants diagnosed with PCOS from approximately 5-7 practices, who would consider using dietary means to achieve weight loss.

8.2. Inclusion Criteria

- Aged ≥ 18 -45 years inclusive
- BMI $\geq 27\text{kg/m}^2$ ($\geq 30\text{kg/m}^2$ if white ethnicity)
- A coded diagnosis of PCOS
- Able to attend GP practice for appointments

- Willing and able to give informed consent

8.3. Exclusion Criteria

The participant may not be enrolled if any of the following apply:

- Current or recent (<3 months) use of oral contraceptives or hormone replacement therapy
- Current or recent (<3 months) use of any hormonal contraception, including the contraceptive implant, contraceptive injection, contraceptive patch, vaginal ring or hormonal IUS systems (Mirena or JadeS)
- Premature ovarian failure
- Postmenopausal and/ or premature menopause
- Pregnant, breast feeding, currently undergoing fertility treatment
- Type 1 diabetes
- Active treatment for cancer (with the exception of non-melanoma skin cancer)
- Following a structured weight-loss programme
- Use of weight loss medication (including GLP1 receptor agonists) currently or in the 3 months prior to study enrolment
- History of bariatric surgery
- SGLT2 inhibitors started in the 3 months prior to study enrolment
- Unwilling to consider dietary changes
- Clinician feels participation is inappropriate due to other reasons (such as, but not limited to mental health, awaiting surgery)
- Diagnosed with a known eating disorder for whom the programme could be unsafe or require extensive monitoring to ensure safety
- Diagnosed with a myocardial infarction or stroke in the past three months, uncontrolled cardiac conduction abnormalities e.g. long QT syndrome, maculopathy or proliferative retinopathy
- People with a diagnosis of type 2 diabetes
- People taking part in other research that would compromise either their participation in POST or the other research study/ies that they are participating in.

There will be no exceptions made to allow into the study people who do not fulfil all these criteria.

NB: If the patient is taking warfarin, they are not excluded from participating in the study, but will be advised to inform their local monitoring service about their participation, and they may be advised to have additional blood test monitoring of their INR as part of their care.

9. PROTOCOL PROCEDURES

An overview of the study procedures is shown in the study flowchart (appendix B).

9.1. Screening and Eligibility Assessment

Enrolling general practices

We are seeking a nationally representative set of practices, so we will use quota sampling to facilitate this. We will create a quota of practices that represent England based on deprivation based on the following index of multiple deprivation (IMD) decile groups- 1-4, 5-7, 8-10, and ethnicity as percentage non-white in increments (0-8.9, ≥9.0). We will create a database of practices holding details expressing interest that holds the practice details, population size, IMD decile, and ethnic composition. This database will cover the progress of the practice through the recruitment process from expression of interest to green light. Practices will fill slots in the quota and as practices formally enrol, we will cease accepting expressions of interest from practices that will worsen any imbalance and accept those from practices that facilitate our nationally representative recruitment.

GPs will be greenlit to begin recruitment of patients contingent on documentation of CVs and GCPs for the relevant staff members, and receiving study specific training. This training will comprehensively outline trial processes, and will comprise of an online webinar, for training on delivering the intervention to participants. This webinar will be available to practices to access throughout the trial period and beyond, and refresher training will be offered where required, such as new members of staff joining the practice who will be supporting the study.

Enrolling patients within practices

We aim to enrol adults with a coded diagnosis of PCOS and with a BMI of at least 27kg/m² (≥ 30kg/m² if white) and who may benefit from weight loss.

Practices will search their registers for potential participants. Practices will invite patients by letter, text or phone call, according to preference and interested patients will contact the trial team, be screened for eligibility, and booked for an appointment with the person facilitating recruitment (RRDN nurse or equivalent). In addition, we will financially support practices to call selected patients to ensure representation from typically under-represented groups. We have previously found that recruitment by letter alone tends to lead to a somewhat higher uptake by more affluent people³⁵, while in-person offer leads to higher take-up by the more deprived³⁶. The RRDN nurse (or equivalent) will see all potential participants to confirm eligibility and consent them onto the trial.

We will develop a search strategy for each computer system that enables us to define a cohort to invite into the study based on coded medical records. GPs will be asked to screen this list to remove patients for whom the invite would be inappropriate and where this is not easily coded, for example people who have been recently bereaved or known to be violent. GPs will invite by letter (including via Docmail, or email if that is standard practice for the site) or text message patients who appear eligible and suitable. In addition, because this procedure tends to over-recruit more affluent patients and women, we will ask practices to phone and invite participants who do not respond to the initial letter or text message and invite them to consider the study. The letter, text message and the phone call will signpost patients to the patient information sheet and/or video to find out more information and then ask participants to contact the trial team for further information.

The trial team will then outline the nature of the study and its requirements and respond to patients' questions, when they initially express interest in taking part. If the patient is interested to participate, the trial team will check eligibility using a checklist of inclusion/exclusion criteria where these are appropriate

for use by a non-clinician. For people who are interested to join the study and appear to be eligible, the trial team will send the PIS and book an appointment for a baseline visit at the patients GP practice.

Participating practices will provide data pertaining to percentage of eligible patients identified as a proportion of the total practice population with PCOS, and total number of invitation letters sent (to identify what percentage of people who fulfil the recruitment criteria and are invited to participate subsequently accept this invitation), to allow assessment of process measures.

RRDN nurses (or equivalent) will perform baseline visits where participants will be consented, and eligibility will be confirmed. Once eligibility is confirmed participants will be enrolled onto the trial. For those who are confirmed to be ineligible, no data collection will take place.

9.1. Informed Consent

Written versions of the participant information and informed consent form will be presented to the participants detailing 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 current or future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The informed consent will also comprise consent for the intervention delivery sessions to be audio recorded, if the participant is allocated to receive the intervention, to enable evaluation of the feasibility criteria; fidelity of the intervention delivery.

The participant information sheet will be sent to patients who respond to the trial team and express interest. After confirmation that the information sheet has been read a member of the research team will conduct an initial eligibility check over the phone. Once these checks have been passed, the research team will contact the patients GP practice and book a baseline appointment. After the phone call, the information sheet may be resent if requested by the patient, ahead of their baseline appointment. This will be sent over email, post or by signposting to the study website, in line with patient preference. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the investigator, their GP, the RRDN nurse, or other independent parties to decide whether they will participate in the study.

Evidence of informed consent will then be obtained by means of participant-dated signature and dated signature of the person who undertook the baseline visit. The participant must personally electronically sign and date the latest approved version of the informed consent form before any study specific procedures are performed. For the health care professional interviews and focus group discussions, consent will be obtained by the means of the dated signature of the researcher undertaking the interview and the attendees.

The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief Investigator. A copy of the signed informed consent form will be given to the participant. The original signed form will be retained in the Trial Master File and a copy will be filed at the study site and included in the medical notes.

9.2. Randomisation

Once participants have completed the consent process, and baseline data collection has been carried out, the study team will randomise all eligible participants to one of the two trial arms (intervention or control), in a 1:1 ratio, using permuted block design randomisation. Allocation will be stratified by practice. Information on future allocations are not accessible to the person randomising. Due to the nature of this study, it will not be possible to further blind participants, clinicians or some of the study team to the treatment allocation beyond this point.

9.3. Blinding and code-breaking

This is an open-label study in which participants, clinicians, and trial staff will know the allocation of the practice. We consider the risk of bias to be low, as the outcomes are measured objectively.

9.4. Description of study intervention(s), comparators and study procedures (clinical)

9.4.1. Dietary Programme

Patients will be advised that with full adherence, the diet is designed to achieve 15kg weight loss. Nurses or suitably qualified alternatives will support patients to achieve this target wherever possible since our weight regain review shows strongly that greater initial weight loss is predictive of greater long term health benefits^{37,38}. The nurse will discuss the participant's goals for their PCOS and health and how remission may achieve these goals. They will see participants at 0, 2, 4, 8, 12, 16 and 26 weeks from the start of the programme, but respond flexibly to participants' needs, as would be the case in routine care. Appointments are up to 20 minutes long in up to week 12 and 10 minutes thereafter. We expect these to be face-to-face, but remote consultations will be offered and patients will be given the option to choose.

The programme is a behaviourally informed low-energy, low-carbohydrate diet delivered by practice nurses in primary care. It draws on the motivational value of the relationship between the practice nurse and the patient for delivery and to provide behavioural support, but it provides most technical knowledge through structured materials such as meal plans, addressing professionals' uncertainties³⁹.

The dietary component of the programme is a low-energy low-carbohydrate diet (800-1000kcal with a maximum of 50g carbohydrate per day, or 20-25% total energy, compared to usual intake of 45%). The core principles include advice to exclude all sugary and starchy foods except very limited dairy and fruit, strict portion control and avoiding energy-dense foods. The maintenance programme supports a transition to a sustainable dietary regimen to control energy intake, provide about 125g/d carbohydrate, less than half the average population intake (for example, 200 ml milk, 2 portions fruit and a modest portion of fibre-rich carbohydrate at each of three meals). It is based around the 3Rs: refrain (from high sugar foods e.g. cakes and biscuits), restrict (frequency and portions of starchy carbohydrates), and replace (swap to high fibre varieties of carbohydrate).

We will provide online nurse training. The design of these training modules, based on those tested in an earlier feasibility study for people with T2D, was informed by behavioural analysis of the existing qualitative literature and findings from the feasibility study, identifying critical domains of the Behaviour Change Wheel and Theoretical Domains Framework^{11,18,40}, to promote successful behaviour change in the healthcare professional delivering the intervention and facilitate effective delivery of the programme.

Using these frameworks, key influencing factors which the training targets are: psychological capability (including knowledge and skills – explaining the scientific rationale for this approach, evidence of effectiveness in other studies/settings, basic dietary principles, and training in brief motivational and behaviour change techniques for consultations), social and physical opportunity (structured dedicated intervention sessions with time set aside to deliver, to facilitate comprehensive but efficient delivery), and reflective motivation (sharing case experiences of healthcare professionals involved in the feasibility study who described how seeing the changes in their own patients improved their own motivation to engage, and the changes they could expect to see). Process analysis of the earlier studies also highlighted the positive impact of providing simple checklists for each intervention session, to ensure core concepts and actions were covered, and the structured comprehensive patient materials designed to contain most core knowledge required for the programme, which could be used independently by patients but also for signposting during the healthcare professional's consultations, serving as effective prompts and giving the healthcare professional confidence that they needed little to no specialist dietary knowledge to support the patient in undertaking the intervention.

We will ask clinicians to withdraw medication for hypertension following the protocols used for the NHS Diabetes Remission Programme i.e. on starting the dietary programme and also to ask patients to inform their local warfarin monitoring service, if applicable, who may advise an additional blood test. Participants will be advised to measure and record their BP for two days per week, if they have a diagnosis of hypertension, which reinforces adherence and reassures participants and clinicians. We will advise participants to contact their GP using a traffic-light system based on guidance in the national rollout of the diabetes remission programme.

9.4.2. Usual Care Arm

Consistent with the pragmatic trial design, we aim to compare the dietary intervention to current usual care for people with PCOS. While 'usual care' risks some diversity in practice, the alternative would be to create a bespoke package for the control group which would in itself constitute a new intervention.

9.5. Baseline Assessments

At baseline, the RRDN nurse (or equivalent) will use the medical records and discuss with the participant and record significant past medical history, including whether there is established cardiovascular disease, hypertension, or other significant medical history. At 3 and 6 months the RRDN nurse or practice nurse will be asked to report any changes in the medication.

The nurse will measure and record weight in light clothing. S/he will record blood pressure, measured after 5 minutes seated, taking 3 measurements at least a minute apart. Participants will be asked to complete questionnaires (EQ_5D_5L and WHO-5) and to detail how many menstrual periods they have had in the past 3 months. The nurse will also either take or arrange for blood tests to be taken to measure HbA1c, lipid profile, hormone profile, and in people with established cardiovascular disease CRP. Once these results are returned, they will be entered into the CRF. After the appointment, participants will be emailed a link where they can record their self assessment of hair growth in androgen sensitive regions, based on the modified ferrimen-gallwey score⁴¹. They will also be emailed a link to a dietary recall questionnaire, to be completed on the day of the appointment or the following day. The data collected at each appointment is summarised in appendices b.

Practice nurses will be trained to measure and/or record each of these at the study training, and procedures will be detailed in the study manual held electronically at each site. Data will be recorded onto an electronic case report form (CRF), using Microsoft excel via SharePoint which will be stored on a secure University of Oxford server, with restricted access to authorised personnel only.

The clinicians at the GP practice will maintain clinical responsibility and will be advised to act on results as per usual processes. New diagnoses, such as those of type 2 diabetes or hypertension will be recorded and reported.

Persons who might not adequately understand verbal explanations or written information given in English will be able to receive translated documents. A video PIS will be provided to support patients who might not adequately understand written information.

9.6. Follow-up Visits in both arms

Once enrolled in the study, if participants are due for their appointments do not attend we will attempt to contact them to remind them that they are due appointment (by telephone, email or post, according to what contact information provided by the participant). We will aim to do this up to 3 times. If we haven't managed to contact the participant after this we will leave it to them to contact us if they still want to continue and book an appointment.

First follow-up visit

This will take place at three months. RRDN research nurses or equivalent or practice staff will record weight, take or appraise the patients' own records of blood pressure, and take or arrange for blood tests to measure HbA1c, and hormonal profile. Participants will also be asked to complete questionnaires as undertaken at baseline.

Second follow-up visit

This will take place at six months. Practice staff will repeat all measures obtained at the baseline assessment (but excluding height). As per the baseline appointment, participant-completed questionnaires, such as those for hirsutism will be completed after the appointment. Additionally, the practice staff will record the occurrence of all serious adverse events that have occurred, most commonly hospitalisations. Participants in the intervention group will be asked to complete a questionnaire about their experience of the intervention.

9.7. Sample Handling

Blood samples (approximately 30-40 ml) will be taken at the 3 specified visits. 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, risk of cardiovascular disease and type 2 diabetes, 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. Therapeutic visits in intervention arm only

In the intervention group only, participants will in addition see the practice nurse (or suitably qualified practice staff) as detailed in 9.4.1. At such visits, the nurse will record that s/he has delivered the intervention and assess and record the patient's adherence to the programme. These visits may be audio recorded, where the participant consents.

As part of appropriate clinical care, s/he may measure blood glucose or blood pressure and may, with medical input, decide on medication changes. Any medication changes for hypertension will be recorded in the CRF.

9.9. Qualitative interviews in the intervention arm

We aim to assess the impact of the programme on the everyday lives of participants randomised to the dietary and behavioural programme and how the support was experienced and its impact on their behaviour. We will ask all participants to consent to interview at baseline, but this will be optional, and will contact to arrange interview only with those who agreed. A researcher will telephone the participant to arrange and then conduct an interview lasting up to 60 minutes covering the impact of the programme, their reactions to the behavioural support programme, and the ways that their behaviour has or has not changed, and their views of the impact of the programme on the participant's PCOS symptoms. All telephone interviews will be audio-recorded.

The semi-structured interviews will follow broad topic areas based on the study objectives, but will encourage participants to discuss their opinions and experiences freely and in depth and confidentially, reassuring the participant that their healthcare providers will not hear their views. Topics will include: their experience of weight and PCOS management before, during and immediately after the study intervention period, and of the intervention itself; whether they self-report a current weight loss or dietary change attempt, and what types of methods are being employed. They will also explore in more depth, preliminary themes generated during pilot qualitative data collection following the feasibility study and follow up cohort study, including: perceptions of the dietary programme as a "diet" vs a "lifestyle change" and its sustainability; the role of external vs internal motivation for health behaviour change in this population; and unintended consequences of engagement with the programme (for example any change in other health behaviours (e.g. exercise), and changes in beliefs (e.g. understanding of and models of obesity)).

Health Care professionals

We will speak with healthcare professionals, who will have taken part in delivering the intervention, using focus groups in the first instance but offering 1:1 interviews as needed. The practices will be informed of the opportunity to give feedback in this way when they are recruited to the wider study. Inclusion criteria are any GP, practice nurse or other HCP who has been involved in intervention delivery or follow up sessions. There are no exclusion criteria. The healthcare professionals who have been involved in this study in this way will be provided with participant information sheets via the practice lead, and asked to contact the study team if they would be willing to take part in this discussion group. They can contact the study team by phone, text, or email, and will be given the chance to ask questions. They will also be given all of the information required for informed consent, to allow adequate consideration time. They will be able to decide if they would like to take part up until the study planned study closure date. Should more participants volunteer than are required, purposive sampling will be used to ensure both GPs and nurses

are represented in the cohort, and to include those who have conducted a greater number of sessions. A mutually convenient time will then be arranged to hold the focus group session, which will last up to 90 minutes. Written informed consent will then be formally taken before the focus group or interview commences (please refer to section 9.1). Practices will be reimbursed for the healthcare professionals taking time out from their clinical duties to participate.

Focus groups and interviews will be held online. All focus groups will be audio recorded, and these audio recordings will be transcribed. The focus groups will follow broad topic areas based upon the study objectives, but will encourage participants to discuss their perceptions and experiences freely and in depth. Topics will include: the acceptability of the intervention; views on which components of their treatment group they felt were effective and which were not effective; thoughts about impact on experience of PCOS and its management; thoughts about weight management for PCOS going forwards. Health care professionals will receive a £25 voucher in recognition of their time taken to attend these discussions and interviews.

Data will be analysed using thematic analysis.

For further details on data recording and record keeping for telephone interviews, please refer to Section 12.3

9.10. Early Discontinuation/Withdrawal of Participants

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 adhere to 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. Participants may also withdraw from active follow-up and further communication but allow the study team to continue to access their medical records, where relevant data may be used.

In addition, the clinical team or trial team may advise the participant to cease treatment on the dietary programme if it is considered necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Clinical decision for other reasons

Follow-up of participants will be unaffected by withdrawal from treatment.

Participants who withdraw from treatment or follow-up will be analysed as allocated, with missing data specified in Section 11. Participants who withdraw will not be replaced in this feasibility study.

The type of withdrawal and reason for withdrawal will be recorded in the CRF. The patient's GP will be informed that they have withdrawn from the study.

Participation is voluntary. If participants decide they do not want to take part in the research at any point, they can withdraw at any time without giving a reason. We will give the participant the opportunity to disclose their reason for withdrawing. Participants legal rights at work or future medical care will not be affected. If a participant withdraws from the study, we will use the pseudonymised data that has been collected up to the point of withdrawal. We will continue to use this anonymised data after withdrawal from the study.

If participants choose to stop taking part in the study, we will continue to collect relevant information about their health from their GP to inform study outcomes. If participants do not want this to happen, they can request that we do not this, or that we stop doing this.

9.11. Definition of End of Study

The end of study is the date of the last data collection from the last participant. This is likely to be at the completion of qualitative data collection.

10. SAFETY REPORTING

We considered but decided to not record adverse events, except adverse events of special concern (see below). It is hard to engage people who are receiving no intervention (not a placebo) in recording adverse events, which seems an irrelevance to them, and these participants are also not attending appointments to collect such data. However, we will ask nurses in the intervention arm to record adverse events of special concern- namely episodes of hypoglycaemia or episodes of symptomatic hypotension that required outside assistance to manage, episodes of ketosis, or hospitalisation for international normalised ratio (INR) out of range in people on warfarin. In addition, at 6 months, we will record serious adverse events from the medical records for all patients, namely episodes of hospitalisation that were not planned at baseline, death or life-threatening event, illness or injury that resulted in permanent significant disability, or resulted in congenital abnormality. We will not prospectively record SAEs because this type of treatment is known to reduce the incidence of serious disease, and our retrospective recording will be sufficient to add to data on this.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- 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 a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to 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.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the 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 should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

A full statistical analysis plan will be prepared before database lock and finalised before any analysis takes place, which will be posted in a public registry.

11.2. Description of the Statistical Methods

As this is a feasibility study, it has not been powered to detect a statistically significant difference in efficacy between the arms. The main progression criteria will be presented in appropriate descriptive statistics with appropriate 95% confidence intervals as described above. Although statistical significance is not expected, efficacy outcomes will be analysed using comparative summary statistics (difference in means) with 95% confidence intervals. The study results will be reported in accordance with the CONSORT statements. A detailed analysis plan will be prepared and finalised before any data analysis.

11.3. Sample Size Determination

As stated above, we estimated the sample size based on the width of confidence intervals around our predicted proportions. Using those criteria, 40 people were sufficient to be randomised 1:1 to be confident that, if the feasibility criteria were met, there was likely to be evidence that they were met.

We will invite participants to take part in interviews or group discussions in line with the principles of information power⁴².

11.4. Analysis populations

The primary analysis population will include all randomised participants, as defined by protocol eligibility criteria, regardless of what intervention they actually received or compliance of intervention. Other analysis populations will be pre-specified in the SAP.

11.5. Decision points

We have allowed 6 months to recruit participants overall. Recruitment draws from an existing pool of patients, rather than waiting for new cases to occur, so full recruitment requires opening sites and for these sites to identify, screen, and write to potential participants, and the RRDN to hold recruitment clinics at the practice.

We will progress to a full, randomised controlled trial for effectiveness if the trial achieves mainly green or amber and stop if the trial achieves mainly red ratings.

11.6. Stopping rules

There are no formal stopping rules.

11.7. The Level of Statistical Significance

A 2-sided 5% level of significance will be used for the primary and secondary outcomes.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data will be reported, with reasons where available, and the missing data mechanism explored. Although, the mixed effect model implicitly accounts for data missing at random (MAR). Additional sensitivity analysis will be carried out to explore the mechanisms of missingness.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

We will report all such deviations in the papers that report these analyses.

12. DATA MANAGEMENT

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

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), laboratory records.

CRF entries will be considered source data where the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the sponsor, relevant NHS trusts, regulatory authorities and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

Participant telephone interviews and intervention sessions will be audio recorded (with participants' consent). The same will be true for the interviews and focus group discussions with healthcare professionals. Each recording will be pseudonymised by patient ID recorded at the beginning, rather than participant name. Recordings will be saved in password-protected files in a folder, with restricted access, separate from any other study data (e.g. the study database) on the University secure network. The audio recordings will be transcribed by an approved University transcriber with whom appropriate information security and confidentiality agreements are in place. Audio recordings of the intervention sessions will be assessed for fidelity of intervention delivery and then deleted. File transfer (of initial audio and then transcriptions) will take place using encrypted files and a University information governance approved method for data transfer, with encryption password sent separately via different means. 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.

Anonymised intervention group participant experience questionnaires will be completed via a JISC online survey platform, which has been assessed by the University's Information Security Team and is a recommended service for gathering confidential data due to its ISO27001 certification and additional security measures. No participant identifiable information will be collected in these questionnaires.

A study specific Data Management Plan (DMP) will be developed for the feasibility trial outlining in detail the procedures that will be put in place to ensure that high quality data are produced for statistical analysis.

A secure online database will incorporate an electronic Case Report Form (CRF) onto which the study team will enter data. In the case of the eCRF not being available, the original of any paper CRFs will be kept and returned by the research team to the University of Oxford research base via a lockable container, and a copy will be held at the research site.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

On completion of the trial and once all study activity has been completed, the trial documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for five years. Personal data contact data will be stored for 1 year after the end of the study, so that participants can be sent a summary of the results of the study. No personal data will be retained for patients screened out at either the initial eligibility check with the research team over the phone, or for those determined to be ineligible at the baseline appointment.

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 archivist as per PC-CTU_SOP_TM124. Procedures in relation to data transfer are documented within the PC-CTU_SOP_DM108 and in accordance with the Information Governance Policy. The anonymised information collected about participants may be used in an anonymous form to support other research in the future and data may be shared with other researchers for research purposes.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Regular monitoring will be performed according to the study specific monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific monitoring plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Specifics will be detailed in the trial Risk Assessment and Monitoring Plan.

13.3. Study Committees

An independent trial steering committee (TSC) will provide oversight of all matters relating to participant safety and data quality. The TSC will include at least one independent clinician, an independent statistician and a participant representative. The TSC will be asked to review the trial protocol and will provide expert advice to the Trial Management Group (TMG) on the trial progress.

A data monitoring and ethics committee (DMEC) will not be convened for this study.

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 as per PC-CTU_SOP_TM125.

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 CI, 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

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 participant facing material 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. Other Ethical 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 PCOS symptoms and general health. There are known no significant risks of this advice. However, participants may experience constipation when changing diet. Advice will be provided to prevent this and/or treatment provided should participants experience constipation. Health care professionals invited to take part in interviews and discussions will be given time to decide if they would like to take part, with opportunities to ask questions to the research team or discuss with their colleagues. It will be made clear that their decision to participate or not will not affect their legal or employment rights.

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. In practices providing the intervention, we will ask clinicians to withdraw medication for hypertension following the protocols used for the NHS Diabetes Remission Programme i.e. on starting the dietary programme and also to ask patients to inform their local warfarin monitoring service, who may advise an additional blood test, if appropriate. The research team will be available to contact should the patient experience distress at any point, such as during filling in questionnaires. They will be assured that they do not need to complete the questionnaires if they do experience any distress. Where appropriate, they may contact their GP practice.

16.5. Reporting

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

16.6. 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 date as specified on the end of trial declaration.

16.7. 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.

For University of Oxford sponsored studies please refer in particular to the University of Oxford's:

Data Protection Checklist <https://researchsupport.admin.ox.ac.uk/policy/data/checklist>

Practical Considerations <https://researchsupport.admin.ox.ac.uk/policy/data/practical>

16.8. Expenses and Benefits

In recognition of the lack of benefit for attending for assessment of study outcomes, participants will receive a £25 voucher for attending their 3 months visit and a £25 voucher for attending for 6 month follow-up in the form of vouchers.

17. FINANCE AND INSURANCE

17.1. Funding

Research funding is provided by the National Institute for Health Research Biomedical Research Centre

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 Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR-BRC. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

On completion of the trial and once all study activity has been complete, the trial documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for five years.

21. REFERENCES

1. Polycystic ovary syndrome, long-term consequences (green-top guideline no. 33). Royal College of Obstetricians and Gynaecologists. <https://www.rcog.org.uk/en/guide-lines-research-services/guidelines/gtg33/>
2. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertility and Sterility*. 2004/03/01/ 2004;81(3):630-637. doi:<https://doi.org/10.1016/j.fertnstert.2003.08.023>
3. Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The Effect of a Hypocaloric Diet with and without Exercise Training on Body Composition, Cardiometabolic Risk Profile, and Reproductive Function in Overweight and Obese Women with Polycystic Ovary Syndrome. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(9):3373-3380. doi:10.1210/jc.2008-0751
4. Scragg J, Hobson A, Willis L, Taylor KS, Dixon S, Jebb SA. Effect of Weight Loss Interventions on the Symptomatic Burden and Biomarkers of Polycystic Ovary Syndrome: A Systematic Review of Randomized Controlled Trials. *Annals of Internal Medicine*. 2024;
5. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P, on behalf of the Behavioural Weight Management Review G. Weight change among people randomized to minimal intervention control groups in weight loss trials. <https://doi.org/10.1002/oby.21255>. *Obesity*. 2016/04/01 2016;24(4):772-780. doi:<https://doi.org/10.1002/oby.21255>
6. Zhang X, Zheng Y, Guo Y, Lai Z. The Effect of Low Carbohydrate Diet on Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. *International Journal of Endocrinology*. 2019/01/01 2019;2019(1):4386401. doi:<https://doi.org/10.1155/2019/4386401>
7. Moran LJ, Ko H, Misso M, et al. Dietary Composition in the Treatment of Polycystic Ovary Syndrome: A Systematic Review to Inform Evidence-Based Guidelines. *Journal of the Academy of Nutrition and Dietetics*. 2013/04/01/ 2013;113(4):520-545. doi:<https://doi.org/10.1016/j.jand.2012.11.018>
8. Unwin D, Delon C, Unwin J, Tobin S, Taylor R. What predicts drug-free type 2 diabetes remission? Insights from an 8-year general practice service evaluation of a lower carbohydrate

diet with weight loss. *BMJ Nutrition, Prevention & Health*. 2023:e000544.
doi:10.1136/bmjnp-2022-000544

9. Diamanti-Kandarakis E, Dunaif A. Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications. *Endocrine Reviews*. 2012;33(6):981-1030. doi:10.1210/er.2011-1034

10. Meckling KA, O'Sullivan C, Saari D. Comparison of a low-fat diet to a low-carbohydrate diet on weight loss, body composition, and risk factors for diabetes and cardiovascular disease in free-living, overweight men and women. *The Journal of Clinical Endocrinology & Metabolism*. 2004;89(6):2717-2723.

11. Morris E, Aveyard P, Dyson P, 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*. 2020;22(4):512-520.

12. Berni TR, Morgan CL, Rees DA. Rising Incidence, Health Resource Utilization, and Costs of Polycystic Ovary Syndrome in the United Kingdom. *The Journal of Clinical Endocrinology & Metabolism*. 2024:dgae518. doi:10.1210/clinem/dgae518

13. Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DIRECT): an open-label, cluster-randomised trial. *The Lancet*. 2018/02/10/2018;391(10120):541-551. doi:[https://doi.org/10.1016/S0140-6736\(17\)33102-1](https://doi.org/10.1016/S0140-6736(17)33102-1)

14. Morris E, Aveyard P, Dyson P, et al. A food-based, low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care: A randomized controlled feasibility trial. <https://doi.org/10.1111/dom.13915>. *Diabetes, Obesity and Metabolism*. 2020/04/01 2020;22(4):512-520. doi:<https://doi.org/10.1111/dom.13915>

15. Scragg J, Morris E, Wane S, et al. Dietary approaches to the management of type 2 diabetes (DIAMOND) in primary care: A protocol for a cluster randomised trial. *Contemporary Clinical Trials*. 2023:107199.

16. Elizabeth M, Paul A, Pamela D, et al. Dietary Approaches to the Management Of type 2 Diabetes (DIAMOND): protocol for a randomised feasibility trial. *BMJ Open*. 2019;9(1):e026460. doi:10.1136/bmjopen-2018-026460

17. Atkins L, Michie S. Changing eating behaviour: What can we learn from behavioural science? *Nutrition Bulletin*. 2013;38(1):30-35. doi:10.1111/nbu.12004

18. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation science : IS*. Apr 23 2011;6:42. doi:10.1186/1748-5908-6-42

19. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Quality and Safety in Health Care*. February 1, 2005 2005;14(1):26-33. doi:10.1136/qshc.2004.011155

20. Rogerson D, Soltani H, Copeland R. The weight-loss experience: a qualitative exploration. *BMC Public Health*. 2016/05/04 2016;16(1):371. doi:10.1186/s12889-016-3045-6

21. Metzgar CJ, Preston AG, Miller DL, Nickols-Richardson SM. Facilitators and barriers to weight loss and weight loss maintenance: a qualitative exploration. *J Hum Nutr Diet*. Dec 2015;28(6):593-603. doi:10.1111/jhn.12273

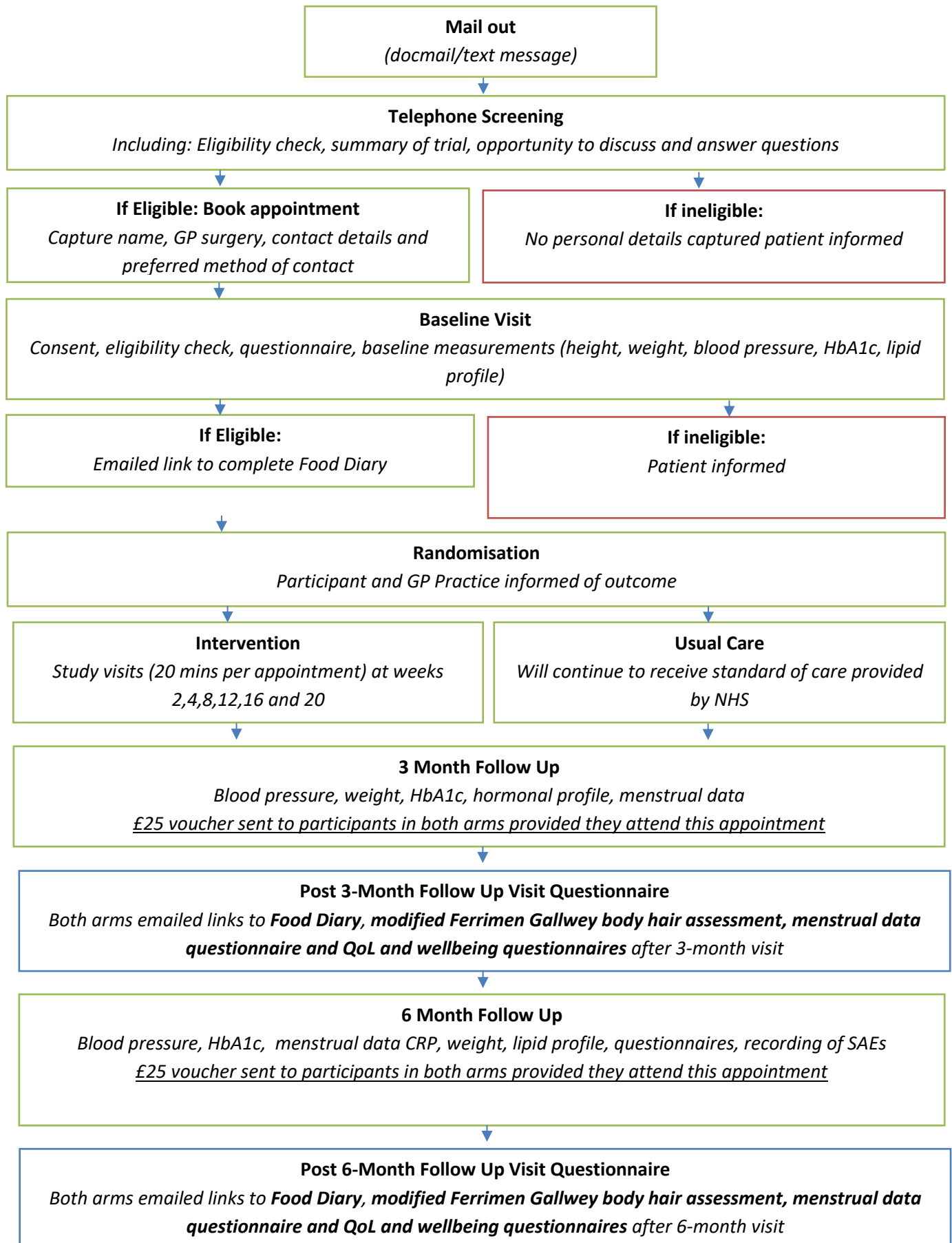
22. Scragg J, Hallsworth K, Taylor G, et al. Factors associated with engagement and adherence to a low-energy diet to promote 10% weight loss in patients with clinically significant non-alcoholic fatty liver disease. *BMJ Open Gastroenterology*. 2021;8(1):e000678.

23. Gupta H. Barriers to and Facilitators of Long Term Weight Loss Maintenance in Adult UK People: A Thematic Analysis. *Int J Prev Med*. Dec 2014;5(12):1512-20.

24. Hammarström A, Wiklund AF, Lindahl B, Larsson C, Ahlgren C. Experiences of barriers and facilitators to weight-loss in a diet intervention - a qualitative study of women in Northern Sweden. *BMC Women's Health*. 2014/04/16 2014;14(1):59. doi:10.1186/1472-6874-14-59
25. Lim S, Smith CA, Costello MF, MacMillan F, Moran L, Ee C. Barriers and facilitators to weight management in overweight and obese women living in Australia with PCOS: a qualitative study. *BMC endocrine disorders*. 2019;19:1-9.
26. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC health services research*. 2017;17:1-13.
27. Gibson-Helm M, Tassone EC, Teede HJ, Dokras A, Garad R. The Needs of Women and Healthcare Providers regarding Polycystic Ovary Syndrome Information, Resources, and Education: A Systematic Search and Narrative Review. *Semin Reprod Med*. 2018/09/06 2018;36(01):035-041. doi:10.1055/s-0038-1668086
28. Teede HJ, Tay CT, Laven J, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome†. *Fertility and Sterility*. 2023/08/14/ 2023;doi:<https://doi.org/10.1016/j.fertnstert.2023.07.025>
29. Ismayilova M, Yaya S. What can be done to improve polycystic ovary syndrome (PCOS) healthcare? Insights from semi-structured interviews with women in Canada. *BMC Women's Health*. 2022;22(1):157.
30. Harrison C, Tay CT, Busby MA, Mousa A, Teede H, Boivin J. Challenges experienced by those with polycystic ovary syndrome in healthcare interactions: a qualitative evidence synthesis. *Reproductive BioMedicine Online*. 2024;49(4)doi:10.1016/j.rbmo.2024.104293
31. Lawson PJ, Flocke SA. Teachable moments for health behavior change: a concept analysis. *Patient Educ Couns*. Jul 2009;76(1):25-30. doi:10.1016/j.pec.2008.11.002
32. Flocke SA, Clark E, Antognoli E, et al. Teachable moments for health behavior change and intermediate patient outcomes. *Patient Educ Couns*. Jul 2014;96(1):43-9. doi:10.1016/j.pec.2014.03.014
33. Aveyard P, Lewis A, Tearne S, et al. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. *Lancet (London, England)*. Oct 21 2016;doi:10.1016/s0140-6736(16)31893-1
34. Leslie WS, Ford I, Sattar N, et al. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. journal article. *BMC family practice*. 2016;17(1):1-10. doi:10.1186/s12875-016-0406-2
35. Ahern AL, Aveyard P, Boyland EJ, Halford JC, Jebb SA. Inequalities in the uptake of weight management interventions in a pragmatic trial: an observational study in primary care. 2016;66(645):e258-e263. doi:10.3399/bjgp16X684337 %J British Journal of General Practice
36. Graham J, Tudor K, Jebb SA, et al. The equity impact of brief opportunistic interventions to promote weight loss in primary care: secondary analysis of the BWeL randomised trial. *BMC Medicine*. 2019/03/01 2019;17(1):51. doi:10.1186/s12916-019-1284-y
37. Hartmann-Boyce J, Theodoulou A, Oke JL, et al. Long-term effect of weight regain following behavioral weight management programs on cardiometabolic disease incidence and risk: systematic review and meta-analysis. *Circulation: Cardiovascular Quality and Outcomes*. 2023;16(4):e009348.
38. Hartmann-Boyce J, Theodoulou A, Oke JL, et al. Association between characteristics of behavioural weight loss programmes and weight change after programme end: systematic review and meta-analysis. *bmj*. 2021;374

39. Morris E, Aveyard P, Dyson P, et al. Dietary Approaches to the Management Of type 2 Diabetes (DIAMOND): protocol for a randomised feasibility trial. *BMJ Open*. Jan 17 2019;9(1):e026460. doi:10.1136/bmjopen-2018-026460
40. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. 2005;14(1):26-33. doi:10.1136/qshc.2004.011155 %J Quality and Safety in Health Care
41. Aswini R, Jayapalan S. Modified Ferriman–Gallwey score in hirsutism and its association with metabolic syndrome. *International journal of trichology*. 2017;9(1):7-13.
42. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qualitative Health Research*. 2016/11/01 2015;26(13):1753-1760. doi:10.1177/1049732315617444
43. Hooper R. NIHR Research Design Service London: Justifying sample size for a feasibility study. http://www.rds-london.nihr.ac.uk/RDSLONDON/media/RDSContent/files/PDFs/Justifying-Sample-Size-for-a-Feasibility-Study_1pdf. Accessed February 2017;

22. APPENDIX A: STUDY FLOW CHART



23. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures				
	Screening	Baseline	3 month	6 month
Eligibility checks	x	x		
Informed consent		x		
Demographics		x		
Medical history		x		
Medication usage		x		x
Questionnaires (EQ_5D_5L, WHO-5, food diary)		x	x	x
Blood pressure		x	x	x
Height		x		
Body weight		x	x	x
Menstrual data and modified Ferrimen-Gallwey score		x	x	x
HbA1c, fasting glucose, fasting insulin, CRP, lipid profile, hormonal profile for FAI		x		x
HbA1c, hormonal profile for FAI			x	
Recording of SAEs				x
Intervention visits (intervention group only)			*	
Intervention group questionnaire (intervention group only)			*	

* Six visits within six months on the discretion of the site staff (suggested weeks 2, 4, 8, 12, 16, 20)

24. APPENDIX C: Calculation of confidence intervals for progression criteria and sample size

Progression criteria 1: *That 60% of allocated “intervention” group participants attempt the dietary intervention after randomisation.*

Progression criteria 2: *Fidelity of intervention delivery: That healthcare professionals conduct the intervention delivery session with at least 60% of essential elements present*

Based on previous trials of a similar nature, we would expect that 75-80% of participants and healthcare professionals achieve this^{33,34}.

Confidence interval calculation for a starting sample size of 20 (intervention group only),

Based on an estimated rate of 80%:

$$95\% \text{ CI} = 1.96 * \sqrt{((0.8 * (1 - 0.8)) / 20)} = 0.175 \text{ 17.5\% ie } \underline{95\% \text{ CI} = 80\% \pm 17.5\%}$$

Based on an estimated rate of 75%

$$95\% \text{ CI} = 1.96 * \sqrt{((0.75 * (1 - 0.75)) / 20)} = 0.19 \text{ 19\% ie } \underline{95\% \text{ CI} = 75\% \pm 19\%}$$

Hence progression criteria threshold set between 56-62.5%.

Progression criteria 3: *That 60% of participants attend the final follow-up session*

Based on previous trials of a similar nature (37), we would expect a 25% drop out rate, i.e. a 75% completion rate.

Confidence interval calculation for a sample size of 40

Based on an estimated completion rate of 75%:

$$95\% \text{ CI} = 1.96 * \sqrt{((0.75 * (1 - 0.75)) / 40)} = 0.13 \text{ 13\% i.e. } \underline{95\% \text{ CI} = 75\% \pm 13\%}$$

Hence progression criteria threshold set at 60%.

Methodology used:⁴³

Notation: p=estimate (percentage expected to be seen), q=1-p, n=sample size, SE= standard error

$$SE = \sqrt{((p * q) / n)}$$

$$95\% \text{ CI} = \text{estimate} \pm 1.96 * SE$$

$$\text{Expressed above as: } 95\% \text{ CI} = 1.96 * \sqrt{((p * q) / n)}$$

25. APPENDIX D: Amendment history

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Amendment 1 (minor)	1.2	30 th July 2025	Jadine Scragg	Correction of typographical errors
Amendment 2 (minor)	1.3	22 nd August 2025	Jadine Scragg	Improved clarity of exclusion criteria
Amendment 3 (substantial)	2.0	16 th September 2025	Jadine Scragg	Addition of exclusion criteria to exclude people with previous bariatric surgery