BAMBINI 2.0

Study Protocol
*Ba*riatric surgery vs. *M*edical care for o*b*esity and polycystic ovar*i*an syndrome related i*n*fertil*i*ty:
Long-term follow-up of the BAMBINI randomised-controlled clinical trial

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Protocol authorised by:

Name & Role	Date	Signature
Dr Suhaniya Samarasinghe Chief Investigator	25th February 2026	

Study Management Group

Chief Investigator: Dr Suhaniya Samarasinghe

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Statistician: Not appointed

Study Management: Dr Suhaniya Samarasinghe

Clinical Queries

Clinical queries should be directed to Dr Suhaniya Samarasinghe who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

NIHR Imperial Biomedical Research Centre

This protocol describes the BAMBINI 2.0 study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

PCOS	Polycystic ovary syndrome
BAMBINI	*Ba*riatric surgery vs. *M*edical care for o*b*esity and polycystic ovar*i*an syndrome related i*n*fertil*i*ty
BMI	Body Mass Index
ART	Assisted Reproductive Technology
T2DM	Type 2 diabetes mellitus
CVD	Cardiovascular disease
MASLD	Metabolic dysfunction-associated Steatotic liver disease
HbA1c	Glycosylated haemoglobin
CRP	C-reactive protein
LH	Luteinising hormone
FSH	Follicle-stimulating hormones
SHBG	Sex hormone binding globulin
DHEAS	Dehydroepiandrosterone
AMH	Anti-Mullerian Hormone
SOPs	Standard Operating Procedures

KEYWORDS
Polycystic ovary syndrome, PCOS, obesity, metabolic, fertility

STUDY SUMMARY

TITLE	*B*ariatric surgery vs. *M*edical care for o*b*esity and polycystic ovar*i*an syndrome related i*n*fertil*i*ty: Long-term follow-up of the BAMBINI randomised-controlled clinical trial
DESIGN	Longitudinal follow-up study
AIMS	To investigate the long-term safety and efficacy of obesity surgery in women with PCOS, obesity and oligomenorrhoea or amenorrhoea
OUTCOME MEASURES	Number of patient-reported menstrual cycles in the last 12 months
POPULATION	76 Women who participated in the BAMBINI clinical trial
ELIGIBILITY	Women who received their randomly allocated intervention as part of the BAMBINI clinical trial
DURATION	1 year

1. INTRODUCTION

1.1. BACKGROUND

Infertility affects 1-in-6 couples globally. According to the British Fertility Society, 30% of infertility is due to female factors[1], with major causes being ovulatory dysfunction, tubal, and diminished ovarian reserve[2].

Polycystic Ovary Syndrome (PCOS) is the commonest cause of ovulatory dysfunction (irregular or absent ovulation), accounting for around 80% of cases[3]. PCOS is the most common endocrinopathy in premenopausal women, affecting up to 20% of women[4]. PCOS causes anovulation, hyperandrogenism (leading to metabolic dysfunction) and polycystic ovarian morphology on ultrasound. The psychological burden of infertility is very high, with many women suffering with depression and anxiety[5]. Over half of women with PCOS (50-80%) also have higher bodyweight or obesity[6]. Increased adiposity exacerbates insulin resistance and hyperandrogenism and worsens features of PCOS, especially metabolic dysfunction. Obesity can also directly cause anovulation via hypothalamic dysfunction independently of PCOS[7].

The World Health Organisation (WHO) estimated that in 2022, 1-in-8 people were living with obesity. Within the UK, from 2022 to 2023, 64% of adults aged 18 years and over in England were overweight or living with obesity, with 58.6% being women[8]. The Third Registry Report 2020 by The UK National Bariatric Surgery Registry found that the ratio of female:male patients undergoing bariatric surgery was 3:1 in England (77%) with 11% having a diagnosis of PCOS[9]. Obesity in women increases the time to conception[10] and the prevalence of PCOS is higher with obesity. The Society for Assisted Reproductive Technology Clinic Outcome Reporting System found that a normal body mass index (BMI) was associated with the highest probability of clinical pregnancy and live birth[11]. A study of 1,231 women from the National Health and Nutrition Examination Survey (NHANES) identified a strong association between elevated age-adjusted visceral adiposity index (AVAI) and female infertility[12].

The interplay between obesity and fertility is complex. There are several recognised mechanisms for infertility in women with obesity, including: hormonal imbalances, oligomenorrhoea/amenorrhoea, poor quality of oocytes, effects on the endometrium, increased risk of pregnancy complications, and lower success rates with Assisted Reproductive Technology (ART)[6].

1.2. RATIONALE FOR CURRENT STUDY

The BAMBINI clinical trial was the first multicentre, open-label, randomised controlled 52-week trial designed to evaluate the effectiveness of bariatric surgery compared to standard medical care in women with PCOS, obesity and oligomenorrhoea or amenorrhoea[13]. It demonstrated that bariatric surgery was superior to standard medical care in restoring spontaneous ovulation in this group of women. In addition to the significant increase in the number of ovulatory events in the surgical group, there were notable improvements in key cardiometabolic and quality-of-life outcomes. At the end of the trial, there were two pregnancies reported in the medical care group and one in the surgical group. In a nationwide prospective cohort study, women with a history of bariatric surgery had a reduced risk of gestational diabetes but an association with small-for-gestational-age infants, a shorter length of gestation and potentially an increased risk of stillbirth or neonatal death[14]. Women with PCOS are also at an increased risk of several metabolic abnormalities such as insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), obesity, dyslipidaemia, metabolic syndrome and metabolic dysfunction-associated steatotic liver disease (MASLD)[15].To date, there are no published RCTs assessing the longer-term effects of bariatric surgery in women with PCOS.

Hypothesis: The effects of bariatric surgery on reproductive and metabolic outcomes in women with PCOS are still present three to five years postoperatively.

2. STUDY OBJECTIVES

The primary objective is to perform longer-term follow-up of the effects of bariatric surgery in women with PCOS, obesity and oligomenorrhoea or amenorrhoea. The secondary objective is to ascertain the long-term effects of bariatric surgery on anthropometric, reproductive, metabolic and quality of life outcomes. The optional sub-studies will provide information on the long-term effects of bariatric surgery on adipose tissue biology and help identify Single Nucleotide Polymorphisms (SNPs) associated with PCOS.

3. STUDY DESIGN

This is a longitudinal follow-up study of the 76 participants with PCOS, obesity and oligomenorrhoea or amenorrhoea who received their randomly allocated intervention as part of the BAMBINI clinical trial. Participants who gave consent to be contacted for future studies will be contacted using for a formal email. Prior to this, the CI will check

electronic medical records and GP records to ensure there is no notification of death or significant disability which would affect their ability to participate in the study. Following the initial email, a further follow-up email will be sent within 7 days. If there is no response to this follow-up email, the CI will attempt to call the participant at the contact number provided once. If the CI is unable to contact the patient after these three attempts, no further attempts will be made.

Participants may withdraw from the study at any time, including before the scheduled visit.

3.1. STUDY OUTCOME MEASURES

Primary outcomes

- Number of reported menstrual periods in the last 12 months

Secondary outcomes

Change from baseline - for each endpoint, temporal changes, mean levels and peak levels will be analysed as appropriate:

Metabolic outcomes:

- Body weight and BMI
- Waist circumference
- Body composition
- Plasma lipid concentration
- Plasma liver function tests
- Plasma HbA1c
- Plasma fasting glucose
- Serum fasting insulin
- Fasting plasma C-peptide
- Arterial blood pressure
- High sensitivity CRP
- Serum steroid metabolomics

Reproductive and hormonal:

- Pregnancy, miscarriage, live birth rates
- Neonatal outcomes
- Use of ART
- Serum LH
- Serum FSH
- Serum Oestradiol
- Serum Progesterone
- Serum SHBG
- Serum Testosterone
- Serum free androgen index

- Serum androgen profile including androstenedione, DHEAS
- Serum AMH
- Salivary progesterone
- Salivary androgens
- A serum/plasma save will be collected for measurement of other novel markers of reproductive or metabolic function e.g. INSL3

Quality of life:

- Hospital Anxiety and Depression Scale score
- Social Functioning Questionnaire score (SF-36)
- PCOS Health-Related Quality of Life score
- Ferriman-Galwey hirsutism score
- Ludwig visual score
- Savin Alopecia Scale score
- Cardiff Acne Disability Index

Number of Medications

Sub-studies

- Adipose tissue biology (see Appendix 2)
- Peripheral blood sample for genetics

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

4.2. INCLUSION CRITERIA

- Participants from the BAMBINI clinical trial who received their randomly allocated trial intervention. As part of the initial trial, participants gave their consent to be contacted for potential participation in other research studies.
- All participants will be ≥ 18 years of age.

4.3. EXCLUSION CRITERIA

- Patients who did not receive their randomly allocated intervention as part of the original BAMBINI clinical trial.
- Any participants < 18 years of age.
- Participants who are involved in current research or have recently been involved in research prior to recruitment and have received medicinal products which would interfere with the reproductive and hormonal blood tests.

4.4. WITHDRAWAL CRITERIA

Potential participants may withdraw from the study **at any point,** including before the scheduled single visit.

Potential participants will be provided with a copy of the patient information sheet, which contains study details. They will be given at least 48 hours to read and understand it prior to the single study visit, where it will be discussed again and any questions answered. Informed consent will be obtained at the visit.

5. ADVERSE EVENTS

5.1. DEFINITIONS

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

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

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

5.2. REPORTING PROCEDURES

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

5.3.1 Non serious AEs

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

5.3.2 Serious AEs

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

All SAEs should be reported to the London-Dulwich REC where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)

Please send SAE forms to: suhaniya.samarasinghe@nhs.net
Tel: 07795180696 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

This study will consist of a single visit conducted between three and five years post-bariatric surgery, during which participants will have the opportunity to discuss the study and sign the consent form, undergo anthropometric measurements, blood tests, a urine pregnancy test, complete questionnaires, and have a subcutaneous adipose tissue biopsy. Incidental findings on blood tests will be reviewed and reported to the participant's GP with their informed consent. A score of 8 or higher on either subscale of the Hospital Anxiety and Depression Scale (HADS) or symptoms requiring potential intervention from the quality of life questionnaires will be reported to the participant's GP with their informed consent.

As this study deals with sensitive topics around fertility and childbirth, if a participant becomes distressed during the visit, the CI will handle the situation sensitively and offer to terminate the visit if the participant wishes.

The end of study is defined as the last patient's last visit.

7. STATISTICS AND DATA ANALYSIS

The total UK sample size for this research is 76 participants. As this is a recall study, there is no power calculation. All participants who received their randomly allocated intervention as part of the BAMBINI clinical trial (n=76) will be invited to take part. As this is a longitudinal observational study to assess the effects of bariatric surgery, follow-up data at various time point 3 to 5 years post-bariatric surgery will be compared with baseline data for all outcomes. Statistical analysis will be performed using STATA. Analysis of the data will only take place after the trial is completed, having written a statistical analysis plan. The baseline data will be presented as mean ± standard deviation (SD) or median IQR for continuous variables. The

primary outcome which is number of self-reported menstrual periods in the preceding 12 months prior to the study visit will be a repeated measures count outcome. Secondary continuous biomarkers will be analysed using a linear mixed-effects model.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre will obtain approval from the Wales REC 4 and the Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

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

8.3. CONFIDENTIALITY

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

Data will be pseudoanonymised.

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

This study is funded by the NIHR Imperial Biomedical Research Centre (BRC). Participants will receive £25 for the study visit. Participants travelling from outside of London will receive reimbursement of their travel costs.

8.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be coordinated through Dr Suhaniya Samarasinghe. A Trial Management Group will be established. The trial will be conducted at the NIHR Clinical Research Facility at Imperial according to their SOPs and with oversight of their QA team.

Individual researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

10. PUBLICATION POLICY

The Trial Management Group will authorise all publications and presentations relating to the study. The results are likely to be published within the 12 months following the study in peer-reviewed journals and websites and presented in medical conferences. Participant confidentiality will always be ensured, and participants will not be identified in any publication, as all data will be anonymised. A lay summary of the key results from the study will be written and sent and/or presented to them.

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Appendix 1. Summary of investigations assessments

Assessment	Visit
Number of reported menses	X
Body weight waist circumference body composition, blood pressure	X
Metabolic hormones and steroid metabolomics	X
Reproductive hormones	X
Urine pregnancy test	X
Questionnaires	X
Number of medications	X
Adipose tissue biopsy	X

Appendix 2. Sub-study

Adipose tissue biology

Studies have demonstrated that in women with PCOS, adipose tissue dysfunction contributes to the metabolic and inflammatory abnormalities[16]. The specific cellular changes within adipose tissue and their responses to different therapeutic interventions remain poorly understood. This study will help us better understand the impact of PCOS and bariatric surgery on the cellular changes in the adipose tissue. Single-nuclei RNA sequencing (snRNA-seq) enables us to analyse the highly heterogeneous nature of adipose tissue, identifying subpopulations of adipocytes, immune cells, and stromal cells that may cause pathological changes. Subcutaneous fat biopsies will be collected from participants at their visit. This procedure is expected to take approximately 15 minutes and will be performed under local anaesthesia using a biopsy punch approach, as described in the first study. The use of the local anaesthetic will minimise any potential discomfort. Once the sample is removed, two-three dissolvable sutures will be used to close the biopsy site and a surgical dressing

will be applied. Participants will be advised to keep the area dry for 48 hours (e.g., no swimming or bathing) and to change the dressing once after this 48-hour period. They can take a simple analgesic, such as paracetamol, for pain. If there are concerns regarding infection, e.g., redness, ongoing/worsening pain, or discharge, they should contact a member of the study team on the dedicated research phone (07795180696).

These samples will be analysed alongside samples collected at baseline and 12 months post-intervention during the initial trial.

Genetic testing

Single nucleotide polymorphisms (SNPs) are found in the DNA between genes and can act as biological markers of disease. Previous genome-wide association studies (GWAS) have identified 15 independent susceptibility SNPs related to PCOS[17,18] , and a subsequent study found that the three key PCOS clinical features of oligo-anovulation, hyperandrogenism and polycystic ovary morphology have different susceptibility SNPs[19]. Participants will have a peripheral blood sample taken during the visit, which will be frozen and stored for genomic DNA isolation at the end of the study to identify selected SNPs associated with PCOS. As this is a simple blood test, we do not anticipate any complications.