Evaluation of Biomarkers in Menstrual Blood Compared with Peripheral Blood

(EBMBcPB-1)

Protocol Version 1.0 13 May 2026

SPONSOR: Genie Fertility Limited
FUNDER: Genie Fertility Limited
CHIEF INVESTIGATOR: Dr Andreas Hadjimitsis

IRAS ID: 368739
REC REF: XX/XX/XXXX

Protocol authorised by:

Name & Role	**Date**	**Signature**
Andreas Hadjimitsis Chief Investigator	17/04/2026	

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agree and accepted and that the Co-Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and Genie Fertility Limited SOPs.

Trial Sponsor:

Name: Anoushka Menon **Signature:** Anoushka Menon

Position: CEO Genie Fertility Ltd **Date:** 17th April 2026

Co-Investigators:

Name: Dr Elpiniki Chronopoulou **Signature:** Elpiniki Chronopoulou

Position: Head of Clinical R&D CGRH **Date:** 17th April 2026

General Information: This protocol described the **Evaluation of Biomarkers in Menstrual Blood Compared with Peripheral Blood** study and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or an an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Co-Investigators in the study. Problems relating to the study should be referred, in the first instance, to Genie Fertility Limited.

Contact Details – Chief Investigator & Co-Investigators

Chief Investigator

Dr Andreas Hadjimitsis
Chief Technical Officer
Genie Fertility Ltd

Co-Investigators

Dr Elpiniki Chronopoulos
Consultant Gynaecologist
Centre for Reproductive & Genetic Health

Study Management Group:

Chief Investigator: Dr Andreas Hadjimitsis, Founder & CTO of Genie Fertility Limited.

Co-investigators:

1. Dr Elpiniki Chronopoulos, Consultant Gynaecologist, CRGH

Study Coordinating Centre: Genie Fertility Limited
Study Manager: Anoushka Menon

Queries:

Please direct all queries to Anoushka Menon (Study Manager) who will forward to the appropriate person where necessary.

Sponsor:

Genie Fertility Limited is the only sponsor for this study. For further information regarding the sponsorship conditions, please contact the Chief Operating Officer at:

Chief Operating Officer
Genie Fertility Limited

Study Sites:

This is a multi-centre study with participants recruited from the following sites:

1. The Centre for Reproductive & Genetic Health, United Kingdom
2. Avenues Fertility Clinic, United Kingdom
3. Hale Clinic, United Kingdom
4. Nuffield Department of Reprodcutive & Women's Heakth, United Kingdom
5. Genie Fertiltiy Ltd, United Kingdom
6. Clinica Tambre, Spain

Contents

Glossary of abbreviations	
AE	Adverse Events
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	NCI Common Terminology Criteria for Adverse Events
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
GP	General Practitioner
HCP	Health Care Professional
HE	Health Economics
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute for Clinical Excellence
nIMP	Non-Investigational Medicinal Product
PI	Principle Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QoL	Quality of Life
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. (specify substantial/non-substantial)	**Protocol Version No.**	**Date Issued**	**Summary of changes made since the previous version**

2. Synopsis

Long title	**Evaluation of Biomarkers in Menstrual Blood Compared with Peripheral Blood**
Sponsor Ref:	
Clinical phase:	
Funder ref:	
Chief Investigator:	Dr Andreas Hadjimitsis
Trial design:	Multi-cente, multi-national non-randomised, non-blinded, observational biomarker feasibility study.
Trial participants:	Females aged 18+ years old.
Planned sample size:	Up to 250 participants
Planned number of sites:	6 sites initially, with others joining if required.
Inclusion criteria	• Aged 18 years or older. • Currently menstruating. • Willing to provide a menstrual blood sample. • Willing to provide a vaginal swab • Willing to undergo peripheral blood sampling. • Able to freely provide informed consent.
Exclusion criteria	• Currently pregnant. • Active vaginal infection at time of sampling. • Known allergy to menstrual cup materials. • Any medical condition preventing safe participation. • Inability to provide freely informed consent.
Trial duration	36 months
Planned trial period:	1st May 2026 – 30th April 2029
Primary objective:	To determine whether biomarkers detectable in peripheral blood are also detectable in menstrual blood.
Secondary objectives:	• Assess feasibility of menstrual blood sample collection in clinical settings. • Optimise laboratory processing methods for menstrual blood samples. • Compare biomarker concentrations between menstrual blood and peripheral blood. • Evaluate feasibility of extracting DNA from both biological sample types. • Assess feasibility of isolating viable cellular material for research purposes.
Primary outcomes:	Detection and quantification of biomarkers in menstrual blood compared with matched peripheral blood samples.
Secondary outcomes:	• Proportion of samples suitable for analysis.

	• Biomarker variability between sample types. • Success of DNA extraction from both biological samples. • Feasibility of isolating viable cellular material for downstream research.
Products:	Menstrual Cup
Manufacturer:	MoonCup

3. Study Summary & Schema

This is a multi-centre, non-randomised, non-blinded, observational feasibility study involving the collection of paired biological samples from participants.
Eligible participants will be identified at participating sites and provided with study information. Following a minimum consideration period, participants who consent to take part will be enrolled into the study.

The study consists of the following key stages:

1. **Screening and Contact**
   Potential participants will be identified and provided with a Participant Information Sheet. Eligibility will be confirmed, and participants will have the opportunity to ask questions prior to consent.
2. **Visit 1 – Enrolment and Preparation**
   Written informed consent will be obtained. Participants will be provided with a menstrual cup and instructions for sample collection.
3. **Visit 2 – Sample Collection**
   Participants will attend during their menstrual period and provide:
   - A menstrual blood sample (collected using a menstrual cup)
   - A peripheral venous blood sample
   - A vaginal swab
4. **Laboratory Processing and Analysis**
   Samples will be transported to the central laboratory for processing, including separation of components, biomarker analysis, DNA extraction, and cellular isolation.
5. **Follow-Up Data Collection**
   Relevant clinical or fertility-related information may be collected from sites where available.

Participants will not receive individual results, as analyses are conducted for research purposes only.

3.2 Participant Flow Diagram

Activity	Screening	Contact 1*	Visit 1	Visit 2	Follow-Up
Identification of potential participants	X				

Study details provided to potential participant		X			
Eligibility confirmed			X		
Informed consent			X		
Menstrual cup provided			X		
Menstrual blood sample collection				X	
Peripheral blood sample collection				X	
Clinic provide Fertility Health Records					X

*Contact 1 – maybe undertaken at clinic or via the central study team (London) via telephone and email correspondence of PIS.

It is anticipated that participants will be in the study for 12 months.

4. Background

Menstrual blood is a biologically complex fluid comprising peripheral blood, immune cells, endometrial tissue, and a range of extracellular molecular components. Despite this complexity and potential biological value, it remains significantly under-utilised as a sample type in clinical and translational research.

Peripheral venous blood sampling is currently the most widely used and established approach for biomarker detection in clinical studies. However, it primarily reflects systemic physiology and may not fully capture localised biological processes within the reproductive system.

Menstrual blood represents a unique, non-invasive biological sample that may provide both systemic and endometrial-specific information relevant to reproductive health and fertility. Its accessibility and potential for repeated sampling also present advantages for research and future clinical applications.

This study seeks to evaluate whether menstrual blood, collected using menstrual cups in a controlled clinical setting, can serve as a reliable and practical source of biological material for biomarker analysis. This includes assessment of its suitability

for molecular analyses such as DNA extraction, as well as cellular isolation, in comparison with matched peripheral blood samples.

4.1 Rationale

Menstrual blood is a complex and biologically rich sample comprising peripheral blood, endometrial tissue, immune cells, and extracellular molecular components. Despite this, it remains significantly under-utilised in clinical and translational research compared with peripheral venous blood, which is the current standard for biomarker analysis.

There is increasing scientific and clinical interest in identifying less invasive, more accessible sampling methods that may improve participant acceptability, enable more frequent sampling, and expand research participation, particularly in women's health and reproductive medicine. Menstrual blood represents a unique, non-invasive biospecimen that may provide both systemic and local (endometrial) biological insights that are not captured through peripheral blood alone.

However, there is currently limited robust evidence demonstrating whether biomarkers detectable in peripheral blood can be reliably identified, quantified, and interpreted in menstrual blood. In addition, there is a lack of standardised methodologies for the collection, processing, and analysis of menstrual blood samples within a clinical research framework.

This study is therefore designed as an exploratory, observational feasibility study to address these gaps. By collecting paired menstrual and peripheral blood samples from the same participants, the study will directly assess concordance of biomarker detection between sample types, evaluate variability, and determine the suitability of menstrual blood for downstream molecular and cellular analyses, including DNA extraction and cell isolation.

The study also aims to establish the practical and operational feasibility of menstrual blood collection using menstrual cups within a clinical setting, including participant acceptability, sample integrity, and integration into laboratory workflows.

The hypothesis underpinning this research is that menstrual blood can serve as a reliable and informative biological sample for biomarker detection, with comparable or complementary utility to peripheral blood. If demonstrated, this could support the development of less invasive diagnostic and monitoring approaches in women's health, fertility, and broader precision medicine applications.

Importantly, this study is not designed to provide clinical diagnoses or direct benefit to participants but to generate foundational data to inform future research, assay development, and potential diagnostic pathways.

5. Study Objectives/Endpoints and Outcome Measures

5.1 Primary Objective

To determine whether biomarkers detectable in peripheral blood are also detectable in menstrual blood.

5.2 Primary Outcome Measures

The primary outcome measure is the successful detection and comparison of selected biological markers in menstrual blood and matched peripheral blood samples collected from the same participant.

5.3 Secondary Objectives

- Assess feasibility of menstrual blood sample collection in clinical settings.
- Optimise laboratory processing methods for menstrual blood samples.
- Compare biomarker concentrations between menstrual blood and peripheral blood.
- Evaluate feasibility of extracting DNA from both biological sample types.
- Assess feasibility of isolating viable cellular material for research purposes.

5.4 Secondary Outcome Measures

The proportion of menstrual blood and peripheral blood samples that are of sufficient quality for planned laboratory analysis.
The feasibility and reliability of processing menstrual blood samples within the laboratory workflow.
The success of extracting DNA from menstrual blood and matched peripheral blood samples.
The feasibility of isolating viable cellular material for downstream research use.
The practical acceptability of the study sampling procedures within the clinical research setting.

6. Study Design and Setting

This is a multi-centre, international, observational biomarker feasibility sample collection stud of paired biological samples.

Initial sites will be:

1. The Centre for Reproductive & Genetic Health, United Kingdom
2. Avenues Fertility Clinic, United Kingdom
3. Hale Clinic, United Kingdom
4. Nuffield Department of Reprodcutive & Women's Heakth, United Kingdom
5. Genie Fertiltiy Ltd, United Kingdom
6. Clinica Tambre, Spain

Sites will recruit participants and collect samples. Sites will not undertake any part of the analysis of the samples. Sites will receive training in sample collection as part of their Site Initiation Visit.

Laboratory analysis will be conducted at the Genie Fertility laboratory in London.

Material Transfer Agreements and Data Sharing Agreements will be in place with all sites.

Additional sites may be added subject to internal and regulatory approvals.

6.1 Risk Assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the Medical Research Council/Department of Health/Medicine and Healthcare products Regulatory Agency (MRC/DH/MHRA) Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This study has been categorised as a TYPE A, where the level of risk is no higher risk than standard care. A copy of the trial risk assessment may be requested from the Study Manager. The study risk assessment is used to determine the intensity and focus of monitoring activity.

This study is to be conducted in compliance with the protocol, the EU Clinical Trial Regulation 536/2014 and Good Clinical Practice (GCP).

6.3 Study Lay Summary

This study aims to find out whether menstrual blood can provide similar useful biological information to a standard blood sample taken from a vein in the arm.

Menstrual and reproductive health have historically been under-represented in research, and menstrual blood remains an under-studied biological sample despite its potential value for understanding women's health.

Women aged 18 years and over who are currently menstruating may be invited to take part. Participants will attend a study visit during their menstrual period, where they will provide a menstrual blood sample collected using a menstrual cup and a small blood sample from a vein in the arm.

The samples will be sent to a research laboratory and analysed to compare the biological information they contain.

Some samples may also be processed to extract DNA and isolate cells for research purposes.
The study is low risk and is not expected to provide a direct medical benefit to participants. However, it may help improve understanding of whether menstrual blood could be used more widely in future women's health and fertility research.
Participants will not receive individual results, as the tests are for research purposes only and are not designed to provide clinical information about their health.

7. Site Investigator Selection

This study will be delivered initially at three participating international sites. All sites who are interested in participating in the study will be assessed by Genie Fertility Ltd to confirm that they have adequate resources and experience to conduct the study.

Before any Site can begin recruitment, a Principal Investigator at each site must be identified.

- Confirmation of Capacity and Capability of being able to recruit and deliver the study
- A signed Study Agreement
- A current signed and dated Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles & Responsibilities document
- A copy of the Source Data Agreement signed by the PI

Additionally, sites will be required to attend a Site Initiation Visit (online) where the study processes, and procedures are explicitly covered by the Chief Investigator. A log of this attendance will be kept. The recording of the Site Initiation Visit will be made to ensure any new staff delegated to the study can be trained immediately.

Upon receipt of all the above documents, the Study Manager will send written confirmation to the Principal Investigator detailing that the centre is now ready to recruit participants into the study.

This correspondence must be filed in each site's Site File. Along with the written confirmation, the site should receive their study supplies and a study pack holding all the documents required to recruit into the study.

Occasionally during the trial, amendments may be made to the trial documentation listed above. Genie Fertility Limited will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of site to inform Genie Fertility Limited that the documents have been locally approved and the date of implementation.

8. Participant Selection

Participants are eligible for the study if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Study Manager before registration. Sites are encouraged to recruit a broad range of participants, including with respect to ethnic diversity, socio-economic status, digital/health literacy and age.

8.1 Inclusion criteria

- Aged 18 years or older.
- Currently menstruating.
- Willing to provide a menstrual blood sample.
- Willing to undergo peripheral blood sampling.
- Willing to give a vaginal swab
- Able to freely provide informed consent.

8.2 Exclusion criteria

- Currently pregnant.
- Active vaginal infection at time of sampling.
- Known allergy to menstrual cup materials.
- Any medical condition that prevents safe participation.
- Inability to provide freely informed consent.

9. Recruitment

9.1 Participant identification

Prospective participants will ask clinic staff about further details of the study if they are interested in taking part. Participant Information Sheets will be provided with all the details of the study.

9.3 Informed consent

Written informed consent will be obtained from all participants. Participants will be given at least 24 hours to consider their participation.

9.3.1 Impaired capacity to consent

No person what cannot consent for themselves will be included in the study. If a person loses capacity to consent then they will be removed from the study. Any samples and/or data already provided will be retained and used as per the consent form.

9.4 Registration

Participants will be registered into the study at sites during Visit 1.

9.5 Reimbursement

Genie Fertility Limited will make a thank-you gesture to participants who provide menstrual and/or peripheral blood samples to the study for £150 in the form of a voucher or a bank transfer.

10. Study Procedures

10.2 Contact 1

Study posters and flyers will be displayed at sites. Sites will provide a summary or full Participant Information Sheet to their patients who are interested in the study.

Potential participants then have an opportunity to review the information, chat with their site clinician and/or with the central study team. Potential participants should be given at least 24 hours to decide whether they would like to participate in the study.

10.3 Visit 1

If potential participants wish to participate, they will be checked for eligibility and if suitable, freely obtained informed consent will be obtained during this visit. A menstrual cup will be provided and participants will be instructed on how to use the cup in order to provide a sample at the next visit.

10.4 Visit 2

At this visit, participants will provide a menstrual and peripheral blood sample as well as vaginal swab.

11. Sample Management

Four biological samples will be collected from each participant: peripheral venous blood, menstrual blood collected via menstrual cup, vaginal swab and if part of standard care a uterine tissue biopsy

Samples will be labelled using a unique study identifier and processed according to Genie Fertility Limited laboratory procedures for this study.

11.1 Transport

Samples will be transported to the Genie Fertility laboratory in accordance with UN3373 Category B biological substance transport regulations.

11.2 Laboratory Processing

Upon receipt at the laboratory, samples will be logged in the laboratory tracking system and assigned unique laboratory identifiers.

- Peripheral blood samples will undergo centrifugation to obtain plasma, serum and cellular fractions.
- Menstrual blood samples will be processed to isolate fluid and cellular components.
- Samples may undergo centrifugation, aliquoting, DNA extraction, molecular biomarker analysis, cellular isolation and short-term cell culture.

Cellular material may be cultured for biomarker discovery and laboratory method development. All procedures will be conducted in accordance with Genie Fertility Limited laboratory SOPs.

11.3 Sample Storage and Governance

Samples may be analysed immediately or stored for later analysis.

Where samples are stored, storage will occur under the approval of the Research Ethics Committee for this study and therefore falls within the Human Tissue Authority research exemption.

Samples will be stored securely using coded identifiers. Derived biological materials, including DNA and cultured cells, may be retained for the duration of the study.
At the end of the study, remaining samples or derived materials will be destroyed, transferred to another REC-approved research study, or transferred to a facility operating under an HTA research licence, subject to appropriate approvals.

12. Withdrawal & Loss to Follow-Up

12.1 Withdrawal

Any participant in whom a change in clinical condition renders them ineligible according to the inclusion criteria will be withdrawn from the study. Participants may withdraw their consent at any time from the study in which case identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant. Withdrawal will also occur if the participant demonstrates non-compliance with study procedures.
If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. For the purposes of this trial, these are:

1. Withdrawal of use of participant contact data (personal identifying data collected for the purposes of contacting participants)
2. Withdrawal from having samples taken
3. Withdrawal of samples for analysis
4. Withdrawal from all aspects of the study (participant fully withdrawn)

The withdrawal of participant consent shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal. Participants will be informed of this before they join the study as outlined in the PIS. All data collected prior to participant withdrawal will be kept with the other study data and archived after the study analysis.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is guidance on this contained in the PIS but briefly: “Please note there might be situations where we cannot fulfil your request immediately (to withdraw), for example if we need to contact you directly about your safety. We will need to keep all safety reports”.
In the event of a withdrawal from all aspects of the trial, any unprocessed samples at site or at the laboratory must be disposed.

The withdrawal CRF should be completed on the participant’s behalf by the researcher/ clinician based on information provided by the participant. This withdrawal CRF should be retained in the ISF with notification made to the Study Manager.

Any queries relating to potential withdrawal of a participant should be forwarded to the Study Manager via email or telephone.

13. Pharmacovigilance

The study involves minimal risk.

- Peripheral blood sampling may cause temporary discomfort, bruising, and rarely infection.
- Menstrual cup use may cause mild discomfort during insertion or removal.
- Use of a vaginal swab may cause mild discomfort.
- Serious complications are rare.

Any serious adverse events related to study procedures will be reported according to HRA safety reporting guidance for non-CTIMP research.

13.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant.
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing

	hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reaction (SAR)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

*The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE 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

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.

13.2 Study Specific SAE Reporting requirements

All adverse events will be reported if arising during study procedures, but as this is a non-interventional study, any other adverse events (AE or SAE), not linked to study procedures will not otherwise be recorded. This is applicable to all participants (including healthy volunteers). 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.

13.3 Causality

Even though this trial is non-interventional, the study team will monitor for any AEs in relation to the menstrual cups used and the peripheral blood draw processes.
The PI (or another delegated medically qualified doctor from the study team as detailed in this protocol) and Clinical co-Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship according to the following categories:

Relationship	Description	Reasonable possibility that the SAE may have been cause by the menstrual cup?
Unrelated	There is no evidence of any causal relationship with the study/materials used.	No
Unlikely	There is little evidence to suggest there is a causal relationship with the study/materials/processes (e.g. the event did not occur within a reasonable time after use of the menstrual cup). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment/lotion/pessary).	No
Possible	There is some evidence to suggest a causal relationship with the study/materials/proccesses (e.g. because the event occurs within a reasonable time after placement of the menstrual cup). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatment/lotion/pessary).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the clinical co-Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

13.4 Expectedness

The clinical Co-Investigator (or another delegated appropriately qualified individual) will assess each AE to perform the assessment of expectedness.
The expectedness assessment should be made with reference to the current Safety Information for the menstrual cup. Expectedness decisions must be based purely on whether the event is listed in the safety information, other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease or condition. AEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) AEs should not be considered expected (unless explicitly

stated in the Safety Information and approved by the General Product Safety Regulation (GPSR). For example, an event more specific or more severe than that described in the Safety Information is considered unexpected.

13.5 Reporting procedures

13.5.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that they have performed the seriousness and causality assessments. Investigators should also report SAEs in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the Study Manager at Genie Fertility Limited within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.
The participant will be identified only by study ID, month, and year of birth and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, Sponsor may request additional information relating to any SAEs/ SARs and the site should provide as much information as is available to them in order to resolve these queries.
Serious Adverse Event (SAE) email address.

SAEs should be reported from time of consent, and up to, and including 7 calendar days after the participant attends Visit 1 where the participant provided a peripheral and/or menstrual blood sample.

SAEs should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
An SAE form should contain at least the minimum information:

• Full participant trial number
• An Adverse Event descriptor.
• Whether the study menstrual cup has been used and any other information relevant to the visit, such as if the participant was feeling well/unwell in general. This will be led by the PI/delegated site team member's experience of the participant.
• A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted, and the information must be provided by the site to Genie Fertility Limited within 24 hours.
Except allergic reactions, no other AEs should be reported on the CRF.

Contact details for reporting SAEs
EMAIL HERE

Chief Investigator
Dr Andreas Hadjimitsis

Please send SAE forms to Study Manager:
NAME: Dr Anoushka Menon

(Mon to Fri 09:00 – 17:00)

- **unexpected** (ie not listed in the protocol as an expected occurrence)

Genie Fertility Limited will complete the Non-CTIMP safety report to REC form and ensuring it is received within the 15 day window of the CI becoming aware of the event.

13.7 Safety Reports

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/safety-and-progress-reports-other-research-procedural-table/

14. Statistical considerations

This study is designed as an exploratory, observational feasibility study and is not powered to detect statistically significant differences between groups. The primary purpose of the statistical analysis is to generate descriptive and preliminary comparative data to inform future studies, including potential diagnostic development and validation studies.

14.1 Sample Size

A target sample size of up to 250 participants has been selected pragmatically to ensure sufficient paired menstrual and peripheral blood samples are available to:

- Evaluate the feasibility of sample collection, processing, and analysis
- Estimate variability in biomarker detection across sample types
- Enable preliminary assessment of concordance between menstrual and peripheral blood biomarkers

No formal power calculation has been performed, as the study is not designed for hypothesis testing but to generate data for future powered studies.

14.2 Statistical Analysis Plan

All analyses will be conducted using appropriate statistical software (e.g. R, Python, or equivalent validated platforms).

Descriptive Analysis

Descriptive statistics will be used to summarise participant characteristics and study outcomes:

- Continuous variables: mean, standard deviation, median, interquartile range
- Categorical variables: counts and percentages

Primary Analysis

The primary analysis will assess the detection and quantification of biomarkers in paired menstrual and peripheral blood samples:

- Proportion of samples in which each biomarker is detectable in each sample type
- Agreement between sample types (e.g. concordance rates)
- Correlation analysis (e.g. Pearson or Spearman correlation coefficients, depending on data distribution)

Where appropriate, exploratory comparisons of biomarker concentrations between sample types may be undertaken using paired statistical tests (e.g. paired t-test or Wilcoxon signed-rank test). These analyses will be interpreted cautiously given the exploratory nature of the study.

Secondary Analysis
Secondary analyses will focus on feasibility and laboratory performance metrics, including:

- Proportion of samples meeting predefined quality criteria for analysis
- Success rates for DNA extraction and cellular isolation
- Variability in biomarker measurements across sample types
- Assessment of operational feasibility (e.g. sample integrity, processing success rates)

Subgroup analyses may be performed where sufficient data are available (e.g. age groups, clinical characteristics), but these will be considered exploratory.

14.3 Missing, Unused and Spurious Data

Missing or incomplete data are expected in a feasibility study of this nature. The extent and reasons for missing data will be described. No formal imputation of missing data is planned.

Analyses will be conducted on available data only. The impact of missing data on interpretation of results will be considered and discussed.

Samples deemed unsuitable for analysis (e.g. due to degradation, insufficient volume, or processing failure) will be recorded and reported as part of feasibility outcomes rather than excluded without documentation.

14.4 Interim Analysis

No formal interim analysis is planned. Ongoing internal review of feasibility metrics (e.g. recruitment rates, sample adequacy) may be conducted by the study team to inform operational decisions.

14.5 Inclusion in Analysis

All participants who provide at least one biological sample will be included in the analysis set.
Primary analyses will focus on participants with paired menstrual and peripheral blood samples. Participants with only one sample type will be included in descriptive and feasibility analyses where appropriate.
No formal per-protocol or intention-to-treat populations are defined, as this is a non-interventional feasibility study.

14.6 Statistical Significance

Given the exploratory nature of the study, emphasis will be placed on estimation (e.g. effect sizes, confidence intervals) rather than formal hypothesis testing. Any p-values reported will be interpreted descriptively and not used to draw definitive conclusions.

15. Analysis

This study is exploratory in nature and is designed to generate preliminary data on the feasibility and utility of menstrual blood as a biological sample for biomarker analysis. As such, analyses will focus on descriptive, comparative, and feasibility-based outcomes rather than confirmatory hypothesis testing.

15.1 Main analysis

The main analysis will be conducted on paired menstrual and peripheral blood samples and the vaginal swab collected from the same participant.

Biomarker Detection and Comparison

- The proportion of samples in which each biomarker is detectable in menstrual blood and peripheral blood will be reported.
- Agreement between sample types will be assessed using concordance measures (e.g. percentage agreement and, where appropriate, kappa statistics).

- Correlation between biomarker concentrations in paired samples will be assessed using appropriate methods (e.g. Pearson or Spearman correlation depending on data distribution).
- Where appropriate, paired comparisons of biomarker concentrations will be explored using parametric or non-parametric tests.

Feasibility Outcomes

- Proportion of samples successfully collected, processed, and analysed
- Sample adequacy rates (e.g. sufficient volume, quality thresholds met)
- Success rates for DNA extraction and cellular isolation
- Laboratory processing success rates and failure modes

These outcomes will be used to assess the operational viability of menstrual blood sampling within a clinical research setting.

Acceptability and Practicality

Where data are available, descriptive analysis of participant compliance and acceptability of menstrual blood collection (e.g. successful use of menstrual cups, completion of sampling procedures) will be undertaken.
All results will be presented with appropriate summary statistics and, where relevant, confidence intervals to support interpretation.

15.1.1 Sub-group & interim analysis

Exploratory subgroup analyses may be undertaken where sufficient data are available. These may include:

- Age categories
- Fertility status or clinical characteristics
- Study site

Subgroup analyses will be considered hypothesis-generating only and interpreted cautiously.
No formal interim analyses are planned. Any internal review of accumulating data will be limited to feasibility and operational metrics.

15.2 Cost effectiveness analysis

A formal cost-effectiveness analysis is not planned as part of this study.
However, high-level exploratory observations may be made regarding:

- Resource requirements for menstrual blood versus peripheral blood collection
- Laboratory processing complexity and scalability

These observations may inform the design of future studies where economic evaluation is appropriate.

15.3 Qualitative Study and Process Evaluation

No formal qualitative study is planned.
However, process evaluation will be undertaken through:

- Monitoring recruitment and retention rates
- Assessing adherence to study procedures
- Identifying operational challenges in sample collection, transport, and laboratory processing

Any informal feedback from study sites or participants relating to the acceptability and practicality of menstrual blood collection may be captured and summarised descriptively.
Findings from this process evaluation will be used to refine study design, sampling procedures, and laboratory workflows for future research and potential clinical application.

16. Data Management

All study data will be collected, handled, stored, and processed in accordance with applicable data protection legislation, including the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018, as well as Good Clinical Practice (GCP) principles.
Data management processes will ensure data integrity, confidentiality, and availability throughout the study lifecycle.

16.1 Data collection

Data will be collected at participating sites and by the central study team using study-specific Case Report Forms (CRFs), which may be electronic or paper-based.
Data collected will include:

- Participant demographic and eligibility information
- Study visit data and sample collection details
- Laboratory sample tracking and processing data
- Feasibility and outcome measures

Where possible, data will be entered directly into a secure electronic data capture system. If paper CRFs are used, data will be transcribed into the electronic system in a timely manner.
Each participant will be assigned a unique study identifier. No directly identifiable personal data (e.g. name, full date of birth, address) will be entered into the main study database.

16.2 Completion of CRFs

CRFs will be completed by authorised study personnel who have been appropriately trained and delegated by the Principal Investigator.

All data entries must be:

- Accurate, complete, and contemporaneous
- Attributable to the individual entering the data
- Legible and traceable

For paper CRFs:

- Corrections will be made by a single line through the incorrect entry, with the correct data entered, dated, and initialled
- No data will be erased or obscured

For electronic CRFs:

- An audit trail will be maintained to capture all data entries, changes, and deletions, including user identification, date, and time

16.3 Data Storage and Security

All study data will be stored securely with appropriate technical and organisational safeguards, including:

- Password-protected systems with role-based access controls
- Encryption of data where appropriate
- Secure servers located within compliant jurisdictions

Access to study data will be restricted to authorised personnel only.
Personal identifiable data required for participant contact or study administration will be stored separately from research data and linked only via the unique study identifier.
Data transfers between sites and the central study team will be conducted using secure, approved methods.

16.4 Data Quality and Validation

Data quality will be ensured through:

- Training of study personnel in data collection procedures
- Use of standardised CRFs and data definitions
- Routine data review and validation checks
- Query management processes to resolve discrepancies

The Sponsor or delegated representatives may perform data monitoring activities to verify the accuracy and completeness of data against source documents.

16.5 Confidentiality

Participant confidentiality will be maintained at all times.

All study data will be pseudonymised using unique study identifiers. Any linkage between identifiers and personal data will be securely maintained at site level or by the central study team with restricted access.
No identifiable participant data will be disclosed outside the study team unless required by law or regulatory authorities.

16.6 Data Retention and Archiving

Study data will be retained and archived in accordance with applicable regulatory requirements and Sponsor policies.
Essential documents, including study data and Trial Master File (TMF), will be retained for a minimum period in line with UK regulatory expectations for non-CTIMP research.
At the end of the retention period, data will be securely destroyed or anonymised, unless further retention is justified for ongoing research use and appropriately approved.

16.7 Data Sharing and Future Use

De-identified data and derived biological data (e.g. genomic or biomarker data) may be used for future research, subject to:

- Appropriate ethical approvals
- Participant consent
- Data sharing agreements where applicable

Any future use of data will comply with relevant legal, ethical, and regulatory requirements.

17. Protocol/GCP Non-Compliance

The Principal Investigator (PI) is responsible for reporting any non-compliance with the trial protocol, Good Clinical Practice (GCP), or applicable regulatory requirements to the Sponsor (Genie Fertility Limited) in writing as soon as they become aware of it.

The Sponsor will assess the nature, severity, and potential impact of any reported non-compliance in accordance with Sponsor standard operating procedures (SOPs).

A trial-related deviation is defined as any departure from the ethically approved protocol, study procedures, GCP, or applicable regulatory requirements (e.g. deviations in the consent process or sample collection procedures). All deviations will be documented using a non-compliance form and retained within the Trial Master File (TMF) and, where appropriate, the Investigator Site File (ISF).

A serious breach is defined as a breach of GCP or the protocol which is likely to:

- Significantly affect the safety or physical or mental integrity of participants; or
- Significantly affect the scientific value or integrity of the study

Genie Fertility Limited maintains SOPs for the identification, assessment, and management of non-compliance, including escalation to potential serious breaches. Where a serious breach is identified, this will be reported to the relevant Research Ethics Committee (REC) and regulatory authorities in accordance with Health Research Authority (HRA) guidance and required timelines.

Appropriate corrective and preventive actions (CAPA) will be implemented where necessary. Persistent or significant non-compliance may result in additional monitoring, retraining, or suspension of site activities.

18. End of Trial Definition

The end of the trial is defined as the date of final data capture for the last participant (i.e. the point at which all required study data have been collected and entered into the study database).

Database lock will occur following completion of data cleaning, validation, and resolution of all outstanding data queries. This is expected to take place within six months of the end of the trial.

The Sponsor will notify the Research Ethics Committee (REC) that provided favourable opinion of the end of the study using the appropriate End of Study Declaration Form, in accordance with Health Research Authority (HRA) guidance. This notification will be made within 90 days of the end of the study, or within 15 days if the study is terminated early.

19. Archiving

At the end of the study, all essential documents and study records will be archived in accordance with Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research, and Sponsor standard operating procedures.
Essential documents will include, but are not limited to:

- Trial Master File (TMF)
- Investigator Site Files (ISF)
- Completed Case Report Forms (CRFs)
- Source data and supporting documentation
- Study correspondence and approvals
- Data management and statistical analysis records

All archived materials will be stored securely in a manner that preserves their integrity, confidentiality, and accessibility for audit or inspection by regulatory authorities.
The Sponsor (Genie Fertility Limited) will be responsible for the archiving of the Trial Master File, while participating sites will be responsible for archiving their respective Investigator Site Files and source documentation, unless otherwise agreed in writing.

Study data will be archived in a pseudonymised format. Any linkage between participant identifiers and personal data will be stored separately with restricted access.
Records will be retained for a minimum period in line with UK regulatory and Sponsor requirements for non-CTIMP research. This is typically at least 5–10 years after the end of the study, or longer where required for scientific, regulatory, or commercial purposes.
Electronic data will be archived in validated, secure systems with appropriate backup and disaster recovery provisions. Paper records will be stored in secure, access-controlled facilities.
At the end of the retention period, records will be securely destroyed or anonymised, unless continued retention is justified (e.g. for ongoing research, regulatory requirements, or intellectual property considerations) and appropriately authorised.
Access to archived materials will be restricted to authorised personnel. Retrieval of archived records will be possible within a reasonable timeframe to support regulatory inspection, audit, or legitimate scientific review.

20. Regulatory Considerations

20.1 Ethical and governance approval

This study will be conducted in accordance with the principles of Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research, and all applicable regulatory requirements.
Favourable ethical opinion will be obtained from an appropriate Research Ethics Committee (REC) via the Health Research Authority (HRA) prior to the commencement of the study.

In addition to REC approval, all participating UK sites will obtain confirmation of Capacity and Capability (or equivalent local governance approval where applicable) before initiating recruitment. For sites outside the UK, appropriate local ethical and regulatory approvals will be obtained in accordance with national requirements.
The study will not commence at any site until all required approvals and permissions are in place.
Any substantial amendments to the protocol or study documentation will be submitted for review and approval to the REC and/or HRA, as required, prior to implementation. Non-substantial amendments will be managed in accordance with HRA guidance.
The end of the study will be declared to the REC in accordance with HRA requirements.

20.2 Data Protection

All personal data will be processed in accordance with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018.

Participants will be assigned a unique study identifier. Personal identifiers (e.g. name, contact details) will be stored separately from research data and linked only via this identifier (pseudonymisation).

Data will be stored in secure electronic databases with restricted, role-based access controls. Appropriate technical and organisational measures will be in place to protect data against unauthorised access, loss, or misuse.

The lawful basis for processing personal data is that the study is conducted in the public interest for scientific research purposes. Where applicable, processing of special category data (including health and genetic data) is justified under the scientific research condition with appropriate safeguards in place.

Access to identifiable data will be limited to authorised members of the study team for the purposes of study conduct and participant management. De-identified data may be shared with collaborators or third parties where necessary for analysis, subject to appropriate data sharing agreements and ethical approvals.

Genetic material obtained from samples will be analysed solely for research purposes and will not be used for clinical genetic testing or to identify individual participants.

All data will be retained and archived in accordance with regulatory requirements and Sponsor policies. At the end of the retention period, data will be securely destroyed or anonymised unless further retention is justified and appropriately approved.

20.3 Indemnity

The Sponsor, Genie Fertility Limited, holds appropriate insurance to cover liabilities arising from the conduct of this study.
Insurance is provided through a Commercial Combined Insurance policy arranged with Nucleus Underwriting Limited. The policy includes the following relevant cover:

- **Clinical Trial Liability**: £5,000,000 in the aggregate
- **Public Liability**: £5,000,000 any one occurrence
- **Products Liability and Professional Indemnity**: £5,000,000 combined single limit in the aggregate
- **Employers' Liability**: £10,000,000 any one occurrence

The Clinical Trial Liability cover provides indemnity for non-negligent harm suffered by participants as a result of participation in the study.
The Sponsor accepts responsibility for the design, management, and conduct of the study and maintains insurance arrangements to cover both negligent and non-negligent harm arising from study participation.
Participating sites remain responsible for ensuring that their staff are appropriately indemnified for clinical procedures performed as part of routine care (e.g. venepuncture), in accordance with local policies and arrangements.
The insurance policy includes an indemnity to principals clause.

20.4 Trial Sponsorship

Genie Fertility Limited will act as the Sponsor for this study and will take overall responsibility for the initiation, management, and financing of the research.
The Sponsor will ensure that the study is designed, conducted, and reported in accordance with Good Clinical Practice (GCP), applicable regulatory requirements, and the approved protocol.

Certain study-related activities will be delegated to participating sites (private clinics), including participant recruitment, informed consent, and sample collection. These responsibilities will be clearly defined in study agreements and site delegation logs. Notwithstanding any delegation, the Sponsor retains overall responsibility for the conduct of the study, including:

- Regulatory and ethical compliance
- Oversight of study conduct across all sites
- Data management and analysis
- Safety reporting and governance

All delegated responsibilities will be performed by appropriately qualified personnel and in accordance with the protocol and Sponsor procedures.

20.5 Funding

This study is funded by Genie Fertility Limited.

Investigators and site staff will not receive any financial incentives linked to participant recruitment or study outcomes, and will be reimbursed only for reasonable study-related activities in line with their normal terms of engagement and site agreements.

Participants will receive a reimbursement of £150 in recognition of their time, inconvenience, and any expenses incurred as a result of participation. This amount has been considered to be proportionate and not unduly influential.

Any study visits required outside of routine clinical care, or attendance by participants who would not otherwise be present at the site (e.g. healthy volunteers or staff participants), will be reimbursed in line with study arrangements.

All financial arrangements have been structured to ensure that they do not influence the conduct of the study or the decision of individuals to participate.

21. Study Management

The study will be managed in accordance with Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research, and Sponsor standard operating procedures.

Oversight will be proportionate to the low-risk, non-interventional nature of the study.

21.1 Trial Management Group (TMG)

The Trial Management Group (TMG) will be responsible for the day-to-day management and operational delivery of the study.
The TMG will include:

- Chief Investigator (CI)
- Study Manager
- Sponsor representative(s)
- Co-Investigator(s)
- Laboratory lead and/or technical representatives (as required)

Responsibilities of the TMG will include:

- Oversight of study conduct across all sites
- Ensuring compliance with the protocol, GCP, and regulatory requirements
- Monitoring recruitment, retention, and study progress
- Oversight of data quality, sample management, and laboratory processes
- Reviewing safety information and ensuring appropriate reporting
- Managing protocol deviations and non-compliance
- Coordinating communication between sites and the Sponsor

The TMG will meet at regular intervals (e.g. monthly or as required) and maintain appropriate records of discussions and decisions.

21.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) may be established to provide independent oversight of the study, where appropriate.
The TSC, if convened, will include individuals independent of the study team with relevant clinical, scientific, and/or methodological expertise.
Responsibilities of the TSC may include:

- Providing independent advice on study conduct and progress
- Reviewing key study milestones and outputs
- Advising on any significant protocol amendments
- Supporting the overall integrity and credibility of the study

Given the exploratory and low-risk nature of this study, a formal TSC may not be required. Oversight functions may instead be fulfilled by the Sponsor and TMG, with external expert input sought as needed.

21.3 Independent Data Monitoring Committee (DMC)

An Independent Data Monitoring Committee (DMC) will not be established for this study.

This is justified on the basis that:

- The study is non-interventional
- The risk to participants is low and comparable to standard clinical procedures
- There are no investigational medicinal products or high-risk interventions

Safety oversight will be conducted by the Chief Investigator and the TMG, with adverse events reviewed and reported in accordance with protocol-defined procedures and Health Research Authority (HRA) guidance.

22. Quality Control & Assurance

This study will be conducted in accordance with the approved protocol, Good Clinical Practice (GCP), the UK Policy Framework for Health and Social Care Research and Sponsor standard operating procedures.

Quality assurance activities will be proportionate to the low-risk, non-interventional nature of the study and will focus on ensuring data integrity, participant safety, and compliance with regulatory and ethical requirements.

22.1 Monitoring

Monitoring of the study will be undertaken by the Sponsor (Genie Fertility Limited) or delegated representatives.
A risk-based monitoring approach will be applied, taking into account:

- The low-risk (Type A) classification of the study
- The non-interventional design
- The nature of study procedures (e.g. sample collection and handling)

Monitoring activities may include:

- Review of site readiness prior to recruitment (e.g. Site Initiation Visit)
- Verification that informed consent procedures are appropriately conducted and documented
- Review of CRFs and source data for accuracy, completeness, and consistency
- Oversight of sample collection, labelling, transport, and processing procedures
- Verification of compliance with the protocol and study procedures
- Review of adverse event reporting and safety documentation

Monitoring may be conducted remotely and/or on-site, as appropriate.
Findings from monitoring activities will be documented, and any issues identified will be followed up to resolution. Sites will be required to implement corrective and preventive actions (CAPA) where necessary.

22.2 Audits & Inspections

The study and associated documentation may be subject to audit by the Sponsor or inspection by regulatory authorities to ensure compliance with GCP and applicable regulatory requirements.
Audits may include:

- Review of the Trial Master File (TMF)
- Review of Investigator Site Files (ISF)
- Verification of data against source documents
- Assessment of compliance with protocol, SOPs, and regulatory requirements

Participating sites must permit direct access to study-related records for the purposes of monitoring, audit, and inspection, subject to applicable confidentiality and data protection requirements.
All study personnel are required to cooperate fully with any audit or inspection.
Any findings identified during audits or inspections will be documented and addressed through appropriate corrective and preventive actions.

22.3 Training and Compliance

All study personnel will be appropriately qualified by education, training, and experience to perform their study-related duties.
This will include:

- Current Good Clinical Practice (GCP) training
- Study-specific training provided at Site Initiation
- Ongoing training as required for protocol amendments or procedural updates

Training records will be maintained and made available for review.

22.4 Quality Management

The Sponsor will maintain oversight of the study through defined quality management processes, including:

- Standard Operating Procedures (SOPs) governing study conduct
- Risk assessment and risk mitigation strategies
- Documentation and management of protocol deviations and non-compliance
- Implementation of corrective and preventive actions (CAPA) where required

These processes are designed to ensure that the study is conducted to a high standard of scientific and operational quality, and that the data generated are reliable and fit for purpose.

23. Public Involvement & Engagement

Patient and public involvement has been incorporated into the development of this study to ensure that the design and procedures are acceptable, proportionate, and sensitive to participants' needs.
Informal input was sought from individuals representative of the study population, as well as healthcare professionals working in reproductive and women's health settings. Feedback focused on the practical aspects of participation, including the acceptability of menstrual blood collection, study visit structure, and the clarity of participant-facing materials.
This input informed several aspects of the study design, including:

- The use of menstrual cups as a collection method, selected for their practicality and participant autonomy
- The timing and structure of study visits to align with routine clinical care where possible
- The development and refinement of the Participant Information Sheet to improve clarity and accessibility

The level and form of participant reimbursement (£150) was also discussed with patient and public contributors and healthcare professionals to ensure that it is appropriate. The reimbursement is intended to recognise participants' time, inconvenience, and travel costs, while avoiding undue influence on the decision to participate.
No formal PPI advisory group has been established for this study. However, feedback from participants and site staff during the study may be captured informally and used to inform ongoing study conduct and the design of future research.
At the conclusion of the study, a summary of findings will be made available to participants on request, in an accessible format.

24. Publication Policy

The findings of this study will be disseminated in a manner that balances scientific transparency with the protection of intellectual property and commercial interests. Genie Fertility Limited does not intend to publish full datasets or detailed reports in the public domain where this may compromise intellectual property, proprietary methodologies, or future commercial development.
However, the Sponsor is committed to appropriate scientific dissemination of study findings. Results will be shared, where feasible, through:

- Peer-reviewed publications
- Scientific and clinical conference presentations
- Other appropriate academic or professional channels

All publications will ensure that participant confidentiality is maintained and that no identifiable data are disclosed.
Participants will be offered access to a summary of the study findings upon request, presented in a format that is understandable to a lay audience.

Any dissemination of results will be subject to Sponsor review to ensure compliance with legal, regulatory, and commercial requirements.

25. Milestones

The study is planned over a 36-month period. Key milestones are outlined below:

Milestone	Timeline (from study start)	Description
Study setup and approvals	Months 0–3	Finalisation of protocol and study documents; ethical and governance approvals; site selection and contracting
Site initiation	Months 2–4	Site Initiation Visits (SIVs); training of site personnel; study materials distributed; sites authorised to recruit
Recruitment period	Months 3–18	Participant recruitment across all active sites
Sample collection and processing	Months 3–20	Ongoing collection, transport, and laboratory processing of biological samples
Interim operational review	Month 9–12	Internal review of recruitment, sample quality, and feasibility metrics (no formal interim analysis)
Completion of recruitment	By Month 18	Target sample size achieved or recruitment period closed
Final sample analysis	Months 18–24	Completion of laboratory analyses, including biomarker assessment, DNA extraction, and cellular studies
Data cleaning and database lock	Months 24–30	Data validation, query resolution, and final database lock
Data analysis and reporting	Months 30–33	Statistical analysis and preparation of study outputs
Study close-out	Months 33–36	Final study documentation, archiving, and end-of-study notification
Dissemination of findings	Months 33–36 and ongoing	Preparation of manuscripts, conference abstracts, and participant summary reports

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