THE UNIVERSITY of EDINBURGH

ENDO1000

The UK-wide Endometriosis Research Project

Sponsor	The University of Edinburgh ACCORD Usher Building, The University of Edinburgh 5-7 Little France Road Edinburgh BioQuarter – Gate 3 Edinburgh EH16 4UX
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CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
BFI	Brief Fatigue Inventory
BMI	Body Mass Index
CI	Chief Investigator
CHI	Community Health Index
CRF	Case Report Form
EHP	Endometriosis Health Profile
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICH	International Conference on Harmonisation
ISF	Investigator Site File
MRI	Magnetic Resonance Imaging
NRS	Numerical Rating Scale
PI	Principal Investigator
PIS	Participant Information Sheet
PROM	Patient Reported Outcome Measure
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure

1 INTRODUCTION

BACKGROUND

Endometriosis is characterised by the presence of endometrial-like tissue ('lesions') outside the uterus, commonly on the lining of the pelvic cavity. It is a chronic, inflammatory gynaecological condition that affects approximately 6-10% of women and those assigned female at birth (1, 2). It is associated with debilitating pelvic pain, gastrointestinal and urinary symptoms, fatigue and infertility (1, 3). Endometriosis can profoundly affect quality of life, limiting daily activities, social engagement, physical and sexual health, relationships, career and educational pursuits, mental well-being, and overall health. It is associated with a 45% reduction in work productivity with an annual cost for caring for women with endometriosis estimated at > £8.2 billion per year in the UK (4).

Challenges in Diagnosis and Treatment

People with endometriosis experience an average of 8 years of delay in the UK from the onset of their symptoms before receiving a diagnosis (5). There are no validated non-invasive tests for endometriosis and the current gold standard for diagnosis is via a diagnostic laparoscopy (6, 7). Currently, the waiting time for this procedure in the UK is variable across NHS Trusts and can be up to two years.

Treatment options typically include:

- Painkillers e.g. paracetamol, NSAIDs.
- Surgery to remove endometriosis lesions, although this is ineffective in an estimated 30 % of women and, even when its effective, symptoms return in up to 50% of women within 5 years of surgery (8).
- Hormone therapies, which are not curative, can have significant side effects and are contraceptive (7).

Some individuals explore lifestyle changes, such as dietary adjustments or exercise, but research on the effectiveness of these approaches remains limited (7).

RATIONALE FOR STUDY

Endometriosis is a heterogeneous disease in terms of symptoms, trajectory, and indicated therapeutic course, which highlights the need to develop personalised and targeted approaches for effective longitudinal management which are acceptable and accessible to patients and their health care team. There is a clear unmet need for earlier diagnosis and more effective pain management for people who suffer from the condition (Horne, Saunders et al. 2017).

Our goal is to accelerate discovery and advance data-driven research into endometriosis diagnosis and treatment by collecting large, multimodal, longitudinal data. This study is for the collection of data which will be retrospectively analysed. No feedback will be given to the individual participants on the results.

To achieve our goal, we plan to deliver a longitudinal cohort study. We will invite approximately 3000 UK individuals with endometriosis to take part in the study. They will be asked to do the following over a 24-month period:

(a) Record information about their pain, physical functioning, mental health/emotional functioning, diet/sleep, medical/surgical interventions and self-management strategies on a bespoke smartphone app specifically developed for the needs of this project

(b) Wear smartwatches for up to four, six-week periods to collect raw actigraphy data (three-dimensional acceleration, wrist temperature, ambient light) from which we can objectively infer longitudinal physical activity, sleep, and circadian variability characteristics using algorithms we have developed in-house. The smartwatches will be posted to participants and include pre-paid envelopes for their return to the research team, following similar protocols we have already developed and successfully deployed at the University of Edinburgh in related longitudinal studies (e.g. the SHAW study, https://www.shaw.business-school.ed.ac.uk/).

(c) Obtain serial self-collected samples of saliva, blood, faeces and urine on up to four occasions. Sample collection kits will be sent to participants by our research team

by post, self-collected at home and posted by participants back to our research team for analysis in our laboratory. This approach in collecting samples remotely will allow us to collect information from a diverse population of patients with endometriosis UK-wide and builds on our experience with longitudinal data collection.

Our proposed study has been informed by those with lived experience of endometriosis and by representatives from the UK patient organisation, Endometriosis UK.

2 STUDY OBJECTIVES

2.1 Primary Objective

To generate a unique biomedical endometriosis resource with detailed clinical and lifestyle phenotyping.

2.2 Secondary Objectives

To use the biomedical endometriosis resource to address fundamental questions in our understanding of endometriosis e.g.

(i) To investigate the potential for patient stratification/prediction of treatment response from clinical/biological data profiles.
(ii) To investigate the relationship between symptoms of pelvic pain and the gut-brain axis (including microbiome) using multi-omics data.
(iii) To demonstrate longitudinal endometriosis symptom trajectories using app-based patient reported outcome measures (PROMs) and wearable technology (13).

3 STUDY DESIGN AND METHODS

ENDO1000 is a UK-wide longitudinal cohort study. Participants will be enrolled into the study, over a period of 36 months, via advertising on university and relevant websites, and by endometriosis support groups. We will also work with our established group to ensure that we can reach as diverse a population as possible. Participants will be asked to download our bespoke ENDO1000 app which will be available for both Android and iPhone

users, and, if needed, there will also be a web-based application. The back-end server where everything will be controlled (from managing the PROMs to collecting data) will be hosted on a University of Edinburgh server and all data will be saved on a REDCap database on the same server. They will then be given information about the trial and asked to sign an on-line consent form. Following consent, they will be asked simple eligibility questions and will have access to the app. The duration of study participation will be approximately 24 months. During this time-period, the study participants will be asked to complete "trackers", via the app, which will capture pain scores, menstrual cycle bleeding patterns, sleep patterns, bowel habits, analgesic use, hormone use, exercise patterns and dietary habits over time. We will also record surgical interventions, self-management strategies e.g. acupuncture, etc. If a participant has a significant change in their physical and mental health, they will also be asked to record this. If a participant's tracker completion is greater than 50%, they will be invited to take part in the biological sample collection component of the study and to wear a smartwatch on up to four occasions over the 24-month period. At intervals, we will also ask participants to complete validated questionnaires which are detailed in Section 7 (this will correspond to when samples are collected, and the Smartwatch is worn).

4 STUDY SETTING

The ENDO1000 study will be delivered entirely remotely via our bespoke mobile app. A web-based page will be available for those who prefer not to download or are unable to use the app (to mitigate against missing participants who might want to participate but do not own smartphones). Participants will be asked to wear a smartwatch and obtain home self-collected biological samples for laboratory analysis (genetics, inflammatory profiling, microbiomics, metabolomics). We have chosen this design to give us the ability to identify and relate changes in self-reported symptoms due to medical, surgical and self-management, and to associate these changes with patterns in the gut microbiome and blood metabolome.

5 STUDY POPULATION

NUMBER OF PARTICIPANTS

We aim to invite up to 3000 participants to take part in our study and obtain multimodal data (PROMs, biological samples and data from the wearables). We envisage that this will enable us to obtain our target of 1000 participants with complete data sets for analysis.

INCLUSION CRITERIA

- Aged 16 or over
- Participants who confirm that they have received a clinical diagnosis of endometriosis (based on MRI, ultrasound or laparoscopy) within the last 10 years
- Living within the UK

Willing and able to consent to installing and using the mobile ENDO1000 app on their smartphone or use our web-based equivalent.

EXCLUSION CRITERIA

- Pregnant
- Known severe coagulation disorder
- Known active Hepatitis B/C and/or HIV (due to Royal Mail restrictions on biospecimen postage)

CO-ENROLMENT

Participants will be permitted to co-enroll in CTIMP and interventional non-CTIMP clinical trials. Participants will also be permitted to take part in non-interventional non-CTIMP research (e.g. questionnaire/tissue only studies).

6 PARTICIPANT SELECTION AND ENROLMENT

IDENTIFYING PARTICIPANTS

We will advertise our study (images of posters and flyers)with the support of relevant UK endometriosis charities and support groups (through their websites and via their social media platforms), through mailshots. Potential participants will self-refer to the study. We will work with our endometriosis PPI group to ensure that we can reach difficult to reach populations.

CONSENTING PARTICIPANTS

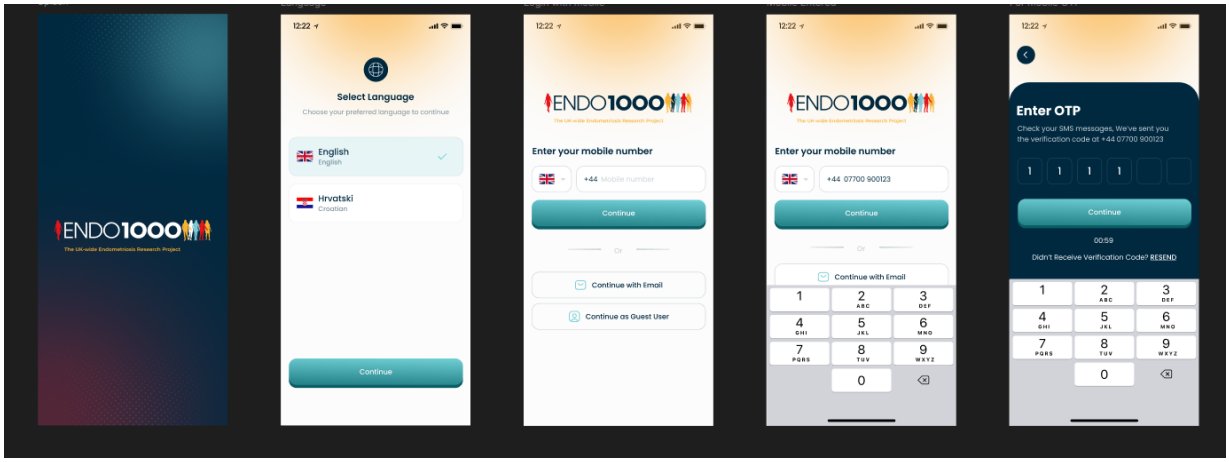
Individuals who decide they wish to take part in our study will be able to install the bespoke ENDO1000 mobile app via a link on the ENDO1000 website (see screenshots below).

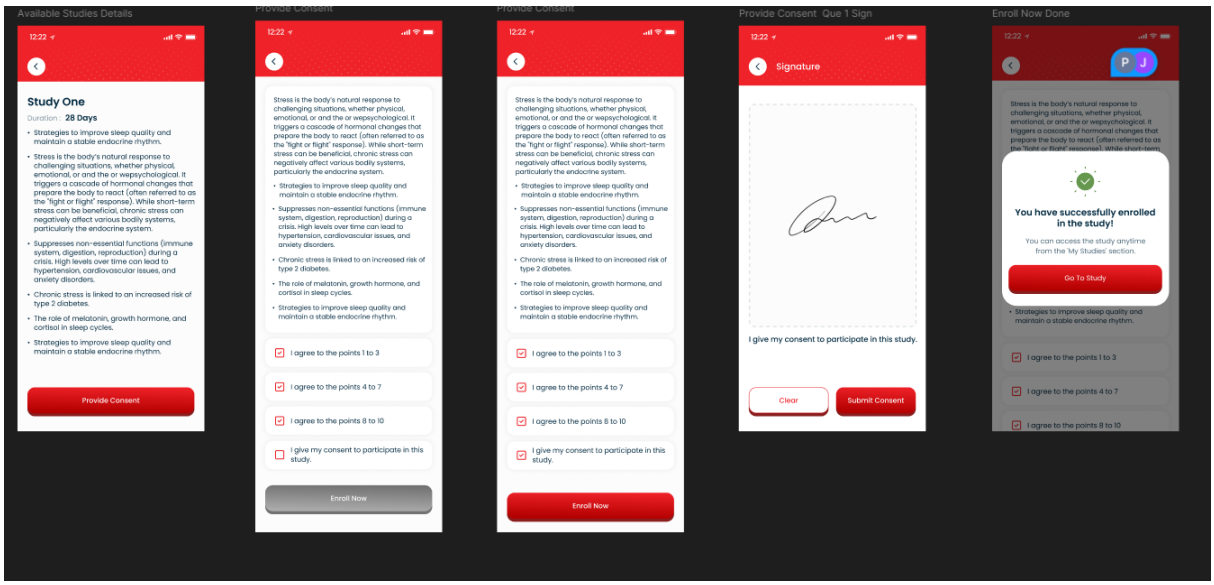
1. For initial registration with the app, they will need to first agree to our 'terms and conditions' and 'privacy policy', by reading them and then confirming acceptance on the app.
2. To register for the study, they will be required to submit minimal information – their name, email address and month and year of birth (this is stored on servers within the University of Edinburgh).
3. If they wish to consider participating in the study, they will be invited to watch a short, animated video detailing the study and be given access to the study participant information sheet, both accessed via the app or via the ENDO1000 website.
4. If they agree to consent, they will then be directed to an online consent form that they will be asked to electronically sign.
5. Once consent has been obtained, we will then ask three short eligibility questions to help us to direct them to relevant sections of the app and also their ongoing 'journey' in the study.

The app will have a "Frequently Asked Questions" section (FAQ). We will also include email contact details for the ENDO1000 research team should they have questions about the study/app that have not been answered within the mobile app itself. We will ensure that it is clear that this email is only for questions related to the study and that clinical questions cannot be answered by the research team.

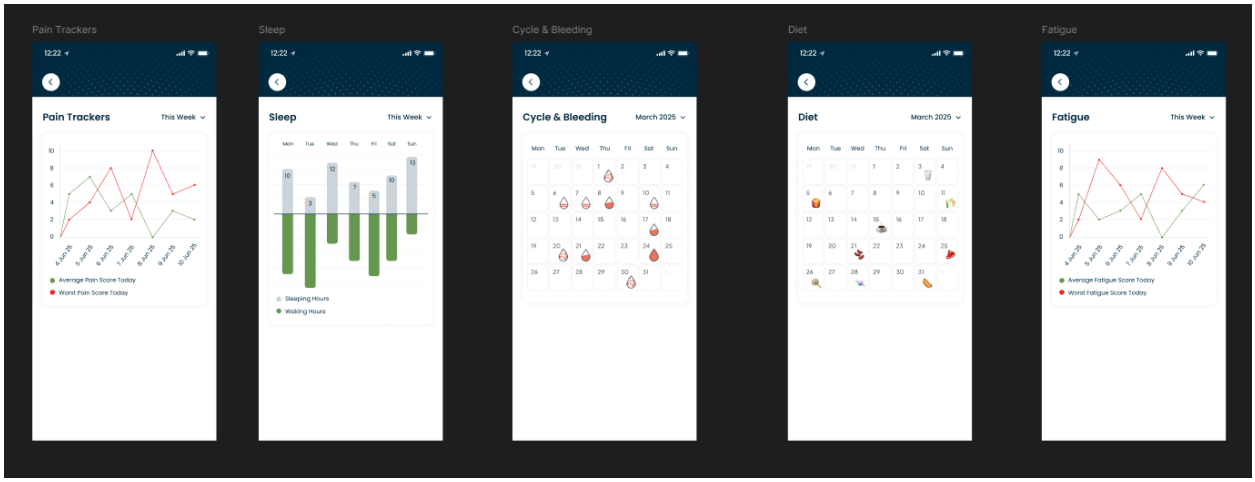
To incentivise participants to contribute their data, we will provide personalised reports on their activity and sleep patterns from the wearing of the smartwatches (if requested). We have delivered these personalised reports in similar projects where participants have contributed to our research, in terms of data from wearables, and it was very well received. Furthermore, we plan ENDO1000 webinars to disseminate findings to the study participants where we will address questions from participants after we have completed our data analysis.

SCREENSHOTS OF ENDO1000 MOBILE APP





SCREENSHOTS OF REAL TIME DATA AVAILABLE FROM THE TRACKERS



Withdrawal of Study Participants

Participants will be free to withdraw from the study at any point by simply stopping using the app and without needing to provide any justification. If they have provided data or biological samples, the data derived from these samples will be used, unless the participant expressly asks for them not to be used. We will make it clear that participants can make this request by contacting the research team directly on etmt@ed.ac.uk.

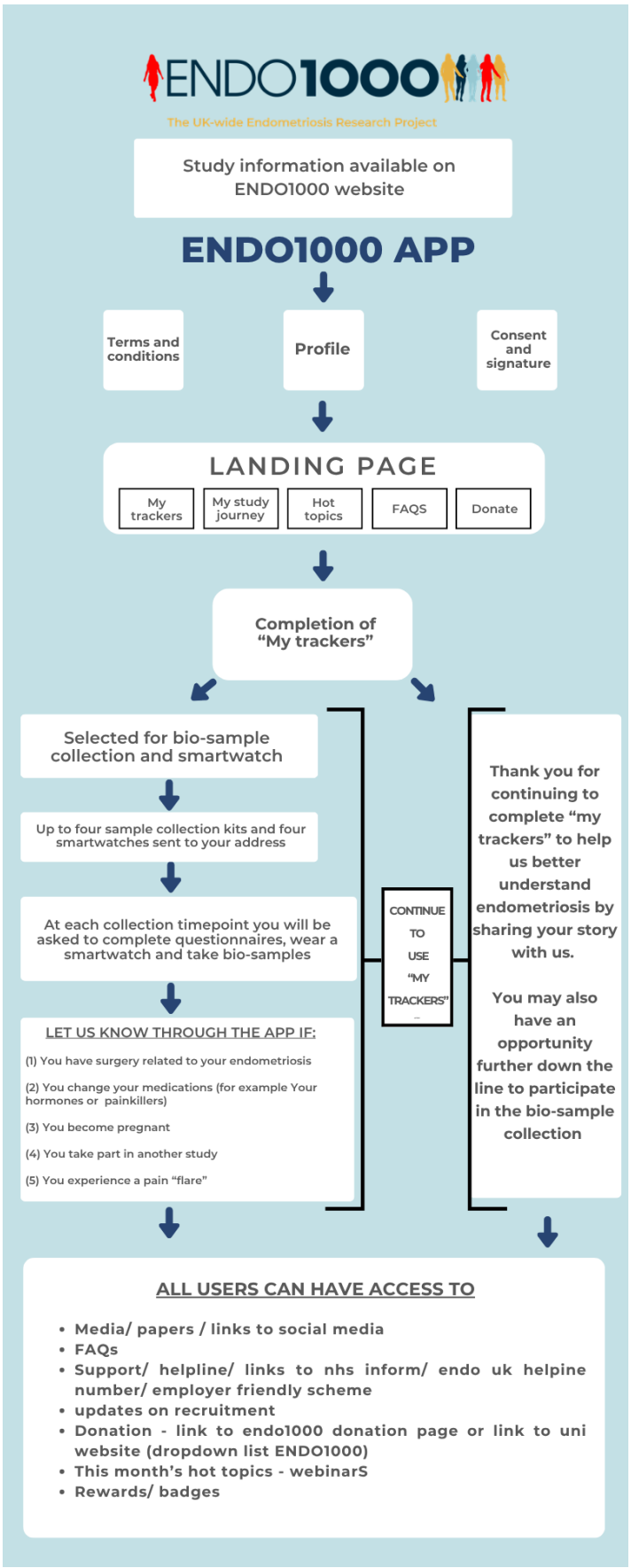
LONG TERM FOLLOW UP ASSESSMENTS

There is no planned longer term follow up for the study participants, but we will seek consent to contact participants for continuation of this study longer term should we obtain funding to extend it. We will also ask their permission to contact them to see if they would like to take part in other related studies, subject to further funding.

7 STUDY ASSESSMENTS

Assessments completed over a 24-month period
Self-referral by downloading the ENDO1000 App via the ENDO1000 website/app store.
Electronic Consent – 'terms and conditions' of the app, 'privacy notice' (including data storage) and study consent.
Eligibility, demographic data, contact details.
Completion of WERF EPHect questionnaire (REF) – a questionnaire to collect medical history and endometriosis symptoms over their lifetime (completed once).
Completion of app 'trackers' – record of pain scores, menstrual cycle bleeding patterns, sleep patterns, exercise patterns, bowel habits, dietary habits, analgesic use.
If a participant's tracker completion is greater than 50%, they will be sent a home self-collection kit for biological sample collection and a smartwatch.
Self-collected sample collection kits will be sent to participant's home address (saliva, blood, faeces and urine - up to four times during the 24-month time-period
Completion of Study Questionnaires (detailed in section below)– a minimum of four times during the 24-month time-period to correspond with sample collection.
Wear Smartwatch – up to four times during the 24-month time-period

Flowchart of participation



Example of ENDO1000 app “Home” page

Biological sample collection

Biosamples (saliva, blood, faeces and urine) will be collected at up to four timepoints over 24 months. The biosamples will be collected using the following approved home self-collection kits (or similar available products):

Biological sample	Collection Kit	Manufacturer	Supplier reference	Website link
Saliva	OMNIgene-Oral	DNA Genotek	OM-501	https://www.dnagenotek.com/row/support/collection-instructions/omnigene-oral/OM-501
Blood	30ul Mitra micro sampling device	Trajan Scientific Europe LTD	30004	https://1806452.fs1.hubspotusercontent-na1.net/hubfs/1806452/VLBL-0125-R_Rev02_web.pdf
	Tasso+ 600ul self-collection	Tasso Inc	K1025-01-EDT	https://www.tassoinc.com/eu/tassoplus-kit-ifu
Faeces	Omnigene-Gut	DNA Genotek	OM-200	https://www.dnagenotek.com/row/support/collection-instructions/omnigene-gut/OM-200
Urine	Colli-Pee UCM 20ml	DNA Genotek	N00176_RUO	https://dnagenotek.com/ROW/products/collection-infectious-disease/colli-pee/colli-pee_first-void-urine-collection#working

Study questionnaires

Questionnaires will include:

WERF EPHect Patient Questionnaire: to collect epidemiological and genetic data in endometriosis research (9).

Endometriosis Health Profile-30 (EHP-30): an endometriosis-specific questionnaire with 30 questions and five scales (10)

Brief Fatigue Inventory (BFI) (11)

The Pittsburgh Sleep Quality Index (12)

Food Frequency Questionnaire (FFQ) (REF)

8 DATA COLLECTION/MANAGEMENT

All patient reported data will be recorded on our ENDO1000 mobile app which will use the Amazon Web Service (AWS) IS cloud, server hosting infrastructure. The app will be hosted on AWS where data will initially be captured but sent to UoE IGMM servers for long-term

storage. This data will include questions to capture the baseline demographic and clinical characteristics of the participants.

Participants will not be able to access any of their data from the smartwatches (there is no display). Anonymised data from the returned smartwatches will be downloaded to UoE servers via the Geneactiv Windows programme and will be matched to PROMs via the participant study IDs. The anonymised data will only be viewed by the research team. There is no identifiable data contained within the dataset generated by the smartwatches, apart from raw three-dimensional acceleration, ambient light, and wrist temperature data. When the data is uploaded to REDcap by our research team, the participants PIN will be allocated to the data. Datasets of raw measurements made from the anonymised human biological samples will only be accessible to members of the research team.

Source Data Documentation

In our study, source documents will include:

Participant completed questionnaires

Smartwatch data held in the GENEActiv PC Software App and uploaded to REDcap

Laboratory results from analysis of biospecimens.

PERSONAL DATA

The following personal data will be collected as part of the study: name, email address, mobile telephone number, postcode, ethnicity and date of birth. An address will be required if participants consent to the collection of biological samples.

All data will be collected, processed and stored in line with the General Data Protection Regulation (GDPR).

Electronic personal data will be stored on UoE secure servers that require user authentication. Computers and database access will be password-protected. . Name, email address, signature, and mobile number will be stored on AWS servers to enable app functionality (e.g., notifications, app logins, and questionnaire delivery). These data items will also pass through AWS servers during transit to UoE's secure servers. AWS will be secured with two-factor authentication (2FA) and encrypted both at rest and in transit, with HTTPS-secured API communications.

Personal data will be stored for a minimum of 5 years following the end of the trial. The personal data will be held with separate access to the pseudo-anonymized data and will be linked via a participant study ID which will be the only identifier used to match the different modalities (PROMs, biological data samples, data from wearables). The data analysis team will only have access to the pseudo-anonymised data.

Data Information Flow

Participants will input their information directly into the app, which will be securely transferred via AWS servers to the REDCap database. Identifiable data (name, email, mobile, signature) is stored in AWS to support app functionality and is also stored within REDCap with restricted access. This identifiable data will not be accessible to the data analysis team.

The electronic consent form and the participant ID log will be the only two places where identifiable data is collected and this will be stored within REDCap with restricted access. This will not be available to be viewed by the data analysis team. The consent forms will contain the participants' name. The ID log will have the name, address including postcode, details will all be stored only to contact the participant for sending of the biological sampling kits.

The REDCap database will also contain email address (with consent) to allow for sending out the questionnaires electronically or via the mobile application (in the form of a notification). All other data collected will be anonymised. Identifiable data will not be released to the data analysis team or any third party.

Data Storage

As stated in section 8.1, personal data will be stored by the research team on a UoE secure server. This will be held separately to the information that can be accessed on the UoE server by the data analysis team.

The trial data will be stored on our REDCap database hosted on the UoE secure server, requiring user authentication for access. The database will be validated, ensuring integrity and security of the data to be collected. This will include mobile numbers (with consent) to send out notifications via the mobile application in the form of a notification should these require completion if non-engagement occurs.

Any exported data from the database will be stored in a DataShare point as a safe data server (which is regularly backed-up) from the University of Edinburgh to exchange information. Authorised (via dedicated personalised credentials) team members will be accessing to download the collected data and provide outputs of the analysis for internal circulation. This will be authorised by the PI who has the responsibility on who is given access to the data.

Data Retention

Personal data collected as part of this trial will be stored for a minimum of 5 years following the completion of the trial, for administration of the trial. This retention period will be longer for those who consent to be contacted about future research. This will be specific item on the consent form.

Trial data will be archived at the end of the trial and stored for a minimum of 5 years on secure servers hosted by the UoE.

Disposal of Data

Data will be archived as per Sponsor's SOPs. When the minimum retention period has been reached, material will not be destroyed without authorisation from the Sponsor. Disposal of data will be as per Sponsor guidance.

External Transfer of Data

Selected anonymised data collected or generated by the study may also be shared with other researchers from other institutions once the study is finished. No participant can be identified by their data as this will be anonymised and the team is experienced in obfuscating e.g. PROMs and data from the wearable sensors to minimize any potential risk. Data transfer will be in accordance with General Data Protection Regulations, ICH GCP and SOPs of the Sponsoring organisation.

Data Controller

A data controller is the organisation that determines the purposes for which, and the manner in which, any personal data are processed. The UoE and NHS Lothian will be joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

Data Breaches

Any data breaches will be reported to the UoE Data Protection Officers (dpo@ed.ac.uk) who will onward report to the relevant authority according to the appropriate timelines if required.

Data Information Flow

Participant data for this study will be collected via our ENDO1000 purpose-built mobile application, which has been developed specifically for secure and user-friendly data capture in the context of clinical research.

Each participant will be required to create a password-protected account to access the app. This ensures that only the individual participant can view or enter their own data. All login credentials are stored securely using hashed encryption, and multi-level safeguards are in place to prevent unauthorised access to personal or study data.

All data entered into the app will be stored temporarily on a secure, region-locked Amazon Web Services (AWS) server located within the European Union (EU). This ensures full compliance with the General Data Protection Regulation (GDPR) in terms of data residency, security, and access controls. Data are encrypted both in transit and at rest, using industry-standard cryptographic protocols.

Data will then be transferred from the AWS environment to the study database hosted on the UoE's REDCap platform. This transfer occurs over encrypted HTTPS channels using REDCap's secure API functionality. Each transmission is authenticated using unique API tokens and logged to maintain a full audit trail.

Once received, the data will be stored within REDCap on secure servers maintained by the UoE. Access to REDCap is strictly role-based, restricted to authorised study personnel, and governed by institutional policies on information governance and data security.

All aspects of data handling, transmission, and storage conform to GDPR and relevant local regulations.

9 BIOSAMPLE STORAGE AND ANALYSIS

The biological samples will be processed, stored and analysed in Professor Andrew Horne's laboratory (unless indicated otherwise) within the Centre for Reproductive Health, Institute of Regeneration and Repair, University of Edinburgh. DNA will be extracted from salivary and faecal samples, and stored for genetic analysis. The faecal DNA samples will be sent to Dr Siobhain O'Mahoney, University of Cork for microbiome analysis (covered by a material transfer agreement and data sharing agreement as required). Other analyses will include profiling of hormones and inflammatory markers (blood), the metabalome (blood/faeces), and proteomics (blood/urine).

10 STATISTICS AND DATA ANALYSIS

SAMPLE SIZE

It is challenging for us to provide a detailed power calculation for the study given that we will be collecting multidimensional data from heterogeneous sources. Therefore, the driving consideration is for us to have sufficient statistical power to explore hypotheses and develop robust statistical learning models. Given our extensive prior experience in endometriosis clinical practice and clinical trials, we are confident that recruitment ENDO1000 of up to 3000 women (to yield 1000 complete data sets) is ambitious yet feasible. This number of complete data sets will be sufficiently large to be hypothesis-generating and enable exploratory statistical analysis, including data stratification to investigate specific subsets that might merit further exploration. It will be large enough to test specific, pre-determined hypotheses in endometriosis, e.g. the association between symptoms of pelvic pain and the gut-brain axis using multi-omics data. We envisage exploring data using standard statistical analysis techniques for visualisation (density plots, scatter plots), statistical association computations (e.g. correlation analysis), and feature selection/feature transformation/latent variable methods. Moreover, we will apply robust supervised machine learning algorithms and standard model validation schemes to assess the performance of the developed statistical learning models, providing robust estimates of

their likely generalisation in new unseen data. The requirement to collect a large sample size is to enable the exploration of different stratification strategies, e.g. exploring age-based strata and other approaches that we may want to explore to study separate certain groups.

DATA ANALYSIS

Demographic information and self-reports on standardised questionnaires: The self-reports will be longitudinal on a regular basis (weekly). The raw data will be provided in *.csv format. WP18 will process these to derive characteristic patterns and summary data to characterize individual participants (e.g. in terms of self-reported symptom variability, symptom trajectory trends, and information for different strata based on age and endometriosis subtypes). Similarly, we will explore the presence of latent variables using a range of embedding algorithms (resulting in different derived datasets), as we have done in related studies processing self-reported outcome measures.

Actigraphy data collected using smartwatches: We will request participants provide repeated entries (i.e. 3-4 times wearing these smartwatches, each time recording about 40 days' worth of data). From the actigraphy data, we will compute physical activity, sleep, and diurnal variability characteristics to infer participant-specific trajectories. The raw data from these devices will be in binary (*.bin) format, and we have 10+ years of experience working with this type of actigraphy data for further processing. We will process the raw actigraphy data to derive information about sleep, physical activity, and diurnal variability for every individual in the study. This will be used to characterise each day and will be used alongside the self-reports by participants to derive a multimodal dataset.

We will process the biological samples to identify patterns in repetitive measurements, and these will complement the extracted information from the self-reports and the actigraphy data to derive a multimodal dataset comprising different types of information.

11 OVERSIGHT ARRANGEMENTS

INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the Sponsor, ethics review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the Sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12 GOOD CLINICAL PRACTICE

ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff named on the list prior to undertaking applicable study-related procedures.

Informed Consent

The trial team is responsible for ensuring electronic informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in research is voluntary and will be based on a clear understanding of what is involved. Participants must receive adequate information – appropriate Participant Information.
It will be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed (if relevant) and agree to their data being inspected by representatives of the Sponsor, if applicable.
Consent will be electronic and a copy of this will be available to them within the App.

Data Recording

The Principal Investigator will be responsible for the quality of the data recorded.

Investigator Documentation

The Principal Investigator will ensure that the required documentation is available.

GCP Training

All researchers involved in the study will be encouraged to undertake GCP training in order to understand the principles of GCP. GCP training status for all investigators will be indicated in their respective CVs.

Data Protection Training

All University of Edinburgh employed researchers and study staff will complete the Data Protection Training training module through Learn.

Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

Confidentiality

All, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or

other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

Data Protection

All Investigators and study site staff involved with this study will comply with the requirements of the appropriate data protection legislation (including the UK General Data Protection Regulation legislation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information. Any members of the team accessing and processing the data will be required to undergo training for sensitive data protection (e.g. the MRC Data confidentiality course) and will be expected to adhere to standard good practices to protect participant anonymity.

Computers used to collate the data will have limited access measures via user names and passwords. Computers where the analysis will take place will be password protected and use the latest anti-virus and anti-malware protection; only anonymised/pseudo-anonymised data will be allowed to protect participant anonymity.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to a Sponsor representative for review and authorisation before being submitted in writing to the appropriate EC (or any other local requirements) for approval prior to participants being enrolled into an amended protocol.

MANAGEMENT OF PROTOCOL NON-COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this will be submitted to the EC, for review and approval if appropriate.

Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subject's rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Sponsor every 3 months. Each protocol violation will be reported to the Sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot.

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies.

SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the research; or

(b) the scientific value of the research.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Sponsor (qa@accord.scot) will be notified within 24 hours. It will be the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the research, to determine whether the incident constitutes a serious breach and report to EC as necessary.

END OF STUDY

The end of study is defined as the last participant's last data collection point.

The Investigators or the Sponsor have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the EC and Sponsor within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Sponsor via email to resgov@accord.scot.

A summary report of the study will be provided to the EC within 1 year of the end of the study.

INSURANCE AND INDEMNITY

The Sponsor will be responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Sponsor responsibilities:

The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

Data Sharing

At the end of the project or following publications we can make anonymised data available (subject to a data access request and appropriate contracts put in place) to other researchers to conform with good research practice allowing reproducibility of findings.

15 REFERENCES

1. Zondervan, K. T., C. M. Becker and S. A. Missmer (2020). "Endometriosis." N Engl J Med 382(13): 1244-1256.

2. Saunders, P. T. K. and A. W. Horne (2021). "Endometriosis: Etiology, pathobiology, and therapeutic prospects." Cell 184(11): 2807-2824

3. Horne, A. W. and S. A. Missmer (2022). "Pathophysiology, diagnosis, and management of endometriosis." Bmj 379: e070750.

4. Simoens, S., G. Dunselman, C. Dirksen, L. Hummelshoj, A. Bokor, I. Brandes, V. Brodszky, M. Canis, G. L. Colombo, T. DeLeire, T. Falcone, B. Graham, G. Halis, A. Horne, O. Kanj, J. J. Kjer, J. Kristensen, D. Lebovic, M. Mueller, P. Vigano, M. Wullschleger and T. D'Hooghe (2012). "The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres." Hum Reprod 27(5): 1292-1299.

5. Amess, S. and E. Cox (2020). All Party Parlimentary Group on Endometriosis.

6. Kuznetsov, L., K. Dworzynski, M. Davies, C. Overton and G. Comm (2017). "GUIDELINES Diagnosis and management of endometriosis: summary of NICE guidance." Bmj-British Medical Journal 358.

7. Becker, C. M., A. Bokor, O. Heikinheimo, A. Horne, F. Jansen, L. Kiesel, K. King, M. Kvaskoff, A. Nap, K. Petersen, E. Saridogan, C. Tomassetti, N. van Hanegem, N. Vulliemoz and N. Vermeulen (2022). "ESHRE guideline: endometriosis." Hum Reprod Open 2022(2):
8. Guo, S. W. (2009). "Recurrence of endometriosis and its control." Hum Reprod Update 15(4): 441-461

9. Vitonis, A. F., K. Vincent, N. Rahmioglu, A. Fassbender, G. M. Buck Louis, L. Hummelshoj, L. C. Giudice, P. Stratton, G. D. Adamson, C. M. Becker, K. T. Zondervan and S. A. Missmer (2014). "World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endometriosis research." Fertil Steril 102(5): 1223-1232.

10. Horne, A. W., P. T. K. Saunders, I. M. Abokhrais, L. Hogg and E. P. Setting (2017). "Top ten endometriosis research priorities in the UK and Ireland." Lancet 389(10085): 2191-2192.
Jones, G., C. Jenkinson, N. Taylor, A. Mills and S. Kennedy (2006). "Measuring quality of life in women with endometriosis: tests of data quality, score reliability, response rate and scaling assumptions of the Endometriosis Health Profile Questionnaire." Hum Reprod 21(10): 2686-2693.

11. Mendoza, T. R., X. S. Wang, C. S. Cleeland, M. Morrissey, B. A. Johnson, J. K. Wendt and S. L. Huber (1999). "The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory." Cancer 85(5): 1186-1196.

Palsson, O. S., W. E. Whitehead, M. A. van Tilburg, L. Chang, W. Chey, M. D. Crowell, L. Keefer, A. J. Lembo, H. P. Parkman, S. S. Rao, A. Sperber, B. Spiegel, J. Tack, S. Vanner, L. S. Walker, P. Whorwell and Y. Yang (2016). "Rome IV Diagnostic Questionnaires and Tables for Investigators and Clinicians." Gastroenterology.

12. Buysse, DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Research 28:193-213, 1989

13. K. Edgley, P.T.K. Saunders, L.H.R. Whitaker, A.W. Horne, A. Tsanas: Characterising endometriosis symptom trajectories through longitudinal actigraphy and self-reports, npj Digital Medicine, Vol. 8:236, 2025