Medical treatment of heavy menstrual bleeding in primary care: Long term follow up of ECLIPSE trial cohort

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Short title: *Long term follow up of ECLIPSE trial cohort*

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SYNOPSIS

Title	Medical treatment of heavy menstrual bleeding in primary care: Long term follow up of ECLIPSE trial cohort
Short title	ECLIPSE long term follow-up study
Chief Investigator	Professor Joe Kai
Objectives	To assess long term rates and nature of surgical interventions; and patterns of medical treatment use in women 10 years after their presentation with, and initial management for heavy menstrual bleeding (HMB) in primary care.
Study Configuration	Observational follow-up study (questionnaire and medical records)
Setting	Primary care. This study will involve general practices in the Midlands and East region whose patients participated in the ECLIPSE study[1].
Sample size estimate	This is solely a follow-up study therefore a power calculation for sample size estimate has not been calculated.
Number of participants	571 women originally participated in the ECLIPSE study. At 5 years follow up, 70 women did not wish further contact and will not be further approached and 6 women had died. Therefore we will approach 495 women. We aim to recruit and obtain follow up data from a minimum of 66% women after 10 years, allowing for further loss to follow-up (due to relocation, emigration, or death), estimated target 276 women. We aim to recruit a purposeful sample of up to 30 – 40 women of these women for qualitative interview.
Eligibility criteria	**Inclusion criteria** - Previous participant of the ECLIPSE trial - Able to provide informed consent **Exclusion criteria** - Not a previous participant of the ECLIPSE trial - Unable to provide informed consent
Description of interventions	Participants will complete a questionnaire and provide consent for access to their medical records for data collection. A purposeful sub-sample will be asked to take part in semi-structured telephone interview to explore their experiences qualitatively.
Duration of study	4 years *Start date*: 1st December 2017 *End date:* 31st December 2020
Methods of analysis	Analyses will be descriptive; and by intention-to-treat, with differences examined by analysis of covariance and paired t-tests. Kaplan-Meyer plots will also be constructed for a time to surgical intervention and a time to treatment change analysis. Qualitative analysis will be conducted using an iterative constant comparison approach.

ABBREVIATIONS

CI	Chief Investigator overall
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practice
HMB	Heavy menstrual bleeding
ICH	International Council for Humanisation
LNG-IUS	Levonorgesterol Intra-Uterine System
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
TSC	Trial Steering Committee (in reference to ECLIPSE study[1])
UoN	University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

SUMMARY

The ECLIPSE trial[1] provides an internationally unique cohort of 571 women. The trial has yielded the most robust evidence available for the initial medical treatment of heavy menstrual bleeding (HMB) presenting in primary care[1], and has reported at 2 and 5 years of follow up. The proposed observational study will follow up the same cohort of women to ten years. This will secure important long term data on women's treatment and health service trajectories for HMB, which may vary considerably as women approach the menopause. This information, for a common and chronic episodic problem, is lacking from existing research.

ADDRESSING A COMMON PROBLEM

HMB is a very common problem, burdensome for 20-30% women of reproductive age, and for health services. In the UK, more than 5% of women aged 30 to 49 years consult annually in primary care with HMB. The problem accounts for 20% of gynaecology referrals, and 28,000 women undergo related surgical interventions annually. ECLIPSE compared the effectiveness of initial medical treatments for women presenting with HMB in primary care. High generalisability was further enhanced by participants from 189 general practice sites, and the successful inclusion of a socially diverse population that is representative of the UK (17% of sample from minority ethnic backgrounds).

This enabled publication of two year outcomes in the *New England Journal of Medicine* in 2013[1]. This showed both levonorgesterol intra-uterine system (LNG-IUS) and standard medical treatments for HMB were helpful in reducing the adverse effects of HMB on women's lives, but that LNG-IUS was the more effective first choice. Rates of surgical interventions were similarly low between groups. The study's major contribution to elucidating effective first line approaches to management of HMB has been highlighted internationally[2]. Our parallel economic evaluation has further provided clear evidence on the relative cost-effectiveness of treatments in this context[3]. These data[1,3] will inform the planned update of NICE guidance on management of HMB in 2017.

Success in answering our original research questions[1-3] has been hard won. Recruitment was a considerable challenge, taking over four years, given the need for both women and their GPs to be in equipoise between initial treatment choices of LNG-IUS (requiring contraceptive intra-uterine 'coil' insertion) or (largely) oral treatments. It is now vitally important to maximise use and follow up of this ECLIPSE cohort to realise the full potential of this research.

CURRENT STATUS

High outcome ascertainment (84% at two years) was sustained to 5 years of follow up, at 74% (424/571 randomised). This analysis found a diminishing effect of LNG-IUS compared with standard treatment in terms of HMB-specific quality of life (MMAS) and generic quality of life (EQ-5D, SF-36) outcomes at five years[4,7]. This is not unexpected given the proportions of women who changed treatments, or had improvement of their symptoms naturally or through treatment or surgery. However the proportion of women having surgery has doubled (since that at two years) to 22%. This is significantly lower than the 58% of women undergoing surgical intervention by 2 years following previous oral medical therapy for HMB, identified in a previous systematic review[5].

Longer term progression to surgical intervention (hysterectomy, endometrial ablation) in our cohort thus appears of key interest. We propose to concentrate further follow-up on tracking surgical interventions, and patterns of treatment use, to ten years post-randomisation. However previous quality of life outcomes will also be followed up given

the possibility that earlier treatment experience earlier in the course of the condition may potentially influenced these at 10 years. This is particularly important given the lack of available data on what happens to women presenting with HMB in primary care (i.e. the vast majority of women with HMB). Moreover, this will enable assessment of whether our large cohort of women, recruited and treated in primary care continues to experience a low surgical intervention rate. This could further underline the important potential of general practitioners in providing medical management of HMB, avoiding referral to secondary care, with progression to higher costs and surgical intervention.

OPPORTUNITY TO ASSESS LONG TERM OUTCOMES FROM ROUTINE RECORDS
We anticipated assessing outcomes in the longer term at study outset. Thus all 571 women have already consented to follow up by questionnaire, including access to their primary care records by the research team and provision of information by their GP, until 10 years post-randomisation, with ethics approval (reference 04/MRE06/7). As the trial has closed as a CTIMP at earlier 5 years follow up, we plan to confirm and re-consent women for this observational follow up study at 10 years.

Given the long natural history of HMB, where treatments may be sought and taken over many years until the menopause, it is important to explore long term outcomes. Such data are greatly lacking and prioritising further research to secure them has been advocated by an NEJM editorial[2], by NICE[6] and by the ECLIPSE TSC. The trial cohort provides an excellent and timely vehicle for doing this, with mean age of 41.9 years (SD 5.0) at randomisation for treatments, and thus mean progression to natural menopause anticipated over the following ten years (mean age of menopause aged 52 years).

The study's existing data capture has been by postal self-completed patient questionnaire which we will send to women as part of this study with the further option for completion online. In addition, with consent, we propose continuing data collection by systematic review of participants' primary care medical records, by manual data extraction in practices.

ADDED VALUE
The added value of this study to enable follow up of women over a further five years is considerable because it will enable 10 year outcomes on surgical interventions, and long term patterns of treatment use for HMB, to be assessed in this primary care context for the first time, from an established high quality cohort. This could not be undertaken without the major challenges of assembling a similar cohort. In addition, we will conduct qualitative interviews will a purposeful sub-sample of women to explore and understand their experiences of, and decisions about treatments or surgical interventions, over this extended time period.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

This study will enable the efficient and timely collection of unique and valuable long term data from women as they approach and reach the menopause - as patterns of heavy menstrual bleeding (HMB), related treatment and service use, and life contexts change.

The study findings can inform HMB related clinical and patient decision making, refining of clinical (NICE) guidance, potential further economic assessment and health care planning to improve effective service responses for this common chronic episodic condition affecting women's health.

PRIMARY OBJECTIVE

To assess long term rates and nature of surgical interventions; and patterns of medical treatment use in women 10 years after their presentation with, and initial management for heavy menstrual bleeding (HMB) in primary care.

SECONDARY OBJECTIVES

This study will inform greater understanding of treatment for HMB, in particular:

a) Assessment of the rate, and detailed nature of surgical interventions women experience a decade following presentation and medical treatment in primary care for HMB;
b) Assessment of whether initial medical treatments in primary care (LNG-IUS or usual medical treatments) may influence these;
c) Assessment of women's pattern of use of long term medical treatments for HMB – for example, whether and to what extent women continue with LNG-IUS, or similarly continue intermittent use of or cease other medical treatments;
d) By qualitatively exploring women's experiences of, and decisions about treatments or surgical interventions, to enable insight into women's choices and what influences them over this extended time period.

STUDY DESIGN

STUDY CONFIGURATION

This is an observational follow-up study involving patient questionnaire, interview and data collection from general practice medical records.

The project will obtain 10 year follow-up data on ECLIPSE participants. 571 women originally participated in the ECLIPSE study. At 5 years follow up, 70 women did not wish further contact and will not be further approached and 6 women had died. Thus a potential maximum of 495 women will be approached. We aim to recruit and obtain follow up data from a minimum of 66% women after 10 years, allowing for further loss to follow-up (due to relocation, emigration, or death), with an estimated target of 276 women. Data from these women will be sought by questionnaire and from their GP medical records. We also aim to recruit a purposeful sample of up to 30 – 40 women of these women for qualitative interview.

STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

A research associate will be responsible for the day to day management of the study and collecting and analysing the data.

The Study Management Group will meet bi-annually and will consist of the research teams at the University of Nottingham and University of Birmingham.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: 4 years

Participant Duration: Up to 1 year [to allow for completion of the questionnaire, interview (where applicable), and access to medical records]

End of the Study

The end of the study will be the last completed questionnaire, interview or medical record data extraction of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

This is a follow-up questionnaire, interview and data collection study. The participants were initially consented as part of the ECLIPSE trial (REC ref 04/MRE06/7) and provided their consent to be contacted for follow-up by questionnaire and review of their medical records at 10 years. The University of Birmingham co-investigating research team maintains the original ECLIPSE trial recruitment log, consent forms, contact details of potential participants and recruiting sites (general practices and hospital trusts). The University of Nottingham has access to the recruitment log (see consent form).

Participants:
The research assistant will contact participants using their last known address recorded on the ECLIPSE database, mailing them a study pack. Women who do not respond may have moved address since the 5 year follow up. To maximise recruitment the research team will contact their recorded general practice (see *Practices* below) to identify whether participants are still with the practice and their current address, if different to that recorded on the study database, and mail out the study pack to participants' updated address. If the participant has left the practice these women will be lost to follow up.

In addition, the research assistant will attempt to contact participants not responding to mailed invitation to their last known address, by using their last known telephone number and/or e-mail address if these were recorded on the ECLIPSE database, to establish if the participant has moved. If the participant verbally agrees the study pack will be sent to their updated address.

Study packs to participants will include invitation to complete the follow up questionnaire (providing implied consent) and also a separate consent form for access to their GP medical records to extract data on relevant treatments and surgical interventions. The consent form will include an optional statement confirming the participant is happy to be contacted about potential participation in a qualitative interview, and a reminder to complete and return the contact details form. Participants declining to take part in this follow up study have the option to complete a feedback form providing brief information about why.

Participants will return their completed consent form, contact details and questionnaire in a freepost addressed envelope to the University of Nottingham. To increase response rate, the option of completing the questionnaire online will also be provided, with an online link in the study pack. Participants will receive £20 in high street shopping vouchers as a token of appreciation for their time and continued contribution to the study after 10 years, upon receipt of the completed questionnaire.

A purposeful sample of participants will be contacted separately with a letter, information sheet and consent form for qualitative interview if they indicated on the consent form that they would like to be contacted about this. The research associate will follow up with a telephone call to check the information has been received and to arrange a convenient date,

for the participant, for the interview to take place. The participant will receive another £20 voucher upon completion of interview, again as a token of appreciation for their time and participation.

Update to interview consent process due to barriers presented with COVID-19.
As University of Nottingham is on full lockdown (from 24/03/2020) the researcher does not have the facilities to send information regarding the interviews to the purposeful sample of women. Equally we have been informed that we will not be able to access the office to collect the post. Due to these barriers it is appropriate to seek approval to verbally consent participants, rather than receipt of a hardcopy consent form, so that the nested qualitative component of study can continue.

The purposeful sample of participants (of those that said yes to optional interview on the main study consent form) will be contacted via telephone to ask if they would still like to participate in the interview. If they say yes a date and time of the interview will be mutually agreed. The researcher will then ask the participant if they have an e-mail address that the consent form and participant information sheet (PIS) can be sent to. If the participant says they do not have an e-mail address a picture message can be sent of the documents. The researcher will explain that for the interview to take place they will need to have read the PIS prior to the interview as they will be asked to verbally consent at the beginning of the interview, which will be audio recorded. At the beginning of the interview, when the audio begins recording the researcher will read through the consent form with the participant and ask them I they consent to each section of the consent form. If the participant provides informed verbal consent the interview will then progress as normal. As the verbal consent is audio recorded it will then be evidenced in the transcription.

It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Translator or interpreter services are not required for this study as this initial ECLIPSE trial participant information was provided in English and participants consented in English.

Practices
Practices recruited participants directly in to the original trial, or identified and referred eligible women to local NHS secondary care trusts who recruited them to the trial. Each practice had 1 to 3, women on average, participating in the trial.

All practices previously involved will be contacted about the follow up study by letter from the University of Nottingham research team. A member of the research team will contact the practice to ensure they received the information and confirm if they are willing to continue to support the follow up study - to help re-contact women participants recorded as registered with them (see above) and, if they still have such women registered, to facilitate extraction of relevant data from their records, with women's consent.

If practices confirm participation they will be asked for an email address to which a password-protected list of women can be sent, the password will provided by phone after the email has been sent). Practices will be asked to check if the potential participant(s) remain at the practice, and their continuing suitability to be followed up, (see eligibility criteria below).

Practices will confirm to the University of Nottingham which participants are no longer at the practice by password protected email between the research team and practice. A follow up

telephone call will inform the specified person of the password to open the document. The University of Nottingham will mail out study packs to all other participants.

Eligibility criteria

Inclusion criteria

- Previous participant of the ECLIPSE trial
- Able to provide informed consent

Exclusion criteria

- Not a previous participant of the ECLIPSE trial
- Unable to provide informed consent

Expected duration of participant participation

Study participants will be participating in the study for up to 1 year.

Participant Withdrawal

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw, the data collected to date cannot be erased and may still be used in the final analysis. Any participants in the ECLIPSE trial (to five years follow up) who withdrew during its course will not be included in this further follow up study.

Informed consent

All participants will provide written informed consent. Completion and return of the questionnaire is considered as implied consent, however participants will be asked to complete a separate consent form for access to their GP medical records. A separate consent form will also be signed for participation in interviews.

Consent Forms will be signed and dated by the participant before they enter the study. The research team will provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator or nominated representative will answer any questions that the participant has concerning study participation.

One copy of the consent form will be kept by the participant, the original will be kept by the Investigator for the study master file, and a second copy will be retained in the participant's primary care (GP) medical records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended Consent Form which will be signed by the participant.

STUDY REGIMEN

On entry to, and consent for the original trial, participants consented to be re-contacted, at 10 years, to complete a follow up questionnaire and access to their medical records by researchers from Universities of Birmingham and Nottingham (please see appendix 1).To contact the potential maximum 495 women (see study configuration above) that were originally recruited into the ECLIPSE trial, the University of Birmingham co-investigating team will share women's recorded details with the University of Nottingham. This transfer

will be delivered securely and safely by saving the data onto an encrypted password protected hard drive, which will be sent to the research team at the University of Nottingham through Royal Mail signed delivery service.

The study research assistant will contact participants using their last known address recorded on the ECLIPSE database by mailing the study pack (letter, information sheet, questionnaire, consent form and contact details/questionnaire completion form). If there is no response from the participants from the postal invitation, attempts will be made to contact the participant using their last known telephone number and/or e-mail address if this is available in the ECLIPSE database; and the research team will also contact their previously recorded practice for assistance (see Recruitment, *Practices* (above).

Following confirmation from the practice by telephone or email that the practice is happy to be involved, the list of their patient participants will be transferred to the practice via an encrypted, password protected file sent via email, with the password telephoned to the relevant contact, e.g. practice manager. The practice will inform the researcher by completing the 'Participant Re-contact Form' if they are unable to identify any patients who may have moved to a different area or practice.

For those patients who continue to be on the practice's list their suitability to be contacted (see above), and for data extraction from records, will be assessed by the GP or practice manager to exclude any patients for whom it would not be appropriate for any data to be collected from records (e.g. if the patient no longer has capacity to consent). The practice will inform the research team of any participants who have been excluded. The research assistant will send the study pack (letter, information sheet, questionnaire, consent form and contact details/questionnaire completion form) to all other potential participants. Excluded patients will not be contacted.

Following receipt of the participant's consent form at the University of Nottingham, the respective general practice will be contacted to arrange data collection from medical records. The participant's consent form will be provided to the practice to confirm consent has been obtained for access to their medical records.

Each practice has an average of 1-3 previous participants in the ECLIPSE trial. Practices will be given the following options for data collection from GP records:

- Providing the data over the telephone to the study research associate/fellow where the research assistant will fill in the CRF with the information provided
- Completing the case report form (CRF) electronically and returning to the study team in a password-protect file via email, with the password telephoned separately
- The research associate will attend the practice in person to complete the CRFs manually from GP records on a password-protected university laptop, backed up to the university servers on return. A letter of access will be in place for this activity.

The data collected will be limited to specific data relevant to the study outcomes on the treatment trajectory of heavy menstrual bleeding (HMB) i.e.:

a) Any surgical interventions for HMB;
b) Use of long term medical treatments for HMB – including LNG-IUS, or other medical treatments prescribed for HMB in general practice;
c) GP contacts and secondary care use in relation to HMB.

The questionnaire for completion by participants will be almost identical to the original questionnaire they completed previously at 6 months, 2 and 5 years. However it has been slightly amended, given the elapse of a further five years to include: an initial section as context for 10 year outcomes (namely, questions on their current menstrual pattern,

whether no longer experiencing HMB, or entered menopause/using HRT); and questions on HMB treatments and interventions now precede question sections on quality of life (now moved to the end of the questionnaire). The original trial questionnaire can be reviewed in Appendix 2.

The questionnaire will also be made available for completion online using Bristol Online Survey (BOS). A general link will be provided on the participant information sheet and participant contact details/questionnaire completion form in the study pack, and we ask the participant to let us know if they have completed the questionnaire online via this form. Participants log in using the general link and then are asked to set up a username and password to access the questionnaire. All survey responses are collected over encrypted SSL (TLS) connections. SSL is the standard technology for establishing an encrypted link between a web server and a browser. It ensures that sensitive information can be transmitted securely. All communications within onlinesurveys.ac.uk are also sent over SSL encrypted connections. BOS user passwords are encrypted using PBKDF2 with a SHA256 hash and a random salt.

Participants do not need to complete a consent form for completion of the questionnaire as completion is implied consent However they will have returned the study consent form, including to confirm consent to extract data from their GP records, and contact details form in hardcopy using the freepost envelope provided in study packs.

If participants do not respond to mailed study pack using their previously known address, or attempts to contact via telephone call and/or e-mail, and it is confirmed they are no longer registered at their previously recorded practice, e.g. due to relocation, they will be considered lost to follow-up.

Once the recruitment period has ended the University of Nottingham (UoN) will securely provide the University of Birmingham (UoB) with a list of participants that have re-consented to their previous trial data being shared. UoB will securely transfer consenting participant's identifiable full trial data to UoN. Anonymised trial data will be securely transferred to UoN for the remaining ECLIPSE cohort.

Interviews

Participants who indicate interest in receiving further information on participating in the study interviews will be sent a letter, information sheet and consent form with a freepost envelope for return. This will be sent via the post and the research associate will follow up with a telephone call to check the information has been received. On receipt of a completed consent form, the research associate will arrange a convenient date and time for the interview with the participant. Interviews will be conducted over the telephone or face to face, according to participants' preferences, and will be audio-recorded. The researcher will further confirm consent as part of the interview. The date of the interview will be logged as the date of consent. The participant will be offered £20 in high street vouchers post interview as a token of appreciation for their time contributing to the study.

Criteria for terminating the study

Early termination of the study is unlikely, however should there be insufficient numbers responding to the questionnaire or consenting for access to their medical records we may require a further amendment to access medical records without consent through the Confidentiality Advisory Group.

ANALYSES

Methods

Analyses of quantitative data will be descriptive to present rates of surgical interventions and use of medical treatments. Differences between groups at ten years will be examined by analysis of covariance, and within groups using paired t-tests. Kaplan-Meyer plots will be constructed for a time to surgery and a time to treatment change analysis, with women censored at date to last follow-up or, if appropriate, date to death, withdrawal or loss to follow-up. A Cox proportional hazards model will be used to construct hazard ratios. The statistical package SAS 9.2 will be used for all statistical analysis.

Qualitative data (transcribed verbatim from audiotaped interviews) will be organised using qualitative software, and analysed thematically. Coding and development of analysis will involve a minimum of two qualitative researchers, and use constant comparison of data. Purposeful sampling of respondents, interview data generation and analysis will be undertaken concurrently, until saturation is achieved with no new themes are emerging.

To further refine and validate analysis, all interviewee participants will be invited to review and comment on summaries of preliminary findings to enable further opportunity to reflect on and refine findings.

Sample size and justification

This is solely a follow-up study therefore a formal power calculation for sample size estimate has not been calculated. It is estimated that qualitative interviews with approximately 30, up to 40 purposefully sampled women will be necessary to achieve qualitative data saturation.

ADVERSE EVENTS

The ECLIPSE trial has completed and reported at 2 and 5 years follow up. The occurrence of an adverse event as a result of participation within this entirely observational follow up study is not expected and no adverse event data will be collected.

ETHICAL AND REGULATORY ASPECTS

Where researchers are required to visit general practices across the country and where face to face interviews are conducted the University of Nottingham Lone Working Policy will be adhered to.

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records. A second copy will be filed in the participant's medical notes.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a study identity code number, for use on CRFs, other study documents and the electronic database. This will consist of a site identifier (for practice 001 upwards, e.g. to 189) and a patient identifier from 01 upwards which is not expected to be larger than two digits given the number of patients at each practice.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Study Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. A CRF may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the study. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the study in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

The Study Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made.

STUDY DATA

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The study results will be written up for publication in peer-reviewed journals and disseminated at conferences. Participants will not be identified in any publications.

USER AND PUBLIC INVOLVEMENT

Patient and public involvement representatives have commented on the protocol, study design and study documentation. They will also be involved in study management meetings, interpretation of the findings and dissemination.

STUDY FINANCES

Funding source

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme.

Participant stipends and payments

Participants will not be paid to participate in the study. However, they will be offered a £20 gift voucher as a “thank you” and inconvenience allowance for returning questionnaires, and any interview participation, given 10 years since their initial recruitment to the ECLIPSE study

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

REFERENCES

(1) Gupta J*, **Kai J*,** Middleton L, Pattison H, Daniels J for ECLIPSE trial investigators. Levonorgestrel Intrauterine System versus Medical Therapy for Menorrhagia. ***New England Journal of Medicine*** 2013;368:128-37 [*Joint first authors and co-chairs of trial collaborative]

(2) Espey E. First Line Therapy for Heavy Menstrual Bleeding. ***New England Journal of Medicine*** 2013;368;2

(3) Sanghera S, et al 2014 Levonorgestrel-releasing intrauterine system vs. usual medical treatment for menorrhagia: An economic evaluation alongside a randomised controlled trial **PLoS ONE**. DOI: 10.1371/journal.pone.009189

(4) Gupta JK, Daniels JP, Middleton LJ, Pattison HM, Prileszky G, Roberts TE, Sanghera S, Gray R, **Kai J***.* A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: the ECLIPSE trial. ***Health Technol Assess*** 2015;19(88**)**

(5) Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database Syst Rev 2006;2:CD003855.

(6) NICE, 2007. Heavy menstrual bleeding. NICE clinical guideline 44.

(7) KAI, J., MIDDLETON, L., DANIELS, J., PATTISON, H., TRYPOSKIADIS, K. and GUPTA, J., Usual medical treatments or levonorgestrel-IUS for women with heavy menstrual bleeding: long-term randomised pragmatic trial in primary care **British Journal of General Practice 2016**. 66(653), e861-e870

APPENDIX 1: Original consent to allow data share between University of Birmingham and Nottingham

ECLIPSE – A STUDY COMPARING THE CONTRACEPTIVE COIL WITH STANDARD MEDICAL TREATMENTS FOR HEAVY PERIODS

PATIENT CONSENT FORM

I confirm that I have read and understand the information sheet (dated 12.09.07, version 4.0a) for the above study and have had the opportunity to ask questions.

I understand what is involved in the ECLIPSE study and agree to participate. I hope to complete the study, but I understand that I am free to withdraw at any time without necessarily giving a reason. If I do withdraw, I can continue to expect the highest standard of care from my GP.

I understand that questionnaires will be posted to my home address for up to ten years and that the study researchers may contact me by telephone or email to remind me to complete the questionnaires or to ask me the questions over the telephone.

I understand that my GP will provide information about my progress, in confidence, to the central organisers. I understand that the information held by the NHS and records maintained by the Office of National Statistics may be used to keep in touch with me and follow up my health status.

I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Universities of Birmingham or Nottingham or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

~~Name of Patient~~	~~Date~~	~~Signature~~
Name of Person taking consent	Date	Signature

White copy to be returned to BCTU; pink copy for participant; yellow copy to be kept with GP note

APPENDIX 2: Original questionnaire that has retained the same questions with an additional question to ask about participants 'current menstrual state' and some formatting.

ECLIPSE – a study comparing the contraceptive coil with standard medical treatments for heavy periods

We would be most grateful if you could complete the enclosed questionnaires to help us find out your views about your health and how you feel about life in general.

Please read through the instructions at the beginning of each section carefully. The questionnaires are simple to complete. All you need to do is tick the appropriate box that best describes how you feel.

There are no right or wrong answers. We are just interested in your own views about your health and how you feel about life in general. Try not to dwell too long on any question, and choose the answer that comes closest to how you have been feeling generally.

It is important to get complete information so please answer all the questions even if some may seem repetitive or less relevant.

If you have any queries about completing this questionnaire do not hesitate to contact:

ECLIPSE Trial Office on 0121 415 9109/9110

Please return the completed questionnaire to:

ECLIPSE Trial Office, University of Birmingham Clinical Trials Unit, FREEEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, Birmingham, B15 2TT or use the envelope provided.

Thank you for your participation in this study.

The information collected in this questionnaire will remain strictly confidential.

ISRCTN86566246

Please check we have the correct address for you and amend it if necessary.

Date form completed: ..../..../....

.....

.....

.....

For Trial Office Use Only

ECLIPSE Trial No. Patient Initials

☐☐☐☐ ……..

Questions about your periods

In each of the following areas of health, select the statement that best applies to you and place a tick in the right hand side box provided. Please tick only one statement in each area.

1. Practical difficulties:

a. I have no practical difficulties, bleed no more than I expect and take no extra precautions. ☐

b. I have to carry extra sanitary protection with me but take no other precautions. ☐

c. I have to carry extra sanitary protection and clothes because of the risk of flooding. ☐

d. I have severe problems with flooding, soil the bedding and need to be close to a toilet. ☐

2. Social life

a. My social life is unaffected during my cycle. I can enjoy life as much as usual ☐

b. My social life is slightly affected during my cycle. I may have to cancel or modify my plans. ☐

c. My social life is limited during my cycle. I rarely make any plans. ☐

d. My social life is devastated during my cycle. I am unable to make any plans. ☐

3. Psychological health

a. During my cycle I have no worries I can cope normally. ☐

b. During my cycle I experience some anxiety and worry. ☐

c. During my cycle I often feel down and worry about how I'll cope. ☐

d. During my cycle I feel depressed and cannot cope. ☐

4. Physical health and wellbeing

a. During my cycle I feel well and relaxed. I am not concerned about my health. ☐

b. During my cycle I feel well most of the time. I am a little concerned about my health ☐

c. During my cycle I often feel tired and do not feel especially well. I am concerned about my health. ☐

d. During my cycle I feel very tired and do not feel well at all. I am seriously concerned about my health. ☐

5. Work/daily routine

a. There are no interruptions to my work/daily routine during my cycle. ☐

b. There are occasional disruptions to my work/daily routine during my cycle. ☐

c. There are frequent disruptions to my work/daily routine during my cycle. ☐

d. There are severe disruptions to my work/daily routine during my cycle. ☐

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6. Family life/relationships

a. My family life/relationships are unaffected during my cycle. ☐

b. My family life/relationships suffer some strain during my cycle. ☐

c. My family life/relationships suffers quite a lot during my cycle. ☐

d. My family life/relationships are severely disrupted as a result of my cycle. ☐

Questions about your overall health

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

1. In general, would you say your health is:

*(Please tick **one** box)*

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

2. Compared to 3 months ago, how would you rate your health in general now?

*(Please tick **one** box)*

- ☐ Much better than 3 months ago
- ☐ Somewhat better than 3 months ago
- ☐ About the same
- ☐ Somewhat worse now than 3 months ago
- ☐ Much worse now than 3 months ago

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

*(Please tick **one** box on each line)*

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b)	**Moderate activities**, such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than a mile**	☐	☐	☐

Please check that you have answered each question before going on to the next page

h)	Walking **half a mile**	☐	☐	☐
i)	Walking **100 yards**	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

4. During the <u>past 4 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

*(Please tick **one** box on each line)*		**All** of the time	**Most** of the time	**Some** of the time	**A little** of the time	***None of the*** time
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b)	**Accomplished less** than you would like	☐	☐	☐	☐	☐
c)	Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
d)	Had **difficulty** performing the work or other activities (eg it took more effort)	☐	☐	☐	☐	☐

5. During the <u>past 4 weeks</u>, how much time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

*(Please tick **one** box on each line)*		**All** of the time	***Most of the*** time	Some of the time	A little of the time	None of the time
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
b)	**Accomplished less** than you would like	☐	☐	☐	☐	☐
c)	Didn't do work or other activities as **carefully** as usual	☐	☐	☐	☐	☐

6. During the <u>past 4 weeks</u>, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(Please tick one box)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

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7. How much bodily pain have you had during the <u>past 4 weeks?</u>

(Please tick one box)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

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8. During the <u>past 4 weeks</u> how much did pain interfere with your normal work (including work both outside the home and housework)?

(Please tick one box)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question please give the one answer that comes closest to the way you have been feeling.

(*Please tick one box on each line)*

How much time during <u>the last 4 weeks</u>:	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a) Did you feel full of life?	☐	☐	☐	☐	☐	☐
b) Have you been a very nervous person?	☐	☐	☐	☐	☐	☐

	How much time during the last 4 weeks:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
c)	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d)	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e)	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f)	Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g)	Did you feel worn out?	☐	☐	☐	☐	☐	☐
h)	Have you been a happy person?	☐	☐	☐	☐	☐	☐
i)	Did you feel tired?	☐	☐	☐	☐	☐	☐

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc.)?

(Please tick one box)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

(*Please tick one box on each line)*

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a)	I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b)	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c)	I expect my health to get worse	☐	☐	☐	☐	☐
d)	My health is excellent	☐	☐	☐	☐	☐

Please check that you have answered each question before going on to the next page

Assessment of Sexual Activity

Although the following questions are sensitive and personal, they are important in determining how different treatments affect this part of your life. Please be assured that your responses to these questions will remain confidential.

	Yes	No
1. Are you currently married or having an intimate relationship with someone?	☐	☐
2. Have you changed your sexual partner in the last 6 months?	☐	☐
3. Do you engage in sexual activity with anyone at the moment?	☐	☐

If you answered yes to question 3, go to the next page.

I answered no to question 3. I am not sexually active at the moment because:

(Please tick as many of these items as apply)

a) I do not have a partner at the moment ☐

b) I am too tired ☐

c) My partner is too tired ☐

d) I am not interested in sex ☐

e) My partner is not interested in sex ☐

f) I have a physical problem which makes sexual relations difficult or uncomfortable ☐

g) My partner has a physical problem which makes sexual relations difficult or uncomfortable ☐

h) Other reasons (please describe) ☐

Please complete this section if you are sexually active (i.e. you answered yes to question 3). Please read each of the following questions carefully and tick the box that best indicates your sexual feelings and experiences during the past month.

During the past month:

		Very much	Somewhat	A little	Not at all
1.	Was 'having sex' an important part of your life this month?	☐	☐	☐	☐
2.	Did you enjoy sexual activity this month?	☐	☐	☐	☐
3.	In general, were you too tired to have sex?	☐	☐	☐	☐
4.	Did you desire to have sex with your partner(s) this month?	☐	☐	☐	☐
5.	During sexual relations, how frequently did you notice dryness of your vagina this month?	☐	☐	☐	☐
6.	Did you feel pain or discomfort during penetration this month?	☐	☐	☐	☐
7.	In general, did you feel satisfied after sexual activity this month?	☐	☐	☐	☐
		5 times or more	**3-4 times**	**1-2 times**	**Not at all**
8.	How often did you engage in sexual activity this month?	☐	☐	☐	☐
		Much more	**Somewhat more**	**About the same**	**Less than usual**
9.	How did this frequency of sexual activity compare with what is usual for you?	☐	☐	☐	☐
		Very much	**Somewhat**	**A little**	**Not at all**
10.	Were you satisfied with the frequency of sexual activity this month?	☐	☐	☐	☐

Any comments .....

.....

Please check that you have answered each question before going on to the next page

Some general quality of life questions

Please answer the questions by ticking one box in each group. Please indicate which statement best describes your own health today.

1. Mobility
   - I have no problems walking about ☐
   - I have some problems in walking about ☐
   - I am confined to bed ☐

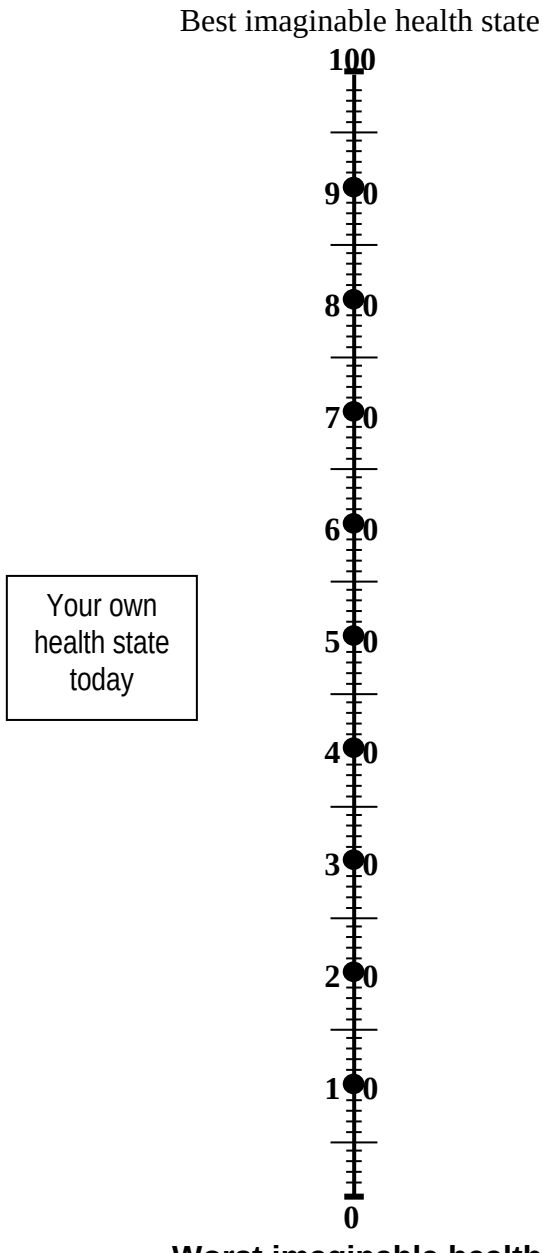
2. Self care
   - I have no problems with self-care ☐
   - I have some problems washing or dressing myself ☐
   - I am unable to wash or dress myself ☐

3. Usual activities e.g. work, study, housework, family or leisure activities
   - I have no problems with performing my usual activities ☐
   - I have some problems with performing my usual activities ☐
   - I am unable to perform my usual activities ☐

4. Pain/ Discomfort
   - I have no pain or discomfort ☐
   - I have moderate pain or discomfort ☐
   - I have extreme pain or discomfort ☐

5. Anxiety/ Depression
   - I am not anxious or depressed ☐
   - I am moderately anxious or depressed ☐
   - I am extremely anxious or depressed ☐

To help people say how good or bad their health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you could imagine is marked by 0. We would like you to indicate on the scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box to whichever point on the scale indicates how good or bad your current health state is.



We would be grateful if you could help our research into the best treatment for heavy periods by answering all of the following questions by ticking the appropriate boxes and providing any necessary additional information.

Thinking about the last 3 months:
Have you had to visit your GP? No ☐ Yes ☐

If YES, how many times did you visit your GP? .....

What for? .....

Has your GP had to visit you at home? No ☐ Yes ☐

If YES, how many times did your GP visit you? .....

What for? .....

Have you had to take time off work because of your heavy periods?
No ☐ Yes ☐ Not currently working ☐

If YES, how many days have you taken off work in the last three months? .....

Have your heavy periods prevented you from doing your other daily activities?
No ☐ Yes ☐

If YES, how many days in the last three months? .....

On average how many tampons/sanitary towels do you use per day of your period? .....

How regular is your cycle?

- ☐ Regular, I know when to expect my period
- ☐ Fairly regular, my period starts within a few days of when I expect
- ☐ Irregular, I cannot predict when my period will start
- ☐ I have bleeding on and off all the time

Do you take any drugs for pain relief during your periods?
No ☐ Yes ☐

If YES, what drugs? Ibuprofen (Neurofen) ☐ Paracetamol ☐ Aspirin ☐

Other (please write the name) .....

Pain during your periods

Please place a mark (x) on the line shown below to indicate how much pain you had in the last month. One extreme of the line represents “no pain at all” while the other represents “as much pain as you can possibly imagine”.

No pain at all ⊢——————————————⊣ Worst imaginable pain

Please turn over for remaining questions

Since you last completed an ECLIPSE questionnaire (upon entering the trial 6mth/1 year/2 years/5 years) have you been to hospital? No ☐ Yes ☐

If YES, was this for a gynaecological (women's health) reason? No ☐ Yes ☐

If NO, can you briefly describe the reason

.....

If YES, you have been to hospital for a gynaecological reason since you last completed an ECLIPSE questionnaire, what was this for?

Tests or investigations:

☐ Laparoscopy (camera via belly) ☐ Hysteroscopy (camera via vagina)

☐ Ultrasound scan

Other (please describe) .....

Treatment or surgery other than hysterectomy or endometrial ablation:

☐ Removal of polyps ☐ Removal of fibroids

☐ Treatment of endometriosis

Other (please describe) .....

Did you have to stay in hospital for the treatment? No ☐ Yes ☐

If YES, how many nights? .....

Have you attended any follow-up clinics No ☐ Yes ☐

If YES, how many times? .....

☐ Hysterectomy

☐ Endometrial ablation (removal of lining of womb)

If you have had a hysterectomy or endometrial ablation, roughly when did you have this surgery? (please give your best estimate if unsure) .....

How many nights did you stay in hospital? .....

If you made two or more visits to hospital, please tell us about each visit – you can use the space at the end if necessary

Have you experienced any hot flushes/night sweats? No ☐ Yes ☐

Have you become pregnant? No ☐ Yes ☐

If YES, when did you become pregnant? .....

Please turn over for remaining questions

What treatment(s) do you take for your heavy periods? Indicate as many as applicable.

- ☐ Mirena coil
- ☐ Ponstan (mefenamic acid)
- ☐ Contraceptive pill (any brand)
- ☐ Norethisterone
- ☐ No treatment
- ☐ Other (Please write the name) .....
- ☐ Copper coil
- ☐ Cyklokapron (tranexamic acid)
- ☐ Depo-provera
- ☐ Cerazette

Have the treatment(s) that you take for your heavy periods changed since you last completed an ECLIPSE questionnaire (upon entering the trial 6mth/ 1 year/ 2 years/ 5 years)?

No ☐ Yes ☐

If YES, when did you change treatment .....

(please give your best estimate if unsure of exact date)

If YES, what treatment(s) were you taking before? *Indicate as many as applicable*

- ☐ Mirena coil
- ☐ Ponstan (mefenamic acid)
- ☐ Contraceptive pill (any brand)
- ☐ Norethisterone
- ☐ No treatment
- ☐ Other (Please write the name) .....
- ☐ Copper coil
- ☐ Cyklokapron (tranexamic acid)
- ☐ Depo-provera
- ☐ Cerazette

If YES, why have you changed your treatment? *Indicate as many reasons as applicable*

- ☐ Lack of effectiveness
- ☐ Irregular bleeding
- ☐ Pelvic pain
- ☐ Skin allergy
- ☐ Coil expulsion
- ☐ Pelvic Infection
- ☐ Other side effects (please describe)
- ☐ Other (please give reason)
- ☐ Vomiting/diarrhoea
- ☐ Prolonged bleeding
- ☐ Depression/ mood swings
- ☐ Weight gain
- ☐ Thread problems

Thank-you for completing this questionnaire.

This page is meant to be blank
You can use it for any other comments you may have

Please check that you have answered each question before going on to the next page

Please check that you have answered each question before going on to the next page

APPENDIX 3: Original PIS for ECLIPSE Trial

ECLIPSE – A STUDY COMPARING THE CONTRACEPTIVE COIL WITH STANDARD MEDICAL TREATMENTS FOR HEAVY PERIODS

Invitation to participate in the ECLIPSE study

You are invited to take part in a research study to find out what is the best treatment for heavy periods (menorrhagia). This study, called ECLIPSE, compares a hormone releasing contraceptive coil with standard medical treatments. The study is optional - you do not have to take part, nor give a reason why, if you decide not to. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it would involve if you do choose to take part. Please take your time to read this information carefully. If there is anything that is not clear, or you would like more information, you should ask your GP or nurse for advice.

What is the purpose of the study?

There are two main ways in which doctors can treat women with heavy periods. Up to now, the usual treatment has been medical these include the contraceptive pill and various non-hormonal drugs. More recently, a hormone releasing coil, which is fitted inside the womb has been used. All these treatments are known to reduce the amount of bleeding a woman has during her period.

What is the recommended treatment for heavy periods?

Recently, the National Institute for Health and Clinical Excellence (NICE) has reviewed all of the treatments available for heavy periods and provided advice for doctors and women. They recommend all of the treatments being compared in the ECLIPSE trial as acceptable choices. They also recommend taking part in the ECLIPSE Trial as a way of generating better evidence on which of the treatments being compared is best on balance. For women not taking part in ECLIPSE, they suggest that the coil might be considered first (if treatment of at least one year is anticipated) followed by tablet treatments or injections if the contraceptive pill is unsuitable. This recommendation is based on the coil being a cheaper option overall. However, NICE concluded that the tablet and injection treatments are as effective as the coil at reducing bleeding. What we do not know is how the coil affects other aspects of a woman's life compared to tablet and injection treatments. Because it is a newer treatment, we need to make sure that there are no unexpected side-effects. The only reliable way to find out which treatments provide the best control of bleeding with the fewest unwanted side-effects is through a research study such as ECLIPSE.

The ECLIPSE study aims to find out:

- Which treatment has the best overall effect on women's quality of life
- How satisfied women are with each of the treatments
- If women can avoid the need for surgery (hysterectomy or other surgical treatments) by using these treatments
- Which is the most cost-effective treatment, based on accurate UK information

ECLIPSE aims to study a large number of women to get reliable results and to follow their experience over the long-term to make sure that there are no unexpected long-term risks from any of the treatments. NICE will use this information when they next update their recommendations.

What exactly are the treatments being compared?
The study compares two groups of treatment, which, have been shown to reduce the amount of bleeding during periods:

- Standard treatments: There is a choice between the contraceptive pill, which is taken regularly: two non-hormonal drugs, tranexamic acid or mefenamic acid, that women take during their periods a contraceptive injection (also called Depo-Provera) or non-contraceptive tablets (norethisterone).
- A special coil, which is fitted inside the womb by your doctor, or another doctor specialising in this procedure, which slowly releases small amounts of a hormone (called levonorgestrel) over a five-year period. This coil also works as a contraceptive.

Why am I being invited to take part?
All women visiting their doctor, or attending gynaecological outpatient clinics, because they feel that they need treatment for heavy periods are being invited at centres taking part in ECLIPSE. There are more than one hundred GPs and Consultant Gynaecologists taking part in the ECLIPSE study, which is being run across the Midlands and Trent Regions and aims to recruit 570 women.
Do I have to take part?
If you do not wish to take part, your doctor will not hold this against you and your decision will not affect the standard of care you will receive. Similarly, if you do decide to take part, you are entitled to withdraw from the study at any time, without having to give a reason, and this will not affect the standard of your medical care in any way. You do not have to make up your mind now. Please take this information home and discuss it with others if you wish. If you do decide to take part, please make another appointment with your doctor as soon as you can.
If I take part, will I have the coil or tablet treatment?
Women who take part in the study are allocated to one of two groups at random by the central study office. There is an equal chance of being allocated to the coil group or the tablet / injection treatment group. Neither you nor your GP will know which of the groups you will be in until after you have been entered into the study. This means that doctors can't choose which women will receive which treatment and this makes the results much more reliable. This is called a 'randomised clinical trial' and it is the standard medical research method for comparing treatments. If you are allocated to the tablet / injection treatment group, the treatment will depend on whether you require contraception or not. If you do need to prevent pregnancy, your doctor will discuss whether the contraceptive pill or the contraceptive injection is more appropriate for you. If you don't require contraception, then the choice is between the non-contraceptive tablets (norethisterone) or the non-hormonal tablets. If you decide to take part, and are happy that you understand what will be involved, you will be asked to sign a consent form to confirm this.
What would taking part in the study involve?
Before you have any treatment, you will be asked to complete three confidential short questionnaires to assess how much your heavy periods affect your quality of life, what additional treatment you have taken for your periods, whether the treatments affect your sexual health and your overall state of health. The same questionnaires will be sent to you at home at 6 months and then 1, 2, 5 and 10 years after the first appointment. This long-term follow-up is important to assess how these treatments affect women over time.
If you are allocated to the standard treatment group, and you are to receive tablets, your doctor will give you a prescription and see you at 3 and 6 months to see how well the treatment is working. If you are in the standard treatment group but are having the contraceptive injection, you will see the doctor every three months to have these. If you are

allocated to the coil group, you will be given an appointment to have the coil fitted by another doctor specialising in this procedure. This maybe at another practice, a family planning clinic or local hospital. You will then be asked to see your GP 6 weeks afterwards to make sure everything is OK. You will not need any additional clinic visits because you are taking part in the ECLIPSE study. You will of course be able to consult your GP at any other time if you or your GP believe this may be appropriate. If the treatment you receive does not suit you then your GP will consider other treatments, or may consider referring you to see a gynaecologist at a local hospital.

Does fitting of the coil hurt?

The coil usually takes around 10 minutes to fit. Some women may experience period-like pain during the procedure but this normally settles within a few minutes to a few hours. To reduce the risk of pain, your doctor may give you a painkiller beforehand, or afterwards, or use a pain-relieving cream. If the pain did become unacceptable your doctor would immediately stop the procedure.

Is the coil safe?

Tens of thousands of women have had coils fitted for contraception with very few problems reported. Most women have spotting (a small amount of blood loss) or an irregularity of their bleeding pattern for the first 3-6 months after the coil is fitted. before a reduction in blood loss is achieved. Overall, there are likely to be fewer days bleeding in each month and eventually, most women's periods stop completely. The coil will not interfere with any medication you are taking, or any other medical conditions. It is also a contraceptive device and therefore you are very unlikely to become pregnant while you have the coil in place. So, if you think that you may wish to try for a baby in the next five years, you should not take part in this study. The coil should be replaced every five years if required. You should read the manufacturer's information leaflet about the coil, which is included with this Information Sheet.

Are there any side effects from the tablet treatments or the injection?

The tablet treatments are also safe forms of treatment with very few problems reported. Some women may not be suitable for some treatments – for example, older women who smoke may not be prescribed the combined contraceptive pill but may be offered the contraceptive injection (Depo-Provera) instead. Women who use Depo-Provera tend to have lower bone mineral density than women of the same age who have never used it, but this recovers to some extent when the injections are stopped. Your doctor will review your history and you will only be prescribed those treatments thought to be appropriate for you.

You should read the manufacturer's information leaflet about the tablets, and the injection, which are included with this Information Sheet.

Are there any benefits for me from taking part in the study?

The treatments being compared in the ECLIPSE study are the ones recommended by the Royal College of Obstetricians and Gynaecologists and by NICE and all are widely used and known to help reduce blood loss. There are no other treatments recommended by the RCOG and so whichever treatment you receive will be best current practice. The main benefit from the study will be that the information obtained will help us to treat women with heavy periods more effectively in the future.

Will participation in the study affect my legal rights?

No, you have the same legal rights whether or not you take part in the study. If you are not satisfied with any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you: ask to speak to the complaints manager for the clinic. Taking part in ECLIPSE should not affect any private medical insurance you may have, but you are advised to contact your medical insurance provider to confirm this.

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, you and your doctor will decide your future care. If you decide to continue in the study you will be asked to sign an updated consent form.

Will information about me be kept confidential?

Yes, all information collected in the study will remain strictly confidential in the same way as your other medical records. If you agree to take part, your doctor will send basic information about you and your condition to the study's central organisers at the University of Birmingham Clinical Trials Unit. This information will be put into a computer and analysed by the ECLIPSE study office staff. The questionnaires will not contain your name and will be identified using a code number and will not be seen by your GP. All information will be held securely and in strict confidence. No named information about you will be published in the trial report. Information held by the NHS and records maintained by the Office of National Statistics may be used to keep in touch with participants and follow up their health status. Occasionally, inspections of clinical trial data are undertaken to ensure that, for example, all participants have given consent to take part. But, apart from this, only the study organisers will have access to the data.

What will happen to the results of the research study?

The results will be reported in a medical journal. It is expected that the first results will be published about two years after the study closes to recruitment. Everyone who took part will then be told the results in a newsletter that will be posted directly to them.

Who is funding and organising the research?

The ECLIPSE study researchers are receiving a grant from the National Health Service's Health Technology Assessment programme to enable them to carry out this study. The central study organisers are based at the Universities of Birmingham and Nottingham. The Clinical Trials Unit at the University of Birmingham will collect and analyse the data. The doctors involved are not being paid for recruiting women into the study. Patients are not paid to take part either, but their help in finding out more about how best to treat heavy periods is much appreciated. The study has been reviewed and approved by the South West Multicentre Research Ethics Committee and local research ethics committees.

Do you have any other questions?

Having read this leaflet, it is hoped that you will choose to take part in the ECLIPSE trial. If you have any questions about the study now or later feel free to ask your doctor or nurse. Their names and telephone numbers are given below. You do not have to decide whether you wish to take part straight away. If you would prefer to delay your decision, perhaps to discuss with friends or relatives, then you can take this information home and make an appointment to come back later.

Doctor: .....

Nurse: .....

Telephone:

NOTES:

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