NIHR HTA Programme

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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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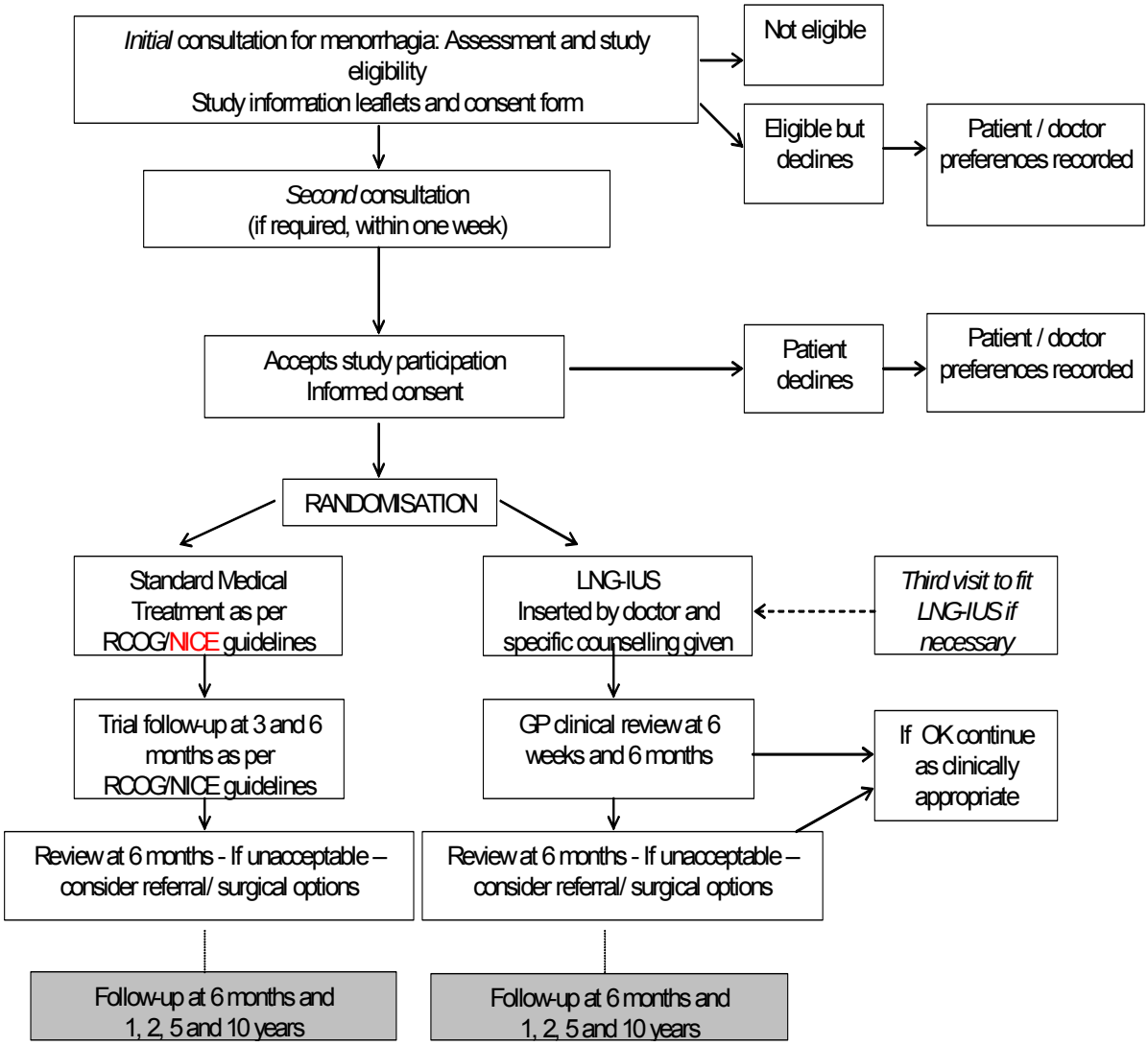
Effectiveness and Cost-effectiveness of Levonorgestrel containing Intrauterine system in Primary care against Standard trEatment for menorrhagia–The ECLIPSE Trial

PROTOCOL

The ECLIPSE trial is a large, pragmatic, "real-life" community based trial that will determine reliably whether a (Levonorgestrel-releasing intrauterine system) LNG-IUS is preferable to standard medical treatments (i.e. tranexamic acid, mefenamic acid, contraceptive pill or injectables as per RCOG / NICE guidelines) for menorrhagia. All of these treatments are known to reduce the amount of bleeding a woman has during her period. However, the treatments can also affect other aspects of a woman's life and what the ECLIPSE study aims to find out is which treatments provide the best control of bleeding with the fewest unwanted side-effects, over the short, medium and long term. Another reason to study a lot of women over a long period is to make sure that there are no unexpected long-term risks from any of the treatments.



Version Number

9.0 Amendment 8 dated 24.0912 Amendment to Addition of sub-study to investigate the appropriateness of the instruments used to measure outcomes in HMB

Protocol Versions

1.0 Submitted to MREC

1.1 Incorporates MREC comments

1.2 Version 1.2 Dated 26/07/04

1.21 Minor typographical alterations

2.0 Amendment 1. Extension to eligibility criteria

2.1 Amendment 2. Extension to eligibility criteria dated 16/02/06 (minor alterations)

3.0 Amendment 2.1 dated 19/06/06. Extension to eligibility criteria

4.0 Amendment 3 dated 03/04/07 response to NICE and revised sample size calculation

4.1 dated 16/05/07 response to NICE and revised sample size calculation

4.2 dated 11/07/07 (new contact details)

5.0 Amendment 4 dated 12/09/07. Inclusion of high dose progestogens and injectables in standard treatment arm

6.1 Amendment 5A dated 21.07.08 inclusion of further information relating to Eclipse Protocol v5.0 dated 12.09.07

7.0 Amendment 6 dated 11.01.11 Amended SAE form and addition of pregnancy notification form

8.0 Amendment 7 dated 15.05.12 Additional of sub-study to investigate the appropriateness of the instruments used to measure outcomes in HMB

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NHS Research and Development Health Technology Assessment Programme (HTA)

Sponsor and Sponsor's Roles

The University of Birmingham replaced the Department of Health as sponsor, with effect from 03/04/07. Prof J.K Gupta, Consultant Gynaecologist, is the Chief Investigator.

The University of Birmingham is responsible for obtaining necessary approvals and for pharmacovigilance, the Trial Management Committee is jointly responsible for overseeing good

clinical practice and the Investigators are responsible for obtaining informed consent and care of the participants.

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V9.0 dated 24.09.12.

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PROTOCOL SIGNATURE PAGE

Protocol Version 9.0 dated 24.09.12

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol.

Site Investigator (PI)	Date Signed

ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
ASR	Annual Safety Report
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
BWH	Birmingham Women's Hospital
CA	Competent Authority
CI	Chief Investigator
COCs	Combined oral Contraception
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial Investigational Medicinal Product
DMEC	Data Monitoring and Ethics Committee
EQ-5D	EuroQol Questionnaire
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDG	NICE guidelines development group
GP	General Practitioner
HMB	Heavy Menstrual Bleeding
ISRCTN	International Standard Randomised Controlled Trial Number
LNG-IUS®	Levonorgestrel Intrauterine System
MBL	Menstrual Blood Loss
MHRA	Medicines and Healthcare Products Regulatory Authority
MRC	Medical Research Council
MREC	Multicentre Research Ethics Committee
NICE	National Institute for Health and Clinical Excellence
PCT's	Primary Care Trusts
PI	Principal Investigator – the local lead investigator for the ECLIPSE Trial
PIS	Participant Information Sheet
Qol	Quality of Life
RCOG	Royal College of Obstetrics and Gynaecology
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

1. BACKGROUND

1.1. Menorrhagia

Menorrhagia (heavy menstrual bleeding - HMB) results in much discomfort, anxiety, inconvenience, financial burden and general disruption in the lives of sufferers. For clinical purposes, HMB should be defined as excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms. Where no organic pathology is present, the term dysfunctional uterine bleeding is used, whereas abnormal uterine bleeding includes that caused by uterine pathology e.g. fibroids, or genetic factors e.g. von Willebrand disease.[1-3] Various cohorts studies have reported prevalence data ranging from 4-51%, although it is acknowledged that differences in definition, measurement (objective versus subjective), clinical and cultural setting will undoubtedly influence reporting.[4] It is widely accepted that only about half seek help from health care providers.[5] A figure of 30% is widely cited for abnormal uterine bleeding[2] and 6.5% for excessive periods.[4]

Heavy menstrual bleeding accounted for 60% of referrals to gynaecologists, from the perspective of the women in a cross-sectional study, although a third of women who did not report heavy periods as a severe problem or believe their referral was due to HMB were ultimately diagnosed as having dysfunctional uterine bleeding, highlighting the mismatch in perception of women and doctors.[6] The number and cost of consultations and treatments impose substantial demands on the NHS. From 1989-90 to 1994-95 an average of 23,056 hysterectomies a year were performed for menorrhagia in the NHS England. Since 1995-6, when endometrial ablation became available, there has been a sustained and substantial fall in this number. In 2002-3, 8332 hysterectomies and 4921 endometrial ablations were performed, representing a 64% and 43% reduction in the number of hysterectomies and procedures for menorrhagia respectively, compared with 1989-90.[7]

1.2. Current therapy for Menorrhagia

There are many treatments used for menorrhagia, including medical therapies and surgical procedures. In early 2007, the National Institute for Health and Clinical Excellence (NICE) produced clinical guidelines for the management of heavy menstrual bleeding.[8] In these guidelines, pharmaceutical treatments were recommended as the first line of therapy, regardless of whether the women presents in primary or secondary care. Endometrial ablation may be considered as initial therapy, although only after full discussion of the risks and benefits of this and other treatments. Hysterectomy should not be offered as first line treatment. It has been estimated that the cost of implementation of this guideline to the NHS will be £8.2 million.[8]

Initial management of menorrhagia is usually medical, using either combined oral contraceptives (COCs), tranexamic acid or mefenamic acid or the LNG-IUS, as also recommended by Royal College of Obstetrics and Gynaecology (RCOG) guidelines. The effectiveness of other drug therapies is limited, and high dose norethisterone and injected long-acting progestogens are only advised if all other medical treatments are unsuitable or unacceptable.[8]

1.3. Levonorgestrel-Releasing Intrauterine Systems for Menorrhagia

Levonorgestrel-releasing intrauterine systems (LNG-IUS; tradename: Mirena®) were developed primarily as a contraceptive devices, but have also been licensed for use in primary menorrhagia.[9]

In many studies now, the LNG-IUS has been shown to significantly reduce menstrual blood loss from baseline, by up to 90%, although no placebo controlled or no treatment

comparisons exist. A systematic review of the effectiveness of LNG-IUS in menorrhagia[10-11] identified 34 studies of LNG-IUS for women with heavy menstrual blood loss (≥ 80ml per cycle) that reported menstrual blood loss (MBL). Of the ten studies of women with confirmed menorrhagia, only five studies were randomised controlled trials.[12-16] In the four randomised controlled trials reporting MBL reduction, the range was 79% to 96% in the LNG-IUS group. The LNG-IUS is also unquestionably an effective contraceptive with some evidence suggesting that it is protective against transmission of sexually transmitted infections and may also have some effect on dysmenorrhoea and pelvic pain.[17]

The adverse events of interest fall into two categories: those related to an intrauterine device, such as dysmenorrhoea, irregular bleeding, ectopic pregnancy and expulsion of the device; and those related to progestogens, such as bloating, weight gain and breast tenderness. The LNG-IUS releases 20 µg per day of levonorgestrel and so drug-related adverse events are assumed to be less frequent than with the oral preparations of progesterone, which result in higher serum concentrations. The trial comparing LNG IUS with norethisterone[12] found no significant difference in the rate of mood swings or withdrawal from treatment because of adverse events. However, breast tenderness and intermenstrual bleeding and irregularity were significantly more common in women with the LNG-IUS at three months follow up.

The device is effective as a contraceptive for five years, and is licensed for this indication, after which it should be removed.[18] Fertility is quickly restored after removal. The LNG-IUS is widely used with a total of 76,300 inserted in England and Wales during 2005[19].

1.4. Effectiveness of LNG-IUS compared with other medical treatments

A systematic review[20] used in the NICE guidelines to describe the clinical effectiveness of LNG-IUS compared with pharmaceutical treatments identified 4 randomised controlled trials (RCTs)[12,21,22,15]

Irvine 1998	LNG-IUS vs norethisterone, n=44, 3 month follow-up
Cameron 1987	Progestasert vs mefenamic acid vs danazol vs norethisterone, n=30, for 2 cycles, groups not comparable at baseline
Reid 2004	LNG-IUS vs mefenamic acid, n=51, 6 month follow-up, company sponsored
Lahteenmaki 1998	LNG-IUS vs continuing existing medical therapy for women on waiting list for hysterectomy, n=56, 6 month follow-up

This collection of small trials represents the sum of evidence for LNG-IUS over other medical therapies. There is no advantage of norethisterone over tranexamic acid or mefenamic acid[20] and it has only a level 3 recommendation in the Royal College of Obstetrics and Gynaecology evidence based guidelines. Progestasert is not available in the UK.

Quality of life (QOL) is not discussed in the NICE guidelines for any of the four trials identified in the review. The trial by Lahteenmaki did report QOL, measured using visual analogue scales and EuroQol EQ-5D. The trial design selected women awaiting a hysterectomy and offered them the option of randomisation between continuing their existing treatment and LNG-IUS. The lack of blinding and choice of treatment is likely to have influenced the women's attitude to treatment, therefore the study is inherently biased for QOL against existing therapy.

The most relevant trial is that of Reid, yet this only compared LNG-IUS against one medical therapy in a small group of women. There was a significant difference in the reduction of objective menstrual blood loss (MBL) from baseline between the two groups, favouring LNG-IUS, but the data were too skewed to be combined in meta-analysis. The

review calculated the odds ratio (OR) for amenorrhoea (> 3 months) as 8.67 (95% CI 1.52 to 49.35) in favour of LNG-IUS. This study is the only one to report side effects in any detail: no significant differences were seen for nausea, diarrhoea, ovarian cysts, respiratory infections and mood swings but significant differences in favour of oral medication for breast tenderness, irregular periods or intermenstrual bleeding and pelvic pain. The author of this trial was in receipt of funding from the manufacturer of the LNG-IUS.

The OR for proportion unwilling to continue with treatment (either mefenamic acid or norethisterone, n = 91) was 0.27 (95% CI 0.10 to 0.67) in favour of LNG-IUS. The OR for the proportion of women satisfied with treatment (one RCT, n = 40) was 2.13 (95% CI 0.62 to 7.33) in favour of LNG-IUS over norethisterone..

The NICE guidelines development group (GDG) stated that in their interpretation of the evidence for pharmaceutical treatments, a high value was placed on reduction of menstrual blood loss and minimising adverse effects. The GDG based their assessment firstly on the clinical effectiveness of treatments and secondly on the cost-effectiveness of treatments. The results of the systematic review showed that LNG-IUS, mefenamic acid, tranexamic acid and COCs could be considered equivalent in terms of effectiveness.

1.4.1 Evidence on cost effectiveness

The only trial to incorporate a cost-effectiveness analysis was the Finnish trial cited above[23], comparing a LNG-IUS with hysterectomy There was no statistically significant difference in quality of life scores at 5 years, as measured by the EQ-5D instrument, between the two treatment groups. Mean direct costs in the LNG-IUS arm remained significantly lower ($1,892) than the hysterectomy arm ($2,787), despite 40% of women in the LNG-IUS arm going on to have a hysterectomy. This trial, however, compared LNG-IUS with hysterectomy in women referred to hospital. No economic analysis relevant to the use of LNG-IUS in a primary care setting is available nor has the relative cost-effectiveness of LNG-IUS relative to medical treatment been assessed.

The health economic modelling performed by the NICE GCG showed that the LNG-IUS was the more effective treatment option when long-term use of a treatment was required. However, as no UK based comparisons of LNG-IUS with any other medical or surgical treatment strategies were identified, a decision analytic model was developed to examine the cost-effectiveness of pharmaceutical treatments as a first-line treatment for menorrhagia. The results of their model showed that LNG-IUS generated more quality adjusted life years (QALYs), at a lower cost, than any other pharmaceutical treatment strategy.

The use of a model based analysis is to be supported as there is clearly much uncertainty relating to the costs and benefits of treatments for HMB and a modelling framework is ideally suited to demonstrate, and explore the importance of, the inherent uncertainty. The GDG developed a straightforward model, in consultation with clinical colleagues, and have populated the model with data (predominantly from the study by Hurskainen *et al*), assumptions and opinions. The results suggest a considerable cost increase and a considerable benefit (in terms of QALYs gained) through the routine first line use of LNG-IUS. The base case result is £840 per QALY gained. The uncertainty in this result is, however, not explored at all and so the result could be highly misleading.

It is clear from the presented analyses that the uncertainties inherent in these clinical and policy questions are considerable, which should be explored by sensitivity analysis. However, the analysis only explored uncertainty in a rudimentary and opaque fashion, stating that there is some robustness of the results to variation in the model inputs. However, the detail is not provided and so it cannot be established with confidence that

the GDG's interpretations are appropriate. The analysis uses only point estimates for model inputs and so an important and missing element from this model-based analysis is a probabilistic sensitivity analysis (PSA), sampling from distributions placed around the main inputs. This would begin to demonstrate more fully the uncertainties in the model results which are currently hidden. The use of PSA does not by itself, however, overcome the central weakness of the effectiveness evidence feeding the model and such analytic extensions should not be viewed as a substitute for high quality randomised controlled trial-based data.

Relative measurements of cost and clinical effectiveness are summarized in Table 1

Table 1 Relative Clinical Effectiveness and Costs of Medical Treatments for Menorrhagia

Medical Treatment	Reduction in MBL (%)	Proportion satisfied with treatment at 1 year	Initial stage cost (3mth treatment/ follow-up)	Total cost at 5 years (discounted present value)
COC	43[31]	0.30 (0.10-0.68)	£56.31 (£55.44–£57.18)	£284.61
LNG-IUS	71-96[13]	0.68 (0.61-0.75)[23]	£229.66 (£206.69-£252.63)	£325.31
Tranexamic Acid	47 (95% CI 47-52)[32] 34-59[33]	0.77 (0.67-0.87) [34]	£26.16 (£23.28-£29.04)	£490.13
Mefenamic Acid	29 (95%CI 28-30)[32]	0.74 (0.64-0.84)	£57.74 (£47.47-£58.01)	£222.69

1.5. Effectiveness of LNG-IUS compared with surgical treatments

Eight RCTs were included in a systematic review that compared pharmacological treatments with surgery (hysterectomy, ablation) in secondary care settings.[24] Two of these preceded the introduction of the LNG-IUS[25-26] and showed that the difference between pharmaceutical treatments and surgery diminished over time until, by 5 years follow-up, there was no statistical difference between the groups .

Six other RCTs were included in the review that compared LNG-IUS with surgery (hysterectomy, ablation) in secondary care settings, with the conclusion that the treatments were equivalent.[27,13,28-30,23] The figures showed that objective measurement of MBL at 12 months was in favour of surgery (one RCT, *n* = 223, OR 25.7 [95% CI 1.5 to 440.0]). Also, the subjective measurement of MBL at 12 months was in favour of surgery (three RCTs, *n* = 189, OR 3.99 [95% CI 1.53 to 10.38]). However, results from QoL measures were more mixed, with no difference being found between groups on the SF36 scale for general health, physical function, mental health, vitality and physical role limitation. Statistically significant differences were found between the groups, on the SF36 scale, for emotional role (*n* = 269, WMD 9.67 [95% CI 1.65 to 17.69]), social function (*n* = 274, WMD 3.64 [95% CI −1.14 to 8.43]) and bodily pain (*n* = 274, WMD 6.98 [95% CI 1.68 to 12.29]) in favour of surgery. In addition, women using LNG-IUS were more likely to undergo additional surgery at 12 months (*n* = 423, OR 0.11 [95% CI 0.04 to 0.30]) and were less likely to have reported adverse effects (OR 0.24 [95% CI 0.11 to 0.49]).

The review concluded that 'surgery reduces menstrual bleeding at one year more than pharmaceutical treatments, but LNG-IUS appears equally beneficial in improving quality of life and may control bleeding as effectively as conservative surgery over the long term".[24] The NICE GDG recognised the effectiveness of LNG-IUS in controlling MBL, as shown by RCT evidence. However, the GDG discussion focused on the high level of subsequent

surgery associated with pharmaceutical interventions, and on data suggesting that women who delay having surgery in order to try pharmaceutical treatment (in a secondary care setting) and then subsequently have surgery have worse long-term QoL than women who have immediate surgery. However, it was noted that this interpretation was based on data obtained prior to LNG-IUS being available. NICE recommends that endometrial ablation may be offered as an initial treatment for HMB after full discussion with the woman of the risks and benefits and of other treatment options and that hysterectomy should not be used as a first-line treatment solely for HMB.[8]

1.6. The need for a large trial of LNG-IUS versus standard treatment for the initial management of menorrhagia

1.6.1 Rationale

The systematic review of the effectiveness of LNG-IUS in menorrhagia highlighted the lack of evidence on the relative benefits of LNG-IUS compared to medical treatment and recommended large pragmatic trials.[10-11] The LNG-IUS is an effective, relatively safe treatment for menorrhagia, at least in the short term, although less effective than endometrial ablation. However, women with menorrhagia often have additional concerns, which may be altered by treatment. These include the presence or absence of pain, risk of sexually transmitted disease and, above all, reproductive function. It is by no means certain that improvements in a symptom-specific outcome such as MBL will necessarily translate into an improvement in a woman's overall quality of life or her need to seek further treatment.

Moreover, the consequences of menorrhagia and its treatment extend for many years, and so a treatment that appears to be effective at one year may merely delay, not prevent, a definitive solution such as surgical intervention. In relation to the LNG-IUS, there may be 'phase shifting' of the patient's journey. For example, once the device is removed some patients' symptoms may recur, resulting in later surgery. This means that it is essential to determine and compare the long-term consequences of different treatments over a prolonged period of time appropriate to the long natural history of menorrhagia.

It is also unclear whether treatment of women presenting to GPs with menorrhagia with a LNG-IUS is associated with better long-term outcome than medical treatment. No randomised controlled trial has compared initial therapy using a LNG-IUS with drug treatments over a long timeframe. The LNG-IUS is slightly more difficult to insert than standard contraceptive coils and specific training for GPs is required.[8] A LNG-IUS is occasionally associated with troublesome menstrual irregularities, especially in the first few months, and is often removed for this reason. Given the potential complications, better evidence to establish the effectiveness of the LNG-IUS as a first-line therapy is needed before it becomes widely used in this setting.

The cost-effectiveness analysis on which NICE based their recommendation for LNG-IUS as first line therapy draws very heavily on the Hurskainen trial. This was a relatively small trial (n=236 women in total) which directly compared LNG-IUS and hysterectomy. Thus, the trial only includes women who were willing to be randomised between LNG-IUS and hysterectomy, and so it seems reasonable to raise concerns in relation to the appropriateness of using data from that trial in the context of first line treatments for HMB. This would be less problematic if data were also being drawn from more relevant trial sources or if the uncertainties inherent in using these data had been fully explored in the model-based analyses. On the former, there is clearly a paucity of appropriate data on which to draw currently and so the authors rely solely on this one small trial. This highlights the central importance of the ECLIPSE study in providing clinically relevant and

robust data for the UK setting. Indirectly, the NICE guideline development work reveals the need to support the continuation of ECLIPSE in order that decision making in this clinical area can be founded on a stronger and more reliable effectiveness and cost-effectiveness evidence base.

1.6.2 The choice of question to be addressed

It is apparent that a randomised controlled trial should take into account a range of patient needs and preferences. These include:

- Women's preferences for contraception: some desire the maintenance of fertility, some require contraception contemporaneously with relief from menorrhagia while some others may want to be sterilised.
- Long-term assessment of the treatment "pathway", with different initial policies.
- Patient based outcome measures that identify the impact of treatment on overall quality of life and further treatment decisions.
- The initial management of menorrhagia in primary care.
- The clinical and cost-effectiveness, and acceptability of treatment policies.

The choice of comparator needs to reflect current practice. The treatment objective in menorrhagia is to alleviate heavy menstrual flow and, consequently, to improve quality of life. Iron deficiency anaemia must also be prevented. In 1998, the RCOG published evidence-based guidelines on the initial management of menorrhagia, whether initiated in a primary care setting or after referral to a hospital outpatient department. In the treatment algorithms for menorrhagia, there is a choice available to the clinician between medical treatments (mefenamic acid, tranexamic acid), combined oral contraceptives and the LNG-IUS. In 2007, NICE recommended, on the basis of cost-effectiveness, that the LNG-IUS be considered as the first line therapy; however the relevance and interpretation of the data can be questioned. To evaluate the effectiveness of LNG-IUS against best medical treatment reliably, it is necessary to randomly allocate the treatment, as opposed to an uninformative *ad hoc* decision based on clinician and/or patient preference.

2. TRIAL DESIGN

2.1. Design

ECLIPSE is a randomised controlled trial (RCT) in primary care assessing the clinical and cost-effectiveness of LNG-IUS for menorrhagia compared with standard medical treatment, based on the RCOG guidelines.

All women will receive standard appropriate clinical assessment and advice. Women randomised to the LNG-IUS will have this inserted by a GP in their practice or by their local community family planning clinic after GP referral or by a gynaecologist. The 'standard medical treatment' group will be prescribed medical treatments according to the RCOG/ NICE guidelines, where either tranexamic acid, mefenamic acid, a combined oral contraceptive pill, high dose progestogens (15mg norethisterone given between day 5-26 of cycle) or injectable progestogen (Depo-Provera) will be offered according to algorithms based upon the need for contraception or existing non-hormonal IUS (see section 5.1.1).[35] Reasons for non-participation such as patient or doctor treatment preferences will be collected.

Follow-up will be by self-completed questionnaires sent directly to the participant's home address at 6 months and 1, 2, 5 and 10 years after randomisation. Additional information on treatments will be collected from the clinicians.

2.2. Large, pragmatic trial: minimal extra workload

In order to obtain the large number of patients necessary for the reliable evaluation of medical intervention for menorrhagia, the trial will need the participation of at least 120 primary care centres and hospital clinics. To make this practicable, trial procedures need to be kept simple, with the minimal extra workload placed on participating clinicians beyond that required to treat their patients. This will be achieved by simple entry procedures (a single phone/fax/internet call to the randomisation office), the use of standard treatment regimens, routine follow-up of patients (with few additional GP/ clinic visits or tests to be performed above those done as part of standard care), minimising documentation and largely patient-based evaluation of outcome. Regular newsletters will keep collaborators informed of trial progress, and regular meetings will be held to report progress of the trial and to address any problems encountered in the conduct of the study.

3. ELIGIBILITY

3.1. Inclusion and Exclusion Criteria

3.1.1 Inclusion criteria

- Women between the ages of 25-50 presenting to General Practitioners or selected clinics in secondary care (see Section 3.3 for definition) with menorrhagia (see Section 3.2 for specific definition).
- Not intending to become pregnant in the next 5 years.

3.1.2 Exclusion criteria

- Women taking HRT
- Women with contraindications to IUD use, with or without Levonorgestrel (see Appendix D)
- Women with contraindications to all medical treatments for menorrhagia
- Women with abdominally palpable enlarged fibroid uteri (10-12 weeks size)
- Women to whom the contraceptive effect of LNG-IUS would be unacceptable
- Women with symptoms suggestive of other pathology:
    - irregular bleeding, unless an endometrial biopsy has been performed and pathology excluded
    - intermenstrual bleeding
    - postcoital bleeding,
- Women with risk factors for endometrial cancer:
    - tamoxifen treatment
    - unopposed oestrogen treatments

3.2. Diagnosis of Menorrhagia

A diagnosis of menorrhagia is required before any approach is made to obtain consent. The RCOG guidelines define menorrhagia as ‘heavy cyclical menstrual blood loss over several consecutive cycles without any intermenstrual or postcoital bleeding’. Several cycles should be considered as a minimum of 3 consecutive cycles. Women will be eligible if they either request treatment or if treatment is indicated.

NICE stated, for clinical purposes, HMB should be defined as excessive menstrual blood loss which interferes with the woman’s physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms and recommended any interventions should aim to improve quality of life measures.

Women fulfilling all the eligibility criteria will be invited to participate by their GP, practice nurse or gynaecologist. Women with menorrhagia, but otherwise ineligible, and eligible women who refuse consent cannot be randomised into the study.

3.3. The Research Setting

The setting will be general practices serving a large, socio-economically and ethnically representative primary care population. This will help the generalisability of findings. At least 120 general practices and hospital clinics will need to participate to achieve the target recruitment. This will include collaboration with practices within Primary Care Trusts and acute hospital trusts in both East and West Midlands regions.

Selected secondary care gynaecology clinics will identify those women with heavy periods who have been referred by their GPs, who on screening their referral letters, may not have received appropriate initial medical treatment options for their heavy periods. These women on the waiting list for secondary care appointments would be invited and offered participation into the ECLIPSE trial. Those referred for endometrial biopsy for irregular and heavy bleeding where the test is negative may be recruited from secondary care. These patients would still constitute being in the primary care setting and if successfully recruited into the trial would have the appropriate treatment instituted as per the randomisation allocation. They would then be sent back to their GPs for further follow-up as per the trial protocol. Those not recruited into the trial would be managed appropriately in the secondary care setting. A log of all referral letters screened, eligible patients; those invited or not will be kept to identify key factors for referral in this cohort of patients.

4. CONSENT AND RANDOMISATION

4.1. Recruitment of Participants

The conduct of the trial will be in accordance with the Medical Research Council (MRC) Guidelines for Good Clinical Practice 1998 and any subsequent amendments. Written informed consent to participate in the trial must be obtained before randomisation and after a full explanation has been given of the treatment options and the manner of treatment allocation. Patient information sheets (Appendix A) and consent forms (Appendix B) will be provided so that patients can find out more about the trial before deciding whether or not to participate. Information about the trial will also be translated into relevant local languages according to practice recruitment; this was helpful in a recently completed MRC trial.[36] Where necessary, trained professional interpreters will be arranged to discuss study participation where language between health professional and patient is not shared. Acceptability of LNG-IUS and willingness to participate in the trial may potentially vary between ethnic groups. Anonymous baseline information on age, ethnic group, parity and risk factors will be recorded for all eligible patients (see Appendix C for eligibility screening) invited to take part and reasons for declining to take part will be sought. This will establish the take-up rate of the study and the generalisability of the study participants.

4.2. Randomisation

Randomisation notepads (Appendix C) will be provided to participating practices and clinics and may be used to collate the necessary information prior to randomisation.

Participants are randomised into the trial by one telephone call (0800 953 0274) or fax (0121 415 9136) to the randomisation service or by using a secure website https://www.trials.bham.ac.uk/eclipse. Randomisation will be carried out centrally by the ECLIPSE Trial Office at The University of Birmingham Clinical Trials Unit (BCTU). Informed consent must have been obtained and the person randomising will need to answer all of the telephone questions before a treatment allocation is given.

Randomisation by phone is available Monday-Friday, 09:00-17:00 GMT or outside these hours by internet.

4.3. Open treatment

It is usually desirable to keep both the patient and any assessor blind to the treatment allocation as outcome assessments may be influenced by knowledge of the treatment. However, clinical management of the patient requires knowledge of the current and previous treatments, and the majority of the outcomes are patient self-reported questionnaires, and therefore patient blinding is not possible either. In a pragmatic trial such as ECLIPSE it is not considered essential, nor is it practicable, to blind the clinicians or the participants to the allocation.

5. TREATMENT ALLOCATION

5.1. Trial treatment

Participants will be randomised to their initial treatment. Clinicians will need to state prior to randomisation whether the patient needs contraception and whether she has a copper or non-hormonal IUS *in situ*. The intended treatment (i.e. either mefenamic acid, tranexamic acid or contraceptive pill) if allocated to the standard treatment arm must also be stated.

5.1.1 Dose and route of administration in the Standard Treatment arm.

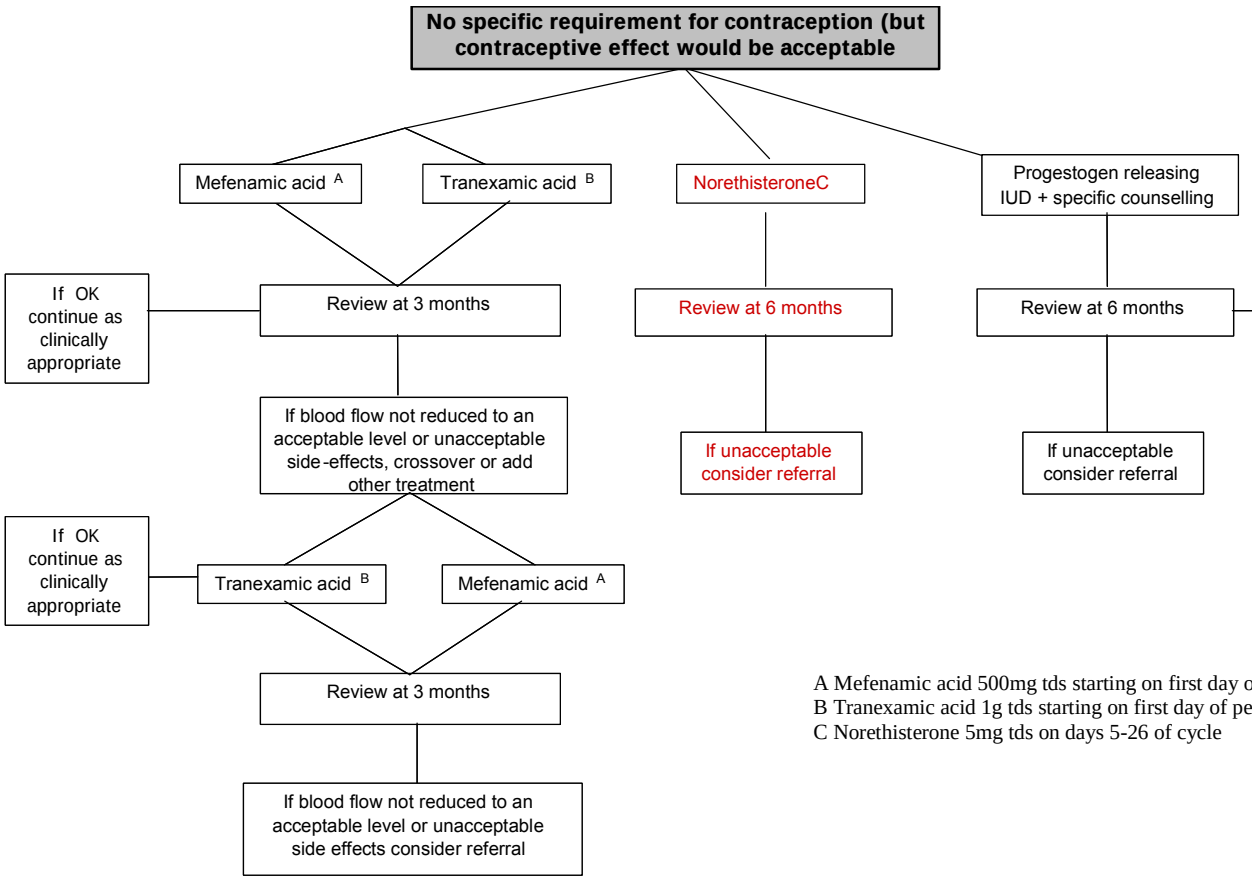
Clinical management, including the dose and route of administration of the drugs, will be according to the RCOG/ NICE guidelines, accommodating any specific need for contraception or current IUS use as appropriate. Treatment algorithms are given below in Figure 1-Figure 3.

Treatments will be prescribed by clinicians in the usual way. Medications should only be prescribed after each clinician has ensured that there are no interactions or contraindications to their use according to the manufacturer's recommendations. Concomitant therapy is allowed if there are no contraindications or interactions with other drugs. See appendix D.

In deciding between medical treatments, the information in Table 1 may be useful. Generally, if participants are satisfied with the treatment they are receiving, they should continue until it is no longer clinically appropriate. When a change of treatment is necessary, another treatment from the standard arm should be considered first, either by addition of a further drug or swapping to an alternative. When standard treatments are no longer perceived to be beneficial, GPs can chose whether to fit a LNG-IUS or refer to secondary care according to their, and the woman's, preference.

Details of treatment changes from the initial allocation will be collected directly from clinicians.

Figure 1 Women not requiring contraception



A Mefenamic acid 500mg tds starting on first day o
B Tranexamic acid 1g tds starting on first day of pe
C Norethisterone 5mg tds on days 5-26 of cycle

Figure 2 Women needing contraception

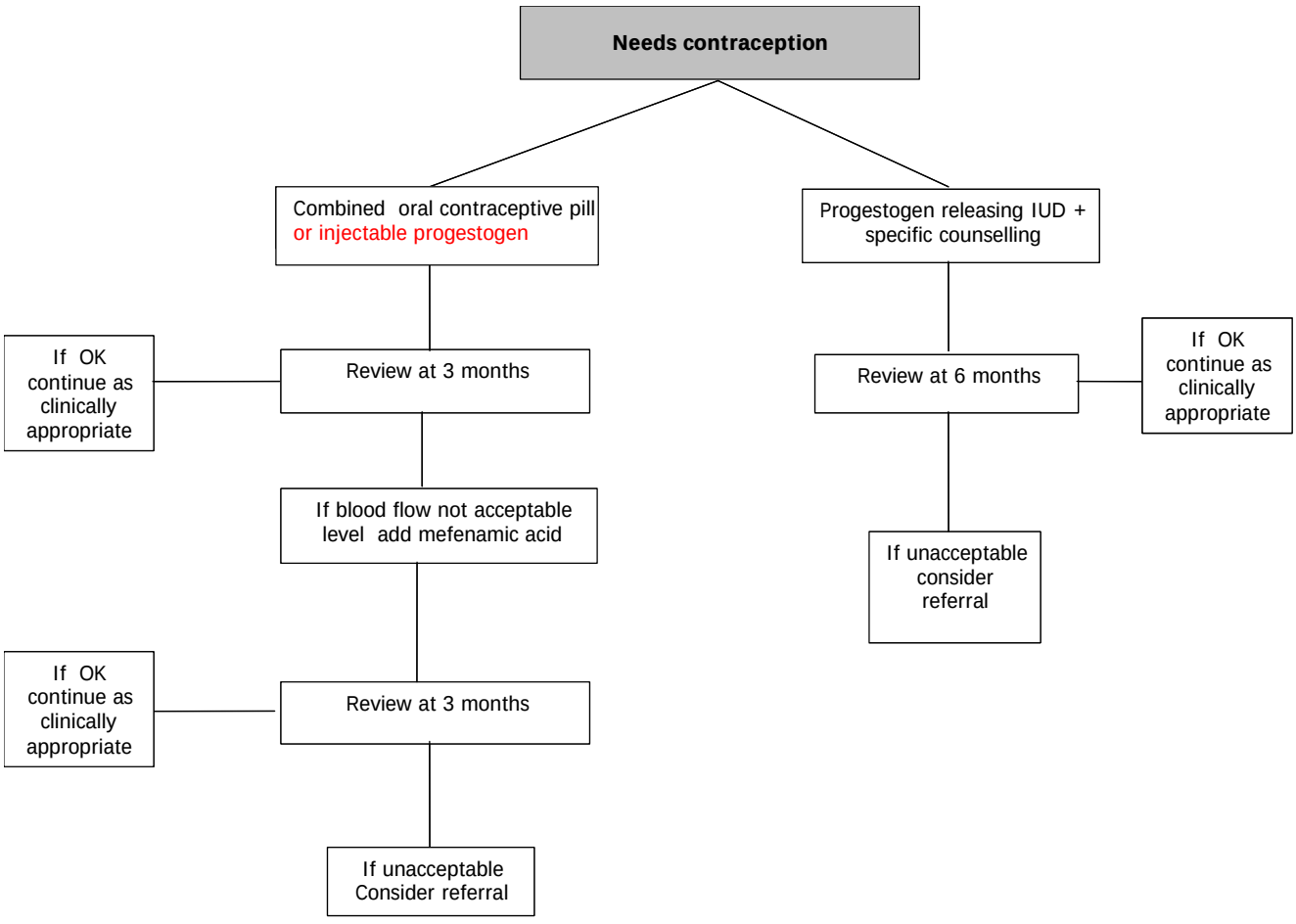
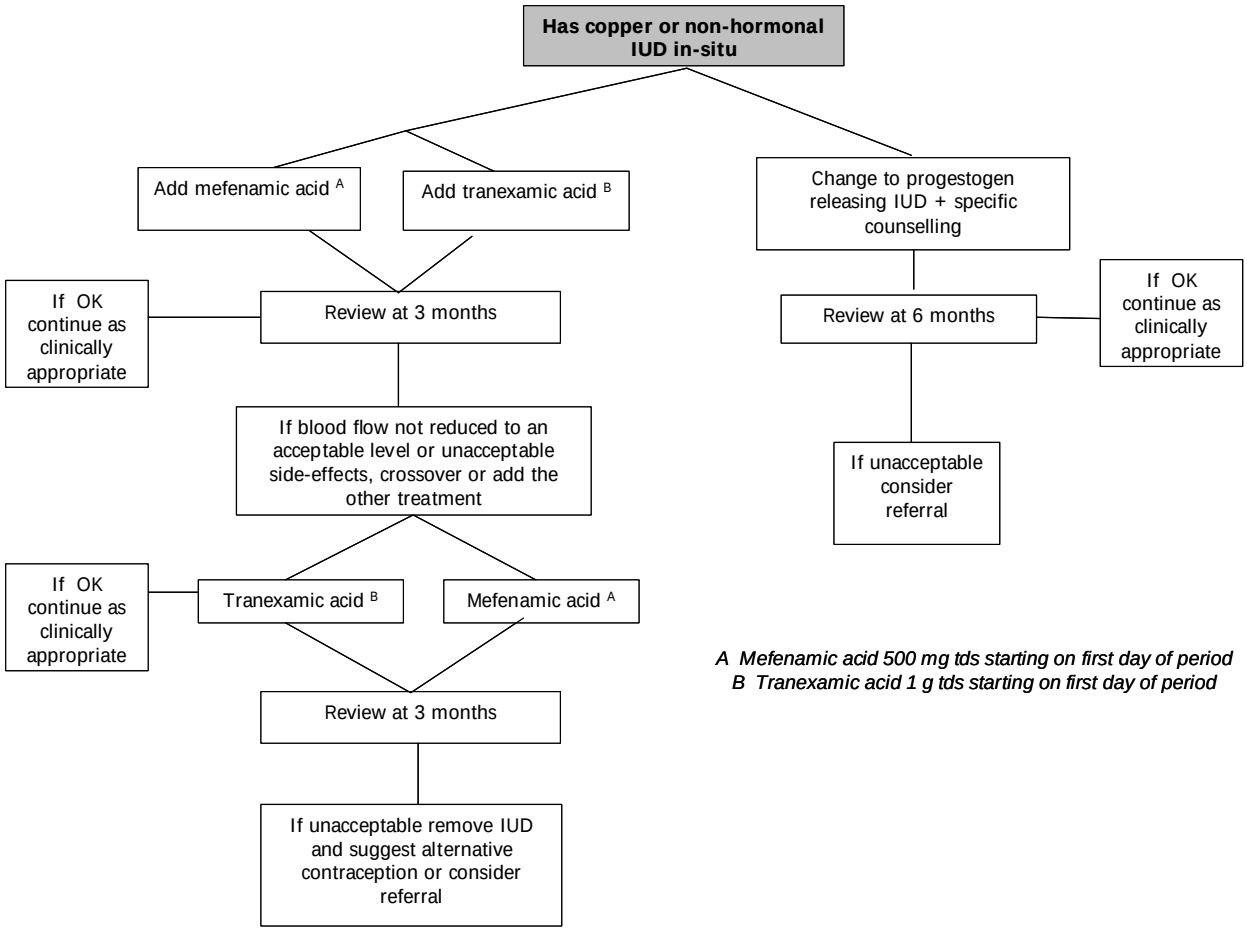


Figure 3 Women with copper or non-hormonal IUS *in situ*



5.1.2 LNG-IUS

The LNG-IUS will be fitted according to the manufacturer's recommendations by the clinician, when clinically appropriate, either at the randomisation appointment or at a subsequent visit. The fitting instructions are included in the pack. The prior use of ibuprofen (oral or gel) to reduce discomfort during fitting is recommended. A six-week follow-up visit should be arranged to check the fitting. GPs who are unable to fit the LNG-IUS themselves, should refer patients to another GP in the practice who does so, or to a family planning clinic or to secondary care clinics approved for participation in ECLIPSE, to have the LNG-IUS fitted there (see 12.1 for practice eligibility).

5.2. Compliance

Some degree of non-compliance can be anticipated in both standard treatment and LNG-IUS groups. The 'survival rate' of the LNG-IUS at 6 months was reported to be 70% in a UK hospital study. Higher retention rates were reported in a large Finnish epidemiological study of women using the LNG-IUS for contraception: with responses from 75% of 23,885 women, the continuation rates at 1, 2, 3, 4 and 5 years were 94%, 87%, 82%, 76% and 65%, respectively.[37] The ECLIPSE study will determine whether this high retention rate can be replicated in primary care.

To improve compliance with LNG-IUS, women should be counselled about the short-term side effects of LNG-IUS – e.g. intermenstrual bleeding - before they are randomised. Apart from this, there are no special measures to enhance patient 'compliance', since these may interfere with normal clinical practice and make the trial results less generalisable. The

importance of compliance with treatment should also be underlined to participants in the standard medical treatment arm, but it is recognised that it might be lower than for those with LNG-IUS still *in situ* after six months. Compliance is an integral part of any treatment, which influences its overall effectiveness. The ECLIPSE study has sufficient statistical power to detect any worthwhile treatment differences even allowing for a dilution of the treatment effect in intention-to-treat analyses due to incomplete compliance.

6. SAFETY MONITORING PROCEDURES

The Medicines for Human Use (Clinical Trials) Regulations 2004 define categories of adverse events, the responsibilities of the investigators to notify adverse events to the sponsor and for the sponsor to report to the regulatory authority and ethics committee. It is therefore imperative that all investigators have a thorough understanding of anticipated adverse events and the reporting process of these events.

6.1. General Definitions

Adverse Events (AEs)

An AE is:

- any unintentional, unfavourable clinical sign or symptom. This will include complications with fitting the LNG-IUS.
- any new illness or disease or the deterioration of existing condition
- any clinically relevant deterioration in any laboratory assessments or clinical tests

The following are not AEs:

- A pre-existing condition (unless it worsens significantly during treatment).
- Diagnostic and therapeutic procedures, such as surgery (although the medical condition for which the procedure was performed must be reported if new)

Adverse Reactions (ARs)

An AR is an adverse event that is considered to have a “reasonable causal relationship” with trial drug.

Serious Adverse Events (SAEs)

An SAE is an untoward event which:

- results in death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed
- hospitalisation or prolongation of hospitalisation
- significant / persistent disability
- a congenital anomaly / birth defect
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

Note that ANY death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events/reactions that are not immediately life-threatening or do not

result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

A procedure that is planned (i.e., planned prior to starting of treatment on study; must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the protocol treatment remains a reportable serious adverse event and should be reported to the trial office as soon as possible by completing and faxing a SAE form (Appendix E), for review by the Independent Data Monitoring and Ethics Committee. Events that might reasonably be expected to occur in women with menorrhagia receiving the study treatments should also be recorded on the Change of Treatment form but do not need to be reported in this way.

Events NOT considered to be SAEs are hospitalisations for:

- routine treatment or uterine surgeries i.e. endometrial ablation or hysterectomy not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen
- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission
- Pregnancy occurring in participants in a Clinical Trial of Investigational Medicinal Product (CTIMP), while not considered an adverse event or serious adverse event requires monitoring and follow up. The investigator must collect pregnancy information for female trial subjects. Any pregnancy should be reported by the PI to BCTU using V1.0 pregnancy notification form (appendix G). The pregnancy should be followed up by BCTU until delivery. Any occurrences that result in a Serious Adverse Event should be reported to the regulatory authority and ethics committee.

6.2. Processing of Serious Adverse Event Reports

The report of an SAE will be the signal for the trials unit to ask the investigator or the responsible clinician to complete and send as soon as possible all relevant details for the involved patient with details of treatment and outcome, where possible.

The CRF (Resource usage questionnaire) captures information on whether the patient has been in hospital at 6mths, 1, 2 and 5yr timepoints and the reason for this admission. SAE's will be collected from this self report and will be presented at TMG meetings where the CI will make the clinical decision on whether these are related to treatment using the table below.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator / CI using the following:

RELATIONSHIP	DESCRIPTION
Unrelated	There is no evidence of any causal relationship to the protocol treatment (also include pre-existing conditions)
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration

	of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not accessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

6.3. Pharmacovigilance responsibilities

Local Principal Investigator (or nominated individual in PI's absence):

- To record **all** AE/Rs that occur in the subjects taking part in the trial. This includes non-serious, serious, expected or unexpected adverse events or reactions.
- Medical judgement in assigning seriousness, expectedness and causality to AEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator's Agreement accepting these responsibilities.

Chief Investigator (or nominated individual in CI's absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment
- To review all events assessed as SAEs in the opinion of the local investigator
- To review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and Chief Investigator with regards to SUSAR status, local assessment will not be over-ruled, but the Chief Investigator may add comments prior to reporting to MHRA.

Birmingham Clinical Trials Unit:

- To report SUSARs, to MHRA and main REC within required timelines as detailed above
- To prepare annual safety reports to MHRA, main REC and TSC.
- To prepare SAE safety reports for the DMEC.
- To report all fatal SAEs to the DMEC for continuous safety review
- To notify Investigators of SUSARs which compromise patient safety

Trial Steering Committee (TSC):

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review data, patient compliance, completion rates, adverse events (during treatment).
- To receive and consider any recommendations from the DMEC on protocol modifications.

Data Monitoring & Ethics Committee (DMEC):

- To review overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop.

6.4. Withdrawal from treatment or protocol violation

A certain amount of crossing-over between allocations is anticipated in this pragmatic trial. If a woman declines the allocated treatment, then the most appropriate alternative treatment should be offered. Failure to fit, decline of allocation and changes in treatment should be recorded in the Change of Treatment form at the follow-up time points. Such women should be advised that this does not mean they have withdrawn from the study and should be encouraged to complete follow-up questionnaires, regardless of the treatment received.

6.5. Other management at discretion of local GPs

Apart from the trial treatments allocated at randomisation, all other aspects of patient management are entirely at the discretion of the patient's GP. Participants randomised in clinics in secondary care will be referred back to their GP for continued management. Patients are managed in whatever way appears best for them, with no other special treatments, no special investigations, and no extra follow-up visits.

7. FOLLOW-UP AND OUTCOME MEASURES

7.1. Primary Outcome Measure

The Shaw Menorrhagia Questionnaire[38]

This is the primary outcome measure. Menorrhagia is a subjective problem and quality of life is affected by practical difficulties and the impact on social life, psychological wellbeing, physical health, work routine and family life. The Shaw questionnaire attempts to capture the consequences of menorrhagia on these domains with 6 questions each with 4 levels of response.

7.2. Secondary Outcome Measures

Short Form-36

The SF-36 v2 is a 36-item short-form survey that measures general health-related quality of life (HRQOL) and can be used to obtain utilities.[39] The SF-36 is a practical and reliable way to obtain important health outcomes data in a variety of settings, measuring eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. The standard format with 4-week recall period will be used to capture the average quality of life over a menstrual cycle.

The Sexual Activity Questionnaire

Sexual activity is an important dimension of quality of life, therefore it is important to be able to assess the impact that treatments may have on sexual functioning. Most of the available sexual functioning questionnaires are designed specifically to investigate sexual dysfunction. These were deemed unnecessarily detailed for the purposes of assessing the impact of treatments for menorrhagia. The Sexual Activity Questionnaire was developed as a self-report questionnaire for use in gynaecological clinical trials, which would be quick to complete and acceptable to the majority of women.[40] The SAQ has been extensively field-tested for this purpose.[41]

Clinical and Treatment Data

The incidence of dysmenorrhoea and pain will be recorded on the randomisation form. Duration of use of initial treatment, referral to secondary care, surgical intervention, hysterectomy, and specific complications such as expulsion of the LNG-IUS will also be recorded.

EuroQol EQ-5D

An additional outcome measure for the economic evaluation will be the EuroQol EQ-5D. EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. Responses will be given valuations derived from published UK population tariffs and the mean number of quality adjusted life-years (QALYs) per patient and incremental QALYs will be calculated.

Patient Satisfaction with Treatment

Specific statements about the experience of the treatment and the beliefs about the value of the treatment will be elicited from a sub-sample of participants. At the end of the study, in addition to disseminating the results in the usual fashion, we will assess the likely impact of our findings on patient preferences. This will be done by carrying out focus groups of approximately 100 women representative of the study population. After ascertaining current preferences and the reasons for these, these groups will be presented with the findings of the study and the impact of these findings on their treatment preferences will be explored, in order to assess the likely impact of the study on the choice of treatment. This would enable the acceptance rate of treatment to be measured with narrow confidence limits. This will also allow better planning of service delivery.

7.3. Timing of assessments

Clinical assessments will be repeated at 6 months, 1, 2, 5 and 10 years. The baseline questionnaires will be completed by the participant prior to randomisation. Thereafter, the questionnaires will be sent out by post with pre-paid envelopes. Non-returners will receive up to 2 postal reminders followed, if necessary, by telephone reminders to ensure maximal response rates.

The decision on whether or not follow-up longer than 5 years is required will be made in the light of the results in the first 5 years of follow-up. If a clear answer has emerged one way or the other from the first 5 years of follow-up, then further follow-up may not be necessary. However, if the situation by 5 years is less clear-cut, or there are concerns about long-term toxicity, then estimates of overall clinical and cost-effectiveness of LNG-IUS therapy may well depend on how long any benefits or risks persist beyond five years. Consequently, longer follow-up will be sought in these circumstances.

7.4. Health economic outcomes and perspective

If the LNG-IUS coil proves to be effective in reducing menstrual blood loss and improved patient satisfaction then it is likely that important cost implications will be seen for the health care sector, patients and for society more generally (in terms of productivity gains). Given this, in order to estimate the full effects of the policy, the economic evaluation will take the perspective of both the NHS and society as a whole.

Resource use data will be collected to estimate the costs incurred by patients in both trial arms. We shall therefore collect data on NHS resource use prospectively from patients, practices and hospitals. The main resources to be monitored include:

1. Visits to hospital (both outpatient appointments and inpatient stays), including details of investigations and procedures (e.g. hysterectomy) - data to be collected from patient follow-up questionnaires and validated by case note reviews of a sub-sample (~10%)

2. Visits to general practitioners (both clinic and home visits), including details of investigations and procedures (e.g. coil removal) - data to be collected from patient follow-up questionnaires and case note review.
3. Use of drugs (both prescribed medications and over-the-counter drugs), e.g. pain relief - data to be collected from patient follow-up questionnaires and case note review.
4. Other patient costs (e.g. patients' travel costs, use of tampons and sanitary towels, etc.) - data to be collected from patient questionnaires.
5. Time off work or normal activities in order to estimate productivity implications - data to be collected from patient questionnaires.

Evidence of good patient recall with respect to health care appointments[42-43] provides support for the plan to collect data directly from patients. Such data will, in part, be verified and supplemented by data collected through case note review in a sub-sample.

Information on unit costs or prices for each resource will then be required to attach to each resource item in order that an overall cost per patient can be calculated. Such data will be collected from relevant routine sources[44] and hospital finance departments.

7.5. Confidentiality of personal data

ECLIPSE will collect personal data and sensitive information about the participants, either directly from them, their GPs or gynaecologists. Participants will be informed about the transfer of this information to the ECLIPSE trial office at the University of Birmingham Clinical Trials Unit (BCTU) and will be asked to consent to this. The data will be entered onto a secure computer database, either by BCTU staff or directly via a secure internet connection. Any data to be processed outside the BCTU will be anonymised.

All personal information obtained for the study will be held securely and treated as (strictly) confidential. All staff, at the GP practice, hospital or BCTU, share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.

7.6. Long-term storage of data

In line with MRC guidelines, all data will be stored for up to 20 years after the last participant has reached the 10-year follow-up to allow adequate time for review, reappraisal or further research, and to allow any queries or concerns about the data, conduct or conclusions of the study to be resolved. Limited data on the participants and records of any adverse events may be kept for longer if so recommended by an independent advisory board.

7.7. Withdrawal from follow-up

Withdrawal from follow-up is the decision of the participant. However, withdrawn patients can bias clinical trial results and reduce the power of the study to detect important differences, so women should be encouraged to complete all follow-up questionnaires. Methods to reduce the burden of follow-up will be explored e.g. online data entry for participants. If the reason for withdrawal is known, it should be communicated to the ECLIPSE Trial Office. To reduce loss to follow-up, we shall record patient's NHS number, which allows us to track patients changing GP practice. With postal and telephone reminders we anticipate that, the completeness of data should surpass 80% although, as set out below incomplete follow-up is incorporated into the power calculations.

8. ACCRUAL AND ANALYSIS

8.1. Sample size

The hypothesis is that LNG-IUS will enhance quality of life in menorrhagia (i.e. improve scores on the Shaw menorrhagia questionnaire) more effectively than standard medical treatment. Two hundred and thirty-five patients are needed in each group (i.e. 470 patients in total) to give good statistical power (90% power at p=0.05) to confirm or refute a small to moderate (0.3 SD: 7 point) effect size at any one time point.[45] To allow for up to 20% loss to follow-up (including patients withdrawing from the study), the target sample size is inflated to 570. It should be noted that, although the sample size is powered to detect differences at any particular time point, the comparison of quality of life will take a long-term view including at least the first two years of treatment. The primary analysis will include multiple outcome measures from each woman randomised in a repeated measures analysis (see section 8.4 below), which will considerably increase the statistical power to detect small average differences between treatments. Repeated measures analysis should also allow meaningful investigation of any clinically relevant variability in treatment efficacy within different subgroups or over time. A study of 570 women will also allow detection of plausible differences in surgical treatment rates. For example, it is estimated that 35% of women with dysfunctional uterine bleeding will subsequently undergo a hysterectomy[46] or some form of endometrial ablation. To show a 33% reduction with LNG-IUS (i.e. 35% reduced to 23%) requires 450 patients (p = 0.05, 80% power).

8.2. Stratification variables

Minimisation will be used to ensure balance of treatment allocation overall and by the following variables to be used in the pre-specified sub-group analyses.

a) older (35-50 years old) or younger (25-34 years old) women;

b) duration of symptoms (< 1 year, ≥ 1 year);

c) menorrhagia alone or menorrhagia and pain;

d) need or no need for contraception.

e) BMI (≤25; >25)

8.3. Projected accrual and attrition rates

Patient recruitment is projected to take 30 months. An average of 3 to 5% of women on general practice lists consult for menorrhagia each year. However, a pilot study conducted by the Investigators indicates that recruitment to this trial is likely to be a significant challenge. Seventy-one patients reporting symptoms of menorrhagia (mean age 35.8 years ± SD 6.4 years), who fulfilled study eligibility criteria, were asked if they would participate in the proposed trial. Overall 20% of women would agree to randomisation, with an expected higher potential consent rate of 30% among older women (35-50 years) compared to 9% for the younger age group (25-34 years). Thus, it is estimated, conservatively, that 20% of eligible women will be suitable for participation, and consent to randomisation. We thus aim to recruit 4 patients per practice per year from 120 practices over a 30-month period, i.e. 10 patients per practice and 570 women in total.

The pilot study GPs considered the above recruitment rate to be achievable in practice, particularly as most of participating GPs have an interest in women's health. Given the relatively low proportion of women expected to accept randomisation, it is anticipated that the study will need to be offered to around 7200 eligible patients in order to recruit 570 participants. By involving a large number of practices each with a target of recruiting 4-5 patients/year to the trial, the pilot study GPs considered the implications for each single practice to be realistic and manageable. The key to successful recruitment is ensuring an

individualised and flexible approach to practices, in particular, by engaging a lead GP interested in this clinical area and its management.

8.4. Statistical Analysis

The statistical analyses will use standard methods (e.g. t-tests for continuous variables and log-rank for time to event analyses). Subgroup analyses will be undertaken for variables for which the randomisation is stratified using standard tests for interactions. Greater statistical power for the treatment comparisons will be obtained by simultaneously analysing different time points using multilevel modelling. Multilevel models allow the duration and underlying type of benefit (e.g. symptomatic relief, or disease-modifying) to be determined. Sensitivity analyses will be undertaken to test the robustness of conclusions.

8.4.1 Handling missing data

The interpretation of missing values in the analysis of clinical trials can be fraught with danger. The methods used to allow for missing data make assumptions about the reasons for data not being present, such as in the "observed case" analysis, where the presence or absence of data is viewed as unrelated to outcome, or in the "Last Observation Carried Forward" analysis where the assumption is that the condition does not improve or worsen following withdrawal from follow-up. To minimise possible biases, participants will continue to be followed up even after protocol treatment violation. Missing data items from the Shaw Questionnaire, the SF36 and EQ-5D will be imputed from given values. Sensitivity analyses will be carried out to determine whether or not the results obtained are robust to the methods used to handle missing data. These approaches are in line with the recent recommendations from the European Agency for the Evaluation of Medicinal Products.[47]

8.5. Health Economic Analysis

8.5.1 Analyses

The first stage of the economic analysis will be conducted at the end of year 5 (when complete follow-up for at least 24 months should be available for all patients). A second and final stage of analysis will then be undertaken after all 5-year follow-up data has been collected. At both stages there will be two components to the analysis: a within trial analysis and a model-based analysis.

8.5.2 Within trial analysis

This will use only data collected within the trial and so, for example, data for the first analysis stage will draw upon follow-up data collected up to 24 months. Estimates of costs and benefits will therefore relate only to this period of follow-up, and no predictions for costs and benefits beyond the trial will be made.

The data available will be patient-specific resource use and costs. Given the skewness inherent in most cost data and the concern of economic analyses with mean costs, we shall use a bootstrapping approach in order to calculate confidence intervals around the difference in mean costs.[48-49] An incremental economic analysis will be undertaken. The base-case analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost, the broad range of consequences including data on menorrhagia symptoms, quality of life, etc. If this identifies a situation of dominance then further analysis will not be required. If no dominance is found, cost-effectiveness (i.e. cost per change in symptom score) and cost-utility analyses (i.e. cost per quality-adjusted life year gained) will be undertaken. The EQ-5D will be used to derive utilities. Recent research has yielded a utility-tariff for the UK for health states defined by the SF-36 instrument.[33,40,44,50.] This tariff will also be used to estimate patient-specific QALYs to validate EQ-5D findings.

Trial analyses will be repeated for the second analysis stage, drawing on longer-term follow-up data, allowing judgements to be made on the sensitivity of within trial analysis results to length of trial follow-up.

8.5.3 Model-based analysis

A decision analytic model will be used to allow the extrapolation of cost and effectiveness parameters beyond the data observed in the clinical trial (and to allow extrapolation to other settings). The model will, therefore, consider treatment over total disease duration and will include surgical treatments provided in the longer term. An individual sampling model (such as a Markov model) will be used since individual patients in the model can, for modelling purposes, be regarded as independent and so interactions are not an important issue. The first stage of model-based analysis will draw upon follow-up data up to 24 months and also make use of published data and assumptions to predict costs and benefits into the long-term. The analysis will then be repeated at Stage 2, using the longer follow-up data, but still predicting costs and effects beyond the trial end.

8.5.4 Discounting

Given the relatively long time horizons being considered in these analyses (both within trial and model-based analyses), much of the data on costs (and benefits) will be incurred (and experienced) in future years. Using discounting, adjustments will be made to reflect this differential timing. The base-case analysis will follow Treasury recommendations for public sector projects: currently the recommendation is a rate of 3% for costs and benefits, although sensitivity analysis using different rates will be performed.

8.5.5 Presentation of results and sensitivity analysis

Results of all economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results. For example, if the use of the LNG-IUS coil proves cost-effective using trial data, we shall explore the feasibility and cost of its use routinely in other centres and other settings.

9. DATA ACCESS AND QUALITY ASSURANCE

9.1. In-house Data Quality Assurance

9.1.1 Monitoring and Audit

The study will adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Double data entry of paper questionnaires will be periodically undertaken on a small sub-sample. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised, and then only in a sub-set of practices.

9.2. Independent Trial Steering Committee

The trial will follow the MRC Guidelines on Good Clinical Practice, upon which the NHS Research Governance Framework draws. This requires that the management of the ECLIPSE trial includes an element of expert advice that is entirely independent from the Principal Investigators and their Host Institution(s). We shall appoint an independent Trial Steering Committee including an independent Chair and at least two other independent members, as well as key Principal Investigators. For practicality, none of these members will be from overseas.

The remit of the TSC is to provide independent supervision for the trial, providing advice to the principal investigators, funding body and the Sponsor on all aspects of the trial and ensuring appropriate conduct of the trial.

9.3. Data Monitoring and Ethics Committee: determining when clear answers have emerged

If LNG-IUS for menorrhagia really is substantially better or worse than medical treatment according to RCOG guidelines, with respect to the major endpoints, then this may become apparent before the trial has been completed. Alternatively, new evidence might emerge from other sources that LNG-IUS is definitely more, or less, effective than treatment according to RCOG guidelines. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) "proof beyond reasonable doubt"[†] that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TSC, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

If the clinical co-ordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the Trial Office to the chair of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

[†] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

10. ORGANISATION

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

10.1. Centre eligibility

GP practices eligible to participate are those with one or more appropriate GP(s) in the practice offering women's and sexual health services in primary care in accordance with local clinical governance, who:

1. routinely insert intra-uterine devices and/or have a valid Diploma of the Faculty of Family Planning (DFFP) and/or Letter of Competence (LOC) for coil insertion or are seeking DFFP/LOC recertification; or
2. have a local Family Planning Clinic willing and competent to undertake LNG-IUS insertion following appropriate GP referral.

Investigator meetings for recruited practice GPs and nurses will involve discussion of study protocol, RCOG guidelines on management of menorrhagia, training on LNG-IUS and its insertion and GCP (Good Clinical Research Practice).

In practice, many eligible patients are likely to consult female GPs and IUS insertions are also more commonly performed by the latter assisted by a practice nurse. In our pilot study, all female GPs were familiar with and had experience in LNG-IUS insertion. All hospital gynaecologists will be experienced in LNG-IUS insertion.

10.2. Local Co-ordinator at each centre

Each practice should nominate a GP to act as the Local Co-ordinator (and Principal Investigator *for that practice*). Each hospital will need to similarly nominate a lead gynaecologist. Close collaboration between all clinical teams is particularly important in the ECLIPSE Trial in order that patients for whom LNG-IUS is an option can be identified sufficiently early for entry. The responsibilities of the local co-ordinator will be to ensure that all medical and nursing staff involved in the care of menorrhagia are well informed about the study. This will involve distributing protocols and patient information sheets to all relevant staff, displaying the wall-chart where it is likely to be read, and distributing the regular newsletters. The local co-ordinator should liaise with the designated local research trial nurse or clinical lead and trial administrator on clinical and administrative matters connected with the trial.

10.3. Trial Research Nurses and Local Nursing Co-ordinators

As part of the trial, one or more research nurses will be appointed in each region to assist the practice in recruitment, consent, data collection and follow-up. Each participating centre should also designate one nurse (practice nurse) as Local Nursing Co-ordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline patient data and for administering the follow-up evaluations in liaison with the research trial nurse. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

10.4. Central co-ordination: supply of all trial materials, randomisation service, and data collection and analysis

The ECLIPSE Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all trial materials, including the trial folders containing printed materials and the training and update slide shows. These will be supplied to each collaborating centre, after relevant approvals have been obtained. Additional supplies of any trial materials can be obtained on request. Trial information will also be available for download from a dedicated trial website. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment) and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

10.5. Regulatory and Ethical Approval

10.5.1 Ethical Approval

The trial organisers have obtained Multi-centre Research Ethics Committee (MREC) approval. The Trial Office will assist the Local Coordinator in the site specific assessment made by the LREC and the Research Management and Governance (RMG) Primary Care Trust (PCT) or hospital Trusts Research Governance approval. Once all necessary approvals have been gained, the Trial Office will send a folder containing all trial materials to the local co-ordinator. Screening and recruitment of patients into the trial can then begin.

10.5.2 Clinical Trial Authorisation

The Trial Office has obtained Clinical Trials Authorisation from the Medicines and Healthcare Regulatory Authority.

10.5.3 Research Governance

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, clinical governance and confidentiality. Deviations from the agreement will be monitored and the Trial Steering Committee will decide whether any action needs to be taken, e.g. retraining, or suspension of centre.

10.6. Funding and Cost implications

The research costs of the trial are funded by a grant from the NHS Health Technology Assessment Programme awarded to the Universities of Birmingham and Nottingham.

NHS R&D Support for Science Funding will be sought and administered by Greater Derby PCT and South Birmingham PCT, the lead 'RMG' Primary Care Trusts involved. The majority of costs will be incurred during the lead-in and 30-month recruitment phase. Service support costs will include appropriate allowance for the low anticipated take-up rate of randomisation.

10.7. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so ABPI/ABHI guidelines on indemnity do not apply. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm. The normal NHS indemnity liability arrangements for clinician-initiated research will therefore operate.

However, it should be stressed that in terms of negligent liability, NHS PCTs and hospital Trusts have a duty of care to a patient being treated within their practices, whether or not that patient is participating in a clinical trial. Apart from defective products, legal liability does not arise where there is non-negligent harm.

10.8. Publication

A meeting will be held after the first stage has been analysed, to allow discussion of the main results among the collaborators prior to publication. A first report of the results will then be prepared. As the success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and other health professionals, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Practices and individuals will not be permitted to publish data obtained from participants in the ECLIPSE Trial, that use trial outcome measures relating to the randomised evaluation and hypotheses tested, without prior written approval from the Trial Management Committee.

10.9. Ancillary studies

The ECLIPSE Trial provides many opportunities for add-on studies, examining further methodological, clinical and acceptability issues concerning the management of menorrhagia. For example:

1. Shaw Menorrhagia Questionnaire validation.
2. Qualitative studies of patient satisfaction with treatment.
3. Methodological study comparing postal and email follow-up

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some patients (e.g. special investigations in selected practices) be referred to the Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and so add-on studies will need to be fully justified.

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APPENDIX A PARTICPANT INFORMATION SHEETS AND CONSENT FORMS

Practice Address here

PCT Logo here

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

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

GENERAL PRACTITIONER: ……

GP PRACTICE TELEPHONE: ……

PRACTICE/ RESEARCH NURSE: ……

NURSE TELEPHONE: ……

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 ECLIPSE 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 all 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, 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, the GP will make an appointment to fit the coil and you will be asked to see your GP 6 weeks afterwards to make sure everything is OK, you will not need 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 manufacturers' 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 thought to be appropriate for you. You should read the manufacturers' 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 General Practice. 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 GP 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: .....

.....

.....

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. ☐

I agree to a researcher contacting me to explain more about the study "Medical treatment for menorrhagia: Understanding women's experiences". YES ☐ NO ☐

_____	_____	_____
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 notes

PCT Logo here

Practice Address here

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

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

GENERAL PRACTIONER: .....

GP PRACTICE TELEPHONE: .....

PRACTICE/ RESEARCH NURSE: .....

NURSE TELEPHONE: .....

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 contraceotive 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: .....

.....

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 4.0b) 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. ☐

I agree to a researcher contacting me to explain more about the study "Medical treatment for menorrhagia: Understanding women's experiences". YES ☐ NO ☐

_____	_____	_____
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 notes

NHS Trust Logo here

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

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

GYNAECOLOGIST: ……

TELEPHONE: ……

RESEARCH NURSE: ……

NURSE TELEPHONE: ……

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 doctor 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 it 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 all 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, 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 who feel that they need treatment for heavy periods are being invited. Your GP referred you to hospital for review by a gynaecologist. If you agree to participate, the gynaecologist will treat you with one of the treatment options available to GPs.

There are more than one hundred GPs 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, neither your gynaecologist or GP will 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. If you do want to take part, please make another appointment with your gynaecologist as soon as you can. 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 gynaecologist 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 gynaecologist will give you a prescription and then your GP will see you at 3 and 6 months later 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, the gynaecologist will make an appointment to fit the coil and you will be asked to see your GP 6 weeks afterwards to make sure everything is OK, you will not need any additional visits back to the hospital because you are taking part in the ECLIPSE study. You will of course be able to consult your GP at any other time and where your GP suggests 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 back to the gynaecologist at a local hospital. If it is necessary to change your treatment, or if you decide not to have the treatment allocated, we would still like you to complete the questionnaires to find out what effect changing treatment has. It is important for the reliability of the study to find out how all women are progressing and the study organisers may, therefore, phone or email you to remind you to complete the questionnaires.

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 gynaecologist may give you a painkiller beforehand or afterwards, or use a pain-relieving cream. If the pain did become unacceptable your gynaecologist 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 Hospital 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 or gynaecologist. 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 gynaecologist, GP 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: .....

.....

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 version4.0c) 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 and gynaecologist. ☐

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. ☐

	YES	NO
I agree to a researcher contacting me to explain more about the study "Medical treatment for menorrhagia: Understanding women's experiences".	☐	☐

_____	_____	_____
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 Hospital notes

ELIGIBILITY SCREENING

Before randomising, please check the following eligibility criteria:

INCLUSION CRITERIA

☐ Women between the ages of 25 and 50 presenting to General Practitioners with menorrhagia (heavy cyclical menstrual blood loss over several consecutive cycles)

☐ Not intending to become pregnant in the next 5 years

☐ The patient has given written informed consent

All the INCLUSION criteria MUST be satisfied for the patient to be ELIGIBLE.

EXCLUSION CRITERIA

- Taking HRT
- Patients with any contraindications to an IUS, with or without Levonorgestrel
- Patients with contraindications to medical therapy
- Women with abdominally palpable enlarged fibroid uteri (10-12 weeks size)
- Women to whom the contraceptive effect of LNG-IUS would be unacceptable
- Women with symptoms suggestive of other pathology
  - Irregular bleeding, unless an endometrial biopsy has been performed and pathology excluded
  - Intermenstrual bleeding
  - Postcoital bleeding
- Women with risk factors for endometrial cancer
  - Tamoxifen treatment
  - Unopposed oestrogen treatments

If ANY of the EXCLUSION criteria are satisfied, the women is INELIGIBLE for randomisation.

To randomise a patient:

- complete all questions on the **Randomisation Notepad (Appendix D)**
- call or fax the randomisation service on the numbers given below
- we will then be able to tell you the patient's treatment allocation and ECLIPSE Reference Number.

FOR RANDOMISATION

Telephone 0800 953 0274 or fax the randomisation form to 0121 415 9136

WEBSITE: https://www.trials.bham.ac.uk/eclipse

APPENDIX C: RANDOMISATION NOTEPAD

PART A: IDENTIFYING DETAILS

Area: E. Midlands ☐ W. Midlands ☐

Name of Centre: .....

Name of Randomising Clinician: .....

Patient's Family Name: ..... Given Name(s): .....

Date of Birth (dd/mmm/yyyy): ..... / ..... / ..... N.H.S. Number: .....

Patient's Address: .....

.....

Telephone Number (daytime): ..... Evening: .....

Mobile: ..... Email: .....

Ethnic Group *(tick ✓ one only)*

White		**Black / Black British**	
British	☐	Caribbean	☐
Irish	☐	African	☐
White Other	☐	Black Other	☐

Asian / Asian British		**Mixed**		**Chinese or Other Ethnic Group**	
Indian	☐	Mixed White/ Black Caribbean	☐	Chinese	☐
Pakistani	☐	Mixed White/ Black African	☐	Any Other	☐
Bangladeshi	☐	Mixed White/ Asian	☐		
Asian Other	☐	Mixed Other	☐	Not given	☐

Parity? .....

PART B: PATIENT'S MEDICAL DETAILS

Height (cm): ..... cm/ ft-in Weight (kg): ..... kg/ st-lb Blood pressure: ..... / ..... mmHg

Does the woman have menorrhagia?

Yes – initial presentation ☐ Yes – subsequent presentation ☐ No (ineligible) ☒

Duration of menorrhagia? Less than one year ☐ One year or more ☐

Does the woman have menstrual pain? Yes ☐ No ☐

Does the woman intend to become pregnant within the next five years? No ☐ Yes (ineligible) ☒

Eligibility Criteria	**No**	**Yes (ineligible)**		**No**	**Yes (ineligible)**
Taking HRT	☐	☒	Irregular bleeding, no biopsy performed	☐	☒
Any contraindication to LNG-IUS	☐	☒	Irregular bleeding, negative biopsy	☒	☐
Abdominally palpable fibroid uteri	☐	☒	Intermenstrual bleeding	☐	☒
Contraceptive effect of coil unacceptable	☐	☒	Postcoital bleeding	☐	☒
			Tamoxifen treatment	☐	☒

Has the women given written informed consent ☒ No (*ineligible*) ☐ Yes

Consent form Version Number: ..... Date consent form was signed: ..... / ..... / .....

All questions must be answered and no shaded boxes ticked in order to be eligible for ECLIPSE.

If the patient is eligible please turn over for randomisation into ECLIPSE.

PART C PLANNED TREATMENT

		Yes	No
Does the patient have a copper / non-hormonal coil in place?		☐	☐
Does the patient require contraception?		☐	☐
If randomised to standard treatment, will the woman be Prescribed (*please select all that apply*)?	Mefenamic acid	☐	☐
	Tranexamic acid	☐	☐
	Combined oral contraceptive	☐	☐
	Norethisterone (high dose)	☐	☐
	Progestogen injection (Depo-Provera)	☐	☐

If randomised to LNG-IUS, who will fit coil?

Randomising GP ☐ Other GP in practice ☐ Refer to family planning clinic ☐
Randomising Consultant ☐ Other Medic at Randomising Centre ☐

PART D TREATMENT ALLOCATION

When all questions are complete, phone 0800 953 0274 for allocation or randomise online at https://www.trials.bham.ac.uk/eclipse

Allocated treatment

Standard treatment ☐ **LNG-IUS (Mirena coil)** ☐

ECLIPSE TRIAL NUMBER ☐☐☐☐

Date of randomisation: ...../...../.....

After randomisation, please return a copy of the consent form to the ECLIPSE Trial Office.

Thank You.

ECLIPSE Trial Office, FREEPOST RRKR-JUZR-HZJG, Birmingham Clinical Trials Unit, Division of Medical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT

APPENDIX D: TOXICITY AND KNOWN SIDE EFFECTS

Contraindications

The stated contraindications to the Mirena® LNG-IUS are

- known or suspected pregnancy
- undiagnosed abnormal genital bleeding
- congenital or acquired abnormality of the uterus including fibroids if they distort the uterine cavity
- current genital infection; current or recurrent pelvic inflammatory disease
- postpartum endometritis
- infected abortion during the past three months
- cervicitis
- cervical dysplasia; uterine or cervical malignancy
- active or previous severe arterial disease, such as stroke or myocardial infarction is a contraindication when Mirena is used in conjunction with an oestrogen for HRT use.
- liver tumour or other acute or severe liver disease
- conditions associated with increased susceptibility to infections
- acute malignancies affecting the blood or leukaemias except when in remission
- recent trophoblastic disease while hCG levels remain elevated
- hypersensitivity to the constituents of the preparation
- confirmed or suspected hormone dependent tumours including breast cancer

Additional contraindications to copper based IUDs

- copper allergy
- Wilson's disease
- coagulation disturbances

Contraindications to the combined oral contraceptive pill

- known or suspected pregnancy
- existing or a history of confirmed venous thromboembolism (VTE). Family history of idiopathic VTE. Other known known factors for VTE
- existing or previous arterial thrombotic disorders, or embolic processes
- conditions with predispose to thromboembolism e.g., disorders of the cotting processes, valvular heart disease and atrial fibrillation.
- sickle-cell anaemia
- severe disturbanes of liver function, jaundice or persistent itching during a previous pregnancy,Dubin-Johnson syndrome. Rotor syndrome, previous or existing liver tumours.
- history of herpes gestationis
- mammary or endometrial carcinoma, or a history of these conditions
- severe diabetes mellitus with vascular changes
- disorders of lipid metabolism
- undiagnosed abnormal vaginal bleeding
- deterioration of otosclerosis during pregnancy
- Hypersensitivity to the active substance or to any of the excipients

Contraindications to Mefenamic Acid

- inflammatory bowel disease
- severe heart failure, hepatic failure and renal failure.
- hypersensitivity to mefanamic acid or any of the other ingredients
- because the potential exists for cross-sensitivity to aspirin or other non-steroidal anti-inflammatory drugs, mefenamic acid should not be given to patients who have previously shown hypersensitivity reaction (e.g. asthma, bronchospasm, rhinitis, angioedemaor urticaria) to these medicines.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- During the last trimester of pregnancy
- Treatment of pain after coronary artery bypass graft (CABG) surgery

Contraindications to Tranexamic Acid

- severe renal failure because of risk of accumulation
- hypersensitivity to tranexamic acid or any of the other ingredients
- active thromboembolic disease.

Contraindications to Norethisterone

- hypersensitivity to Norethisterone or ethinylestradiol or to any of the excipients
- Breast feeding mothers less than 6 weeks post-partum
- Major surgery with prolonged immobilisation
- Moderate to severe hypertension (systolic ≥ 160mm Hg or diastolic ≥ 95mm Hg), current or history of ischaemic heart disease, stroke, peripheral vascular disease or presence of multiple risk factors for arterial disease.
- Complicated valvular and congenital heart disease (e.g. with pulmonary hypertension, artrial fibrillation, history of subacute bacterial endocarditis)Migraine with focal aura.
- Diabetes with nephropathy/retinopathy/neuropathy or other vascular involvement or> 20 years' duration.
- Smoking 15 or more cigarettes per day in patients aged 35 years or more.
- Known or suspected carcinoma of the breast.
- Raynaud's disease, with Systemic Lupus Erythematosus (SLE) if lupus anticoagulant is present.
- acute or chronic liver disease, including hepatitis (viral or non viral) or severe cirrhosis, or a history of these conditions until at least 3 months after abnormal liver function tests have returned to normal; hepatic adenomas or carcinomas.venous thrombo-embolism (VTE) requiring concurrent anticoagulant therapy, personal history of confirmed VTE or known thombogenic mutations.

Contraindications to Depo-Provera

- Depo-Provera is contra-indicated in patients with a known sensitivity to medroxyprogesterone acetate or any ingredient of the vehicle
- Depo-Provera should not be used during pregnancy, either for diagnosis or therapy

- Depo-Provera is contra-indicated as a contraceptive at the above dosage in known or suspected hormone-dependent malignancy of breast or genital organs
- Depo-Provera is contra-indicated in patients with the presence or history of severe hepatic disease whose liver function test have not returned to normal.
- Whether administered alone or in combination with oestrogen, Depo-Provera should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital tract malignancy eliminated

Contraindications to Cerazette

- Known or suspected pregnancy.
- Active venous thromboembolic disorder.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Known or suspected sex-steroid sensitive malignancies.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substance or to any of the excipients.

APPENDIX E: SERIOUS ADVERSE EVENT FORM

Appendix E

The Eclipse Trial:

ECLIPSE: Effectiveness and Cost-effectiveness of Levonorgestrel containing Intrauterine system in Primary care against Standard trEatment for menorrhagia

SERIOUS ADVERSE EVENT FORM

Please report immediately any SERIOUS ADVERSE EVENTS (see protocol section 8 for definition), occurring at any time during treatment, by completing all of the details below and faxing this form to the Eclipse Trial Office on 0121 415 9136.
Please also complete the Pregnancy Notification form if the patient becomes pregnant.

PATIENT IDENTIFICATION

Consultant: _____ Mother's Full Name: _____

Centre: _____ Hospital Number: ☐☐☐☐☐☐☐☐☐☐

Eclipse Trial Number: ☐☐☐☐ Mother's date of birth: DD / MMM / YYYY

SAE TYPE

Is this an initial or follow-up report? Initial Report ☐ Follow-up report ☐

Is this the final report? Yes ☐ No ☐

REASON FOR REPORTING	Yes	No	
Fatal?	☐	☐	Date of death: DD / MMM / YYYY
Life-threatening event?	☐	☐	
In-patient hospitalisation or prolongation of existing hospitalisation?	☐	☐	If yes, no of days? ☐
Persistent or significant disability/ incapacity?	☐	☐	
Is a congenital anomaly or birth defect?	☐	☐	
Other pertinent medical reason for reporting?	☐	☐	

If other, please specify: _____

SAE DESCRIPTION

Date Event Started: DD / MMM / YYYY Date Event Ceased: DD / MMM / YYYY

Details of Adverse Event (please attach copies of relevant reports): _____

TRIAL TREATMENT

This section must be completed by a clinician

Date last treatment administered	Causality Assessment	Action taken due to SAE
	1 Clearly unrelated to treatment 2 Probably unrelated to treatment 3 Possibly related to treatment 4 Probably related to treatment 5 Definitely related to treatment	1 None 2 Treatment stopped 3 Treatment delayed
DD / MMM / YYYY	_____	_____

Please give reasons if you consider the event to be treatment-related: _____

Once faxed, please return this form (with copies of relevant reports) to: Eclipse Trial Office, FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT

ISRCTN86566246 Version 2.0 Date 01/09/2010

Was the SAE **unexpected**, i.e. of a **type** or **severity** which is NOT consistent with the up-to-date SPC of Eclipse trial treatments (available at http://emc.medicines.org.uk/) **This section must be completed by a clinician**

Unexpected ☐ **Expected** ☐

Please give reasons if you consider the event to be unexpected: _____

_____

CONCOMITANT MEDICATION

Has the patient taken any other medication within the last week? Yes ☐ No ☐ If yes, please complete below:

Drug	Start date	Tick if continuing or specify stop date	Dose (mg)	Indication
	DD / MMM / YYYY	☐ DD / MMM / YYYY		
	DD / MMM / YYYY	☐ DD / MMM / YYYY		
	DD / MMM / YYYY	☐ DD / MMM / YYYY		
	DD / MMM / YYYY	☐ DD / MMM / YYYY		
	DD / MMM / YYYY	☐ DD / MMM / YYYY		
	DD / MMM / YYYY	☐ DD / MMM / YYYY		

OUTCOME OF SAE

Outcome: Fatal ☐ Recovered ☐ Continuing ☐

Please describe final outcome if event continuing at time of faxing initial report: _____

_____

_____

Signature of Person Reporting: _____ Date: DD / MMM / YYYY

You must have signed the Site Delegation Log

Name: _____ Position: _____

Telephone No: _____

Signature of Investigator: _____ Date: DD / MMM / YYYY

If not completed by investigator

SUSAR Reporting – BCTU USE ONLY

SAE reference number: ☐☐☐

Date reported to BCTU? DD / MMM / YYYY

Date reported to CI? DD / MMM / YYYY Date reply received from CI? DD / MMM / YYYY

Is this event a SUSAR? Yes ☐ If yes: ☐ 7 day report or ☐ 15 day report

No ☐ If NO, is this an SAE? ☐ Yes ☐ No

CI comments: _____

_____

Signature: _____ PRINT Name: _____

Date due to be reported to MHRA and MREC: DD / MMM / YYYY

Once faxed, please return this form (with copies of relevant reports) to: Eclipse Trial Office, FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT

ISRCTN86566246 Version 2.0 Date 01/08/2010

APPENDIX F: FURTHER INFORMATION RELATING TO ECLIPSE PROTOCOL V5.0 DATED 12.09.07

Further Information relating to ECLIPSE Protocol Version 5 dated 12/09/07

Section 9.2 Patient Satisfaction with Treatment

Medical treatments for heavy menstrual bleeding:
Understanding women's experiences.

This research on patient satisfaction with treatment is part of the current ECLIPSE trial (www.eclipse.bham.ac.uk), an ongoing randomised controlled trial which aims to investigate the effectiveness and cost-effectiveness of current medical treatments for menorrhagia. This research aims to generate qualitative insights from women's perspectives that contextualise ECLIPSE trial outcome measures, which include measures of quality of life in addition to reduction in blood loss. This should enhance the utility of the quantitative trial findings and their application in practice.

Objectives

1. To explore and develop understanding of women's experiences and expectations of medical treatments for menorrhagia.
2. To explore women's views, beliefs, attitudes and decision making relating to treatments for menorrhagia including treatment preferences, how they may change over time and why.
3. To explore women's perspectives on indicators of quality of life in the context of heavy menstrual bleeding and the effects of treatment on their symptoms and quality of life.
4. To explore potential cultural variations in women's experiences, contexts and decision-making in relation to medical treatments for menorrhagia.

Background Menorrhagia and other changes in menstrual experience can impact on many aspects of health, well being and social functioning for women (Chapple 1999). Recent publication of NICE Guidelines for Heavy Menstrual Bleeding (HMB) (NICE, 2007) recommends Levonorgestrel releasing intrauterine system (LNG-IUS) be considered as first line treatment for HMB, with other medical treatments as further choices. While there is some evidence comparing effectiveness of various treatments for menorrhagia, there has been much less interest in examining women's experiences of menorrhagia and its treatment, including ethnic variation (O'Flynn 2006, O'Flynn and Britten 2004, Chapple 1999). It is thus timely to explore their effects on quality of life by exploring women's satisfaction with, and perspectives of treatment.

Earlier work has found many women who require treatment for menorrhagia have predetermined expectations and preferences for a particular treatment (Vuorma et al 2003, Sculpher et al 1998, Coulter et al 1994). Individual expectations about treatment prior to consultation have obvious implications in discussing treatment options, use of NICE guidelines and compliance with treatment.

Given the paucity of relevant research, and in particular a need to understand impact of medical treatments on quality of life (Santer 2008), this research seeks to provide further understanding of women's perspectives to contextualize evidence from ECLIPSE and other trials of treatments in this field.

Methods

Design: Interviews with purposeful sample of women recruited those who have either consented to participate in the ECLIPSE Trial or declined due to an expressed treatment preference. Data will be generated by series of semi-structured interviews, with grounded approach to data analysis.

Sampling

A purposeful sample of women willing to participate in this research will be selected from women consulting health professionals about heavy menstrual bleeding who have been identified as eligible and approached for inclusion to the ECLIPSE trial, and who have subsequently agreed to be randomized to treatment arms or have declined to participate in the trial because they had a strong treatment preference for a particular medical treatment, which they have then commenced.

Sampling will include women of varying demographic (age, social and educational background, ethnicity) experiencing different medical treatments for menorrhagia, of differing treatment duration, seeking a purposeful range (Mason, 1996) of respondent characteristics and contexts in relation to the study objectives.

Recruitment & consent

Access to participants will be through GP practices and gynaecology clinics participating in the ECLIPSE trial. Practitioners will identify potential participants at the time that interest in participation in the ECLIPSE trial is discussed, and trial participation accepted or declined. Permission will be sought to pass contact details to the researchers (part of the trial research team) by means of an additional sentence on the ECLIPSE trial consent form or the use of consent to contact form for those declining the ECLIPSE trial because they had a strong preference for or against a particular treatment. The researchers will send information and request for written consent, translated where appropriate, to participate in the qualitative component.

Data generation and analysis

Semi-structured face-to-face interviews will be conducted at respondents' convenience with respondents given the option of being interviewed in English or their mother tongue as appropriate. These will normally be conducted in the respondent's home unless preferred elsewhere by respondents. Interviews will be audiotaped and transcribed verbatim.

Data will be analyzed using constant comparison (Strauss & Corbin, 1990) by the researcher, with research colleagues of different disciplinary and professional backgrounds contributing to development of the analysis and conceptual framework to maximize theoretical sensitivity. Analysis will acknowledge the impact where appropriate of use of

interpreters during data generation. Coding will be aided by application of NVivo software in identifying emerging categories and concepts from the data. Data generation and analysis will be iterative, each informing the other, with the seeking of deviant cases (Mason, 1996) and further theoretical sampling and data collection to extend and challenge earlier data and interpretation. This will test the integrity and credibility of the analysis, until no new categories or concepts emerge suggesting theoretical saturation. It is estimated up to 40 initial and up to 30 follow-up interviews may be necessary.

Validation

Findings will be fed back and reviewed with a sample of up to a third of interview participants (i.e. up to 20), who are willing to be approached again. This will be by audiotaped telephone interview following distribution of written summaries, translated where appropriate. Respondents will be asked to consider and comment on the results, enabling the research team to confirm or further refine data interpretation and analysis if appropriate.

References

Chapple A (1999) Menorrhagia: women's perceptions of this condition and its treatment. Journal of Advanced Nursing 29(6):1500-1506

Coulter A, Peto V, Doll H (1994) Patients preferences and the general practitioners decisions in the treatment of menstrual disorders. Family Practice 11:67-74

Mason J. (1996) Qualitative Researching. London: Sage

National Institute of Clinical Excellence (2007) Heavy menstrual bleeding. NICE clinical guideline 44. National Institute of Clinical Excellence, London

O'Flynn N (2006) Menstrual symptoms: the importance of social factors in womens experiences. British Journal of General Practice 56 (533): 950-957

O'Flynn N, Britten N (2004) Diagnosing menstrual disorders: a qualitative study of the approach of primary care professionals. British Journal of General Practice 54(502): 353-358

Santer M.(2008) Heavy menstrual bleeding: delivering patient-centred care (editorial). BJGP ;58:151-2

Strauss A, Corbin J (1990) Basics of Qualitative Research. Grounded theory procedures and techniques. Newbury Park, CA: Sage.

Vuorma S, Teperi J, Hurskaninen R, Aalto A, Rissanen P, Kujansuu E (2003) Correlates of women's preferences for treatment of heavy menstrual bleeding. Patient Education and Counseling 49(2):125-132

APPENDIX G: PREGNANCY NOTIFICATION FORM

R&D reference: EudraCT number: Study Title: Eclipse	Centre (if multicentre trial): Subject ID: Subject initials:	DO NOT SEND IDENTIFIBLE DATA OR SOURCE DOCUMENTS WITH THIS REPORT

PREGNANCY NOTIFICATION FORM

1. MATERNAL INFORMATION

DOB (dd/mm/yyyy)	Date of last menstrual period (dd/mm/yyyy)	Expected date of delivery(dd/mm/yyyy)
Method of contraception	Contraception used as instructed? ☐Yes ☐No ☐Uncertain	

2. MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy. If none, mark as N/A)

3. PREVIOUS OBSTETRIC HISTORY (provide details on all previous pregnancies, including termination or stillbirth)

	Gestation week	Outcome including any abnormalities
1		
2		
3		

4. DRUG INFORMATION (list all therapies taken prior to and during pregnancy)

Name of drug	Daily dose	Route	Date started (dd/mm/yyyy)	Date stopped (dd/mm/yyyy)	Indication	Treatment start (week of pregnancy)	Treatment stop (week of pregnancy)

5. PRENATAL INFORMATION

Have any specific tests, eg amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?

☐No ☐Yes ☐Not known

If yes, please specify test date and results:

6. PREGNANCY OUTCOME

Abortion: ☐Therapeutic ☐Planned ☐Spontaneous Please specify the reason and any abnormalities (if known):	Delivery: ☐Normal ☐Forceps/Ventouse ☐Caesarean Maternal complications or problems related to birth:

R&D reference: EudraCT number: Study Title: Eclipse	Centre (if multicentre trial): Subject ID: Subject initials:	DO NOT SEND IDENTIFIBLE DATA OR SOURCE DOCUMENTS WITH THIS REPORT

Date of abortion (dd/mm/yyyy):	Delivery at week (dd/mm/yyyy):

7. MATERNAL PREGNANCY ASSOCIATED EVENTS:
If the mother experiences an SAE during the pregnancy, please indicate here and complete an SAE form and submit to BCTU immediately

8. CHILD OUTCOME

☐Normal ☐Abnormal ☐Stillbirth If any abnormalities, please specify and provide dates

Sex	Height	Weight	Apgar scores	Head circumference
☐Male ☐Female	cm	kg	1 min 5 mins 10 mins	cm

9. ASSESSMENT OF SERIOUSNESS (OF PREGNANCY OUTCOME)

☐Non serious ☐Involved prolonged inpatient hospitalisation ☐Results in persistent or significant disability/incapacity

☐Life-threatening ☐Mother died Please provide date (dd/mm/yyyy) ☐Stillbirth/neonate died Please provide date (dd/mm/yyyy)

Other seriousness criteria ☐Congenital anomaly/birth defect ☐Other significant medical events

10. ASSESSMENT OF CAUSALITY (OF PREGNANCY OUTCOME)

Please indicate the relationship between pregnancy outcome

☐Unrelated ☐Possibly* ☐Probably* ☐Definitely*

If any of the *fields have been checked, the outcome is considered to be RELATED to the study drug.

11. ADDITIONAL INFORMATION

12. INFORMATION SOURCE

Name, address and telephone number of PI:	
Date of report (dd/mm/yyyy)	
PI signature	

ALL REPORTS MUST BE SIGNED AND DATED BY THE PRINICPAL INVESTIGATOR.
PLEASE SEND ALL REPORTS TO BCTU FAX: 0121 415 9136
Email: eclipse-trial@contacts.bham.ac.uk

13 BCTU TRACKING (INTERNAL USE ONLY)

Report received by	
Report received on (dd/mm/yyyy)	
Action taken	

Practice Address here

PCT Logo here

ECLIPSE - Medical TREATMENT FOR heavy MENSTRUAL BLEEDING: UNDERSTANDING WOMEN'S EXPERIENCES

APPENDIX H: UNDERSTANDING WOMEN'S EXPERIENCES PARTICIPANT INFORMATION SHEET AND CONSENT FORM

GENERAL PRACTIONER: .....

GP PRACTICE TELEPHONE: .....

RESEARCH ASSOCIATE: Gail Prileszky

TELEPHONE: 01332 724722 or 07964 631193

PROF OF PRIMARY CARE Prof Joe Kai
UNIVERSITY OF NOTTINGHAM

TELEPHONE: 01332 724606 (PA Angela Beighton)

Patient Information Sheet Version 1.1

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take the time to read this information carefully. Talk to others about the study if you wish.

Part 1 tells you the purpose of the study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study

Please contact us if anything is not clear or you need to ask for more information, or if you would like this information in another language. Contact details are given below.

Part 1

1.1 Purpose of the study

Heavy menstrual bleeding (sometimes called by the medical term 'menorrhagia') is a very common condition affecting large numbers of women. There are several medical treatment options available including hormonal medications such as the contraceptive pill or injection (such as Depo-Provera), non-hormonal medications such as tranexamic acid and mefenamic acid, or treatment using a hormone releasing coil (a Mirena coil) fitted inside the womb. All of these treatments are known to reduce heavy menstrual bleeding.

The purpose of the study is explore the experience of heavy menstrual bleeding and its treatment from the perspective of women themselves. We hope to better understand this condition and the effects of the differing treatments by collecting detailed information from individuals who are undergoing medical treatment.

1.2 Why have I been invited?

You have been invited to take part *either* because you are taking part in the ECLIPSE Trial of these treatments *or* you have expressed a strong preference for or against a particular treatment (and so declined/were not suitable to take part in the ECLIPSE Trial). In either case you are currently receiving medical treatment for menorrhagia from your GP or gynaecologist.

1.3 Do I have to take part?

It is up to you to decide. We will describe the study and go through this information sheet with you. If you decide to participate we will ask you to sign a consent form. You will be given copies of this information sheet and your consent form. You are free to withdraw at any time without giving a reason. Deciding not to participate or withdrawing from the study will not affect your care in any way.

1.4 What will happen to me if I do take part?

A researcher will visit you at home or somewhere else if you prefer, to interview you at a date and time best suited to you. The interview will last about one hour. You will be asked to talk about your experience of menorrhagia and its effect on your life and also the treatment that you have received. We would like to do one further interview with you between six months and up to two years after your initial interview in order to talk to you about any changes in your experiences and views about treatment over time and to assess the impact of your treatment over time.

In order to make sure that we remember the information that we collect from all the different interviews, the interviews will be taped with your consent. Before the interview begins we will check again that you consent to the interview being taped. If it is more convenient for you the second interview may be conducted over the telephone.

Participating in this study will not change your treatment in any way.

1.5 What are the possible disadvantages and risks of taking part?

There are no disadvantages or risks of taking part in this study and participation will not change your treatment in any way. For some people talking about their personal experiences can be upsetting. Please consider this before making your decision.

1.6 What are the possible benefits of taking part?

We cannot promise this study will help you but with the information that we get from this study we hope to improve the treatment of women with menorrhagia. We hope that the information you give us might help us to understand the impact of menorrhagia and its treatment on the lives of women. Some women may find it useful to talk about their experiences.

1.7 What happens when the research study stops?

We can send you a summary of the research findings once the study is completed. Your medical treatment will continue without interruption.

1.8 What if there is a problem?

Any complaint about the way that you have been dealt with during the study will be addressed. More information in given in Part 2.

1.9 Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be kept confidential.

This completes Part 1, if you are interested in taking part in the study please read the additional information in Part 2 before making your decision.

Part 2

2.1 What will happen if I decide not to continue with the study?

You are free to withdraw from the study at any time without giving a reason. Your treatment for menorrhagia will not be affected. If you decide to withdraw from the study we will destroy both your contact details and any taped or paper record of your interview.

2.2 What if there is a problem?

If you have concerns about the study or about how you have been treated by the researcher please contact the research team. Details are provided below. If you are still unhappy you can make a formal complaint through the NHS Complaints Procedure. Details can be obtained from your GP surgery or local hospital.

2.3 Will my taking part in the study be kept confidential?

Yes. We will keep information in accordance with the 1998 Data Protection Act. Contact details will be kept in a locked filing cabinet at the University of Nottingham. Interview tapes and printed copies of interview transcripts will not have your name on.

Only members of the research team will see the information given by you and all have a duty of confidentiality to you as a research participant. We will do our best to meet this duty.

2.4 What will happen to the results of the research study?

We will send a summary of the main findings to all of the women who were interviewed. A full report will be sent to Health Technologies Assessment as they are sponsoring this research. We anticipate that the results of this study will be published in the medical and nursing press. You will not be identified in any of the reports or publications.

2.5 Who is organising and funding the study?

The study is being organised by the University of Nottingham, University of Birmingham and Birmingham Clinical Trials Unit. It is sponsored by the University of Birmingham. It is being funded by Health Technologies Assessment program, which is part of the National Health Service.

2.6 Who has reviewed the study?

All research in the NHS has been looked at by independent group of people called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by South West Mulit-Centre Research Ethics Committee.

Gail Prileszky Research Associate
University of Nottingham
Graduate Medical School
Derby City General Hospital
DE22 3DT
Tel: 01332 724722 or 07964 631193
gail.prileszky@nottingham.ac.uk

Prof Joe Kai
University of Nottingham
Graduate Medical School
Derby City General Hospital
DE22 3DT
Tel: 01332 724606
angela.beighton@nottingham.ac.uk

APPENDIX I: UNDERSTANDING WOMEN'S EXPERIENCES PATIENT CONSENT FORM

I confirm that I have read and understood the information sheet (version 1.1 dated 21/07/08) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at anytime without giving any reason, without my medical care or legal rights being affected. ☐

I give permission for the interviews to be tape-recorded. ☐

I give permission for the study researcher to contact me by telephone or email to arrange interviews. ☐

I understand that relevant sections of my medical notes and the data collected may be looked at by responsible individuals from the University of Nottingham, University of Birmingham or from regulatory authorities. I give permission for these individuals to have access to my records. ☐

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 the reporting of results. ☐

I agree to take part in this study. ☐

_____	____/____/____	_____
Name of Patient	Date	Signature
_____	____/____/____	_____
Name of Person taking consent	Date	Signature

When completed:

White copy for patient; pink copy for researcher site file; yellow copy to be kept in medical notes

APPENDIX J: UNDERSTANDING WOMEN'S EXPERIENCES CONSENT TO CONTACT FORM

Researcher **Gail Prileszky** *Please ✓box*

I agree to the above named researcher from the ECLIPSE Trial and the University of Nottingham contacting me to explain more about this study ☐

These are my preferred contact details;

Telephone .....

Email .....

_____	___/___/___	_____
Name of Patient	Date	Signature
_____	___/___/___	_____
Name of Person taking consent	Date	Signature

When completed:

White copy for patient; pink copy for researcher site file; yellow copy to be kept in medical notes

APPENDIX K: MEASURING BENEFIT OF TREATMENT IN HEAVY MENSTRUAL BLEEDING FOR ECONOMIC EVALUATIONS

Further Information relating to ECLIPSE Protocol Version 8 dated 15.05.2012: Measuring benefit of treatment in heavy menstrual bleeding for economic evaluations: Which instrument is most appropriate?

A woman's perceived change in quality of life is the sole measure of improvement in the condition of heavy menstrual bleeding following treatment. The measures used to capture this change in the ECLIPSE trial include the generic measures SF-36 and EQ-5D, in addition to the disease-specific measure Shaw.

The interim results of the ECLIPSE trial suggest that neither EQ-5D nor SF-36 are fully responsive (or responsive enough) to changes in women's quality of life when compared to Shaw. Whilst the Shaw measure is, due to its nature, more sensitive to condition specific changes in quality of life it is not an ideal measure for policy decision-makers who need to make a decision about the allocation of scarce health care resources based on cost-effectiveness. Shaw is not ideal because it is not possible to compare the cost-effectiveness results for heavy menstrual bleeding against the cost-effectiveness results of another condition due to the disease specific nature of the instrument. As the generic measures EQ-5D and SF-36, which can be used to compare cost-effectiveness across conditions, have been shown to be minimally responsive, an alternative generic instrument, namely willingness-to-pay (WTP) is proposed. The WTP questionnaire enables women to take into account a broader range of factors, beyond health that are known to be important in this condition, when assigning a value for quality of life. WTP also allows women to consider factors that are associated with the *process* of care (i.e. the initial side effects and possible ineffectiveness of Mirena for the first 6 months that are thought to subside after this time period, leading to no bleeding). The theoretical foundations of WTP enable the instrument to measure factors that are important to the condition, and allow these results to be compared across conditions. The results of the willingness-to-pay measure feed into a cost benefit analysis which provides a framework to measure whether or not the costs involved in providing treatment are worth the benefit produced from such a service.

The research is part of a PhD which is approved and supported by the HTA. The ECLIPSE study has funded the PhD to investigate the appropriateness of instruments used in economic evaluations in heavy menstrual bleeding given the lack of sensitivity of instruments. This research will involve both ECLIPSE trial participants and menstruating women who are not part of the trial and are not necessarily suffering with the condition. By administering the willingness-to-pay measure in addition to the other instruments we can draw comparisons and attempt to make conclusions about the appropriateness of these instruments in economic evaluations. The extent to which the different instruments impact on the results of the economic evaluation can also be assessed.

Objective: To estimate the maximum willingness-to-pay for Mirena or oral treatment for heavy menstrual bleeding and to identify the appropriateness of this measure compared to previous measures

Participants: A purposeful sample of women willing to participate in this sub-study will be selected from the ECLIPSE trial and also from women consulting health professionals in the Birmingham Women's Hospital. **Recruitment and consent:** Access to participants will be through the Birmingham Women's Hospital and the ECLIPSE trial with ethical and local NHS approval to do so. Potential participants in the Birmingham Women's Hospital will be identified by the consultant and researcher. Permission will be sought (consent to contact) to pass contact details to study researchers (part of the ECLIPSE trial research team), a patient information sheet, self-complete questionnaire booklet and request for written consent will be given.

Data collection: The participants will be asked to complete a questionnaire booklet that will ask for information on socio-demographic details, income details, attitude towards treatment options, duration of menorrhagia, perception of severity of condition, several follow-up questions from the ECLIPSE follow-up, willingness-to-pay questions, EQ-5D and the disease-specific Shaw measure. The WTP questions and scenarios have been assessed according to the Delphi method, as clinicians, psychologists and health economists have reviewed the questions.

The WTP questionnaire will be administered to non-ECLIPSE women, visiting the Birmingham Women's Hospital. These are women who have the potential of being in the heavy menstrual bleeding health state but are not yet experiencing the condition (ex-ante) and to ECLIPSE women after treatment (ex-post). There is a debate within the health economics literature regarding which approach is the most appropriate. Whilst the ex-ante approach is theoretically favoured the ex-post approach is the most widely used. By obtaining WTP values in both cases the WTP for both Mirena and oral can be compared across those women that have experienced the treatment and those that have yet to experience them. The appropriateness of each approach can then be explored.

Where a non-ECLIPSE patient is visiting the clinic the patient will be asked to complete the booklet questionnaire (ex-ante). As is typically done in the literature the women will be presented with the scenario of outcomes associated with heavy menstrual bleeding. These outcomes will be based on the ECLIPSE baseline Shaw outcomes. These patients will be asked to imagine themselves in the health state, and provide willingness to pay valuesfor a given treatment. As shown in the booklet questionnaire two scenarios are presented, for oral and Mirena, outlining the possible changes in health states that the woman may experience on each treatment. The scenarios presented for the effectiveness of each treatment for the ex-ante approach are based on the average values obtained from the ECLIPSE trial data at 6 months.

Where ECLIPSE trial participants are used they will be asked to state their WTP for the treatment that they are currently taking and comparisons between approaches for eliciting expected changes in utility following treatment (ex-ante approach) and actual changes in utility following treatment (ex-post approach) will be made. The ECLIPSE patients will also be given an amended version of EQ-5D to identify if changing the wording improves the sensitivity of the instrument to this patient group. The order of EQ-5D instruments (original and amended) will be randomly changed for each patient to ensure that the order of presentation does not impact on the results.

Where non-ECLIPSE patients are used, questionnaires will either be completed in the clinic or patients home. Where ECLIPSE trial participants are used the booklet of questionnaires will be posted to the patient. It is estimated that approximately 50-100 non-ECLIPSE women will be required to complete the questionnaire and 15-20 women will be required to complete the interviews.

At the start of the WTP questionnaire a statement will clarify that these scenarios are hypothetical and designed solely to obtain an estimate of the patients' value of the treatment and that under no circumstances would the women be expected to pay for their healthcare. This is a tried and tested approach. One of the supervisors (Dr Emma Frew) has expertise in this area and direct experience with this approach having used it in over 4000 individuals in funded and published studies.

It is proposed that the willingness-to-pay questions may be piloted beforehand on a small subgroup of women.

In the questionnaire booklet the participant will also be asked if they would like to participate in a semi-structured interview in order to obtain a greater understanding of their choices and to conduct an in-depth analysis of the values given in the questionnaire. Semi-structured face to face interviews will be conducted in English at the respondents' convenience. The estimated duration is 30 minutes and will normally be conducted in the Birmingham Women's hospital clinic or a University of Birmingham building.

Analysis:

1. Evaluation of all willingness-to-pay questions: acceptability will be assessed (proportion of questions answered in relation to total number of questionnaires completed). The distribution of WTP values will be assessed by calculating skewness and Kurtosis. Reliability will be estimated using Kappa statistics and the intra-class correlation coefficient. Floor and ceiling effects will be considered by looking at the lowest and highest scores possible for each scale/item.

2. Descriptive statistical analyses will be conducted to explore frequencies, mean/median values, standard error of mean, and standard deviation

3. To test the theoretical validity of the WTP data we will use univariate correlative analyses of the clinical outcome parameters (disease severity of patient), income levels and WTP values

4. Multivariate linear regression analyses using ordinary least squares (OLS) to explore predictive variables for WTP.

5. Net-benefits will be estimated by subtracting the costs from WTP values. The costs will then be bootstrapped to generate 95% confidence intervals.

Where possible the interview will be conducted within 1-2 months of agreeing to participate. Interviews will be audiotaped and transcribed verbatim. All data will be transcribed and anonymised to remove personal identifiable data and stored in password-protected files. Data will be analysed using appropriate techniques and coded using appropriate software such as NVivo.

APPENDIX L: SUB-STUDY PATIENT INFORMATION SHEET

We would like to invite you to take part in a research study. A research team based at the University of Birmingham and Birmingham Women's Hospital would like to ask you a few questions about how you feel about the treatment for heavy menstrual bleeding that you receive. We would like to know if you would be willing to complete a questionnaire, at your own convenience. Before you decide you need to understand why the research is being done and what it would involve for you. Please take the time to read this information carefully.

Please contact Miss Sabina Sanghera if anything is not clear or you have any questions. Contact details are at the end of the form.

1 Purpose of the study

Heavy menstrual bleeding (sometimes called by the medical term 'menorrhagia') is a very common condition affecting large numbers of women. There are several medical treatment options available including hormonal medications such as the contraceptive pill or injection (such as Depo-Provera),non-hormonal medications such as tranexamic acid and mefenamic acid, or treatment using a hormone releasing coil (a Mirena coil) fitted inside the womb. All of these treatments are known to reduce heavy menstrual bleeding.

As heavy menstrual bleeding is known to have a significant impact on your quality of life the purpose of the study is to identify the extent to which the condition affects your life by looking at the value you would place on treatment for heavy menstrual bleeding. We realise that current measures to assess this value may not be entirely appropriate and this alternative measure may improve our ability to evaluate the value you place on treatment. We hope to better understand the value of the different treatments by collecting detailed information from individuals who are either undergoing treatment or are soon to undergo medical treatment.

2 Do I have to take part?

It is up to you to decide. If you decide to participate we will ask you to sign a consent form. You are free to withdraw at any time without giving a reason. Deciding not to participate or withdrawing from the study will not affect your care in any way.

3 What will happen if I take part?

You will be asked to complete a questionnaire which should take no longer than 15 minutes to complete and will ask questions about your wellbeing and how much you value the treatment you have been given. The questionnaire will only need to be completed once:

- If you have not yet started treatment, the questionnaire will need to be completed before you have treatment.
- If you are already taking treatment the questionnaire can be completed at anytime.

The questionnaire can either be completed in the Birmingham West Midlands clinic or at your convenience as it can be returned in a pre-paid stamped addressed envelope. At the end of the questionnaire a sample of women may then be asked to have a follow-up interview at a convenient date and time to delve deeper into the responses given in the

questionnaire and to find out how appropriate the questions were. If you tick that you agree to an interview, and are subsequently selected, it is likely that the interview will last about 30 minutes. In order to make sure that we remember the information that we collect from all the different interviews, the interviews will be taped with your consent.

4 What are the possible benefits of taking part?

The information that we get from this study will be used to help understand your views and opinions on the current treatments that you receive for heavy menstrual bleeding. The information you give us will help us to understand the impact of treatment of heavy menstrual bleeding on women's lives and better evaluate the treatment.

5 Will my taking part in the study be kept confidential?

Yes. Answers will be anonymous. We will follow ethical and legal practice and all information about you will be kept confidential. You will not be identified in any of the reports or publications.

6 Who is organising and funding the study?

The study is organised and sponsored by the University of Birmingham. It is being funded by Health Technologies Assessment program, which is part of the National Health Service.

7 Who has reviewed the study?

All research in the NHS has been reviewed and given a favourable opinion by an independent Research Ethics Committee to protect your safety, rights, wellbeing and dignity.

Contact Details:

Miss Sabina Sanghera
Health Economics Unit
Public Health Building
University of Birmingham
Edgbaston
B15 2TT

Email: sxs574@bham.ac.uk
Tel: 0121 414 8176

APPENDIX M: SUB- STUDY CONSENT TO CONTACT FORM

Researcher **Sabina Sanghera**

Please initial box to confirm consent

I agree to the above named researcher from the ECLIPSE Trial and the University of Birmingham contacting me to arrange an interview ☐

These are my preferred contact details;

Address .....

Email .....

_____	___/___/___	_____
Name of Participant	Date	Signature

_____	___/___/___	_____
Name of Person taking consent	Date	Signature

Copies of Consent Forms: Original copy for BWH site file, 1 copy for participant, 1 copy to be kept in patient's hospital notes and 1 copy to be sent to Trial Office:
Eclipse Trial Office, FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT

APPENDIX N: SUB-STUDY PATIENT CONSENT FORM

Eclipse Trial No (if appropriate)

Please Initial each box to confirm consent

I confirm that I have read and understood the ex-ante information sheet v1.0 dated 24.09.12 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

If applicable, I give permission for the study researchers to contact me by telephone or email to arrange an interview. ☐

If applicable, I give permission for the interviews to be tape-recorded. ☐

I understand that relevant sections of my medical notes and the data collected may be looked at by responsible individuals from the University of Birmingham or from regulatory authorities. I give permission for these individuals to have access to my records. ☐

I understand that the information will be used for research only and that I will not be identified in any way in the analysis and the reporting of results. ☐

I agree to my GP being informed of my participation in the above study. ☐

I understand what is involved and agree to take part in this study. ☐

_____	____/____/ ____	_____
Name of Participant	Date	Signature
_____	____/____/____	_____
Name of Person taking consent	Date	Signature

Copies of Consent Forms: Original copy for BWH site file, 1 copy for participant, 1 copy to be kept in patient's hospital notes and 1 copy to be sent to Trial Office:
Eclipse Trial Office, FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT

APPENDIX O: EX-ANTE SUB-STUDY PATIENT INFORMATION SHEET

A research team based at the University of Birmingham and Birmingham Women's Hospital would like to ask you a few questions about how you feel about different treatments for heavy menstrual bleeding (heavy periods). You do not yourself have to experience heavy menstrual bleeding.

We would like to know if you would be willing to complete **ONE** questionnaire, at your own convenience. Before you decide you need to understand why the research is being done and what it would involve for you. Please take the time to read this information carefully.

Please contact Miss Sabina Sanghera if anything is not clear or you have any questions. Contact details are at the end of the form.

1. Purpose of the study

Heavy menstrual bleeding (sometimes called by the medical term 'menorrhagia') is a very common condition affecting large numbers of women. There are several medical treatment options available including hormonal medications such as the contraceptive pill or injection (such as Depo-Provera), non-hormonal medications such as tranexamic acid and mefenamic acid, or treatment using a hormone releasing coil (a Mirena coil) fitted inside the womb. All of these treatments are known to reduce heavy menstrual bleeding.

As heavy menstrual bleeding is known to have a significant impact on quality of life the purpose of this work is to identify which treatment is better by looking at the value you would place on treatment for heavy menstrual bleeding. We realise that current measures to assess this value may not be entirely appropriate and the new measure used in this questionnaire may improve our ability to evaluate the value women place on treatment.

2. Do I have to take part?

It is up to you to decide. If you decide to participate we will ask you to sign a consent form. You are free to withdraw at any time without giving a reason. Deciding not to participate or withdrawing from the study will not affect your care in any way.

3. What will happen if I take part?

You will be asked to complete ONE questionnaire which should take no longer than 10 minutes to complete. The questionnaire will provide you with a description of someone who

has heavy periods and ask you to place yourself in that situation. It will then ask questions about how much you would value different treatments. The questionnaire will only need to be completed **once**. The questionnaire can either be completed in the Birmingham Women's Hospital clinic or at your convenience as it can be returned in a pre-paid stamped addressed envelope. The last question in the questionnaire asks if you would be happy to take part in a follow-up one-to-one interview at a convenient date and time to delve deeper into the responses given in the questionnaire and to find out how appropriate the questions were. If you tick that you agree to an interview, and are subsequently selected, it is likely that the interview will last about 30 minutes. In order to make sure that we remember the information that we collect from all the different interviews, the interviews will be taped with your consent.

4. **What are the possible benefits of taking part?**

The information that we get from this study will be used to help understand your views and opinions on the current treatments available for heavy menstrual bleeding. The information you give us will help us to decide which treatment is better and understand the impact of treatment of heavy menstrual bleeding on women's lives.

5. **Will my taking part in the study be kept confidential?**

Yes. Answers will be anonymous. We will follow ethical and legal practice and all information about you will be kept confidential. You will not be identified in any of the reports or publications.

6. **Who is organising and funding the study?**

The study is organised and sponsored by the University of Birmingham. It is being funded by Health Technologies Assessment program, which is part of the National Health Service.

7. **Who has reviewed the study?**

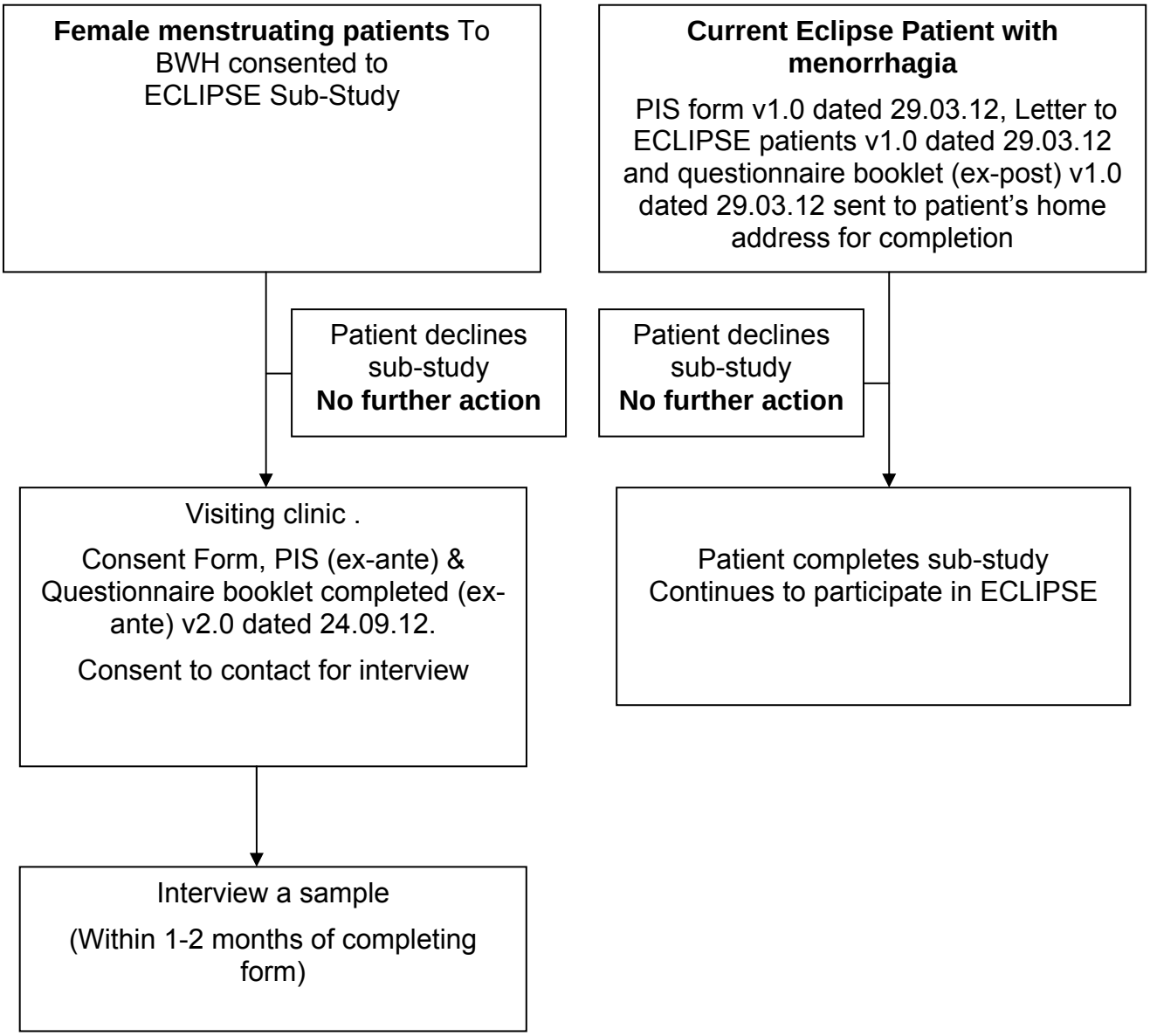
All research in the NHS has been reviewed and given a favourable opinion by an independent Research Ethics Committee to protect your safety, rights, wellbeing and dignity.

Contact Details:

Miss Sabina Sanghera
Health Economics Unit
Public Health Building
University of Birmingham
Edgbaston
B15 2TT

Email: sxs574@bham.ac.uk
Tel: 0121 414 8176

APPENDIX P: SUB STUDY SCHEMA ECLIPSE & NON ECLIPSE PARTICIPANTS

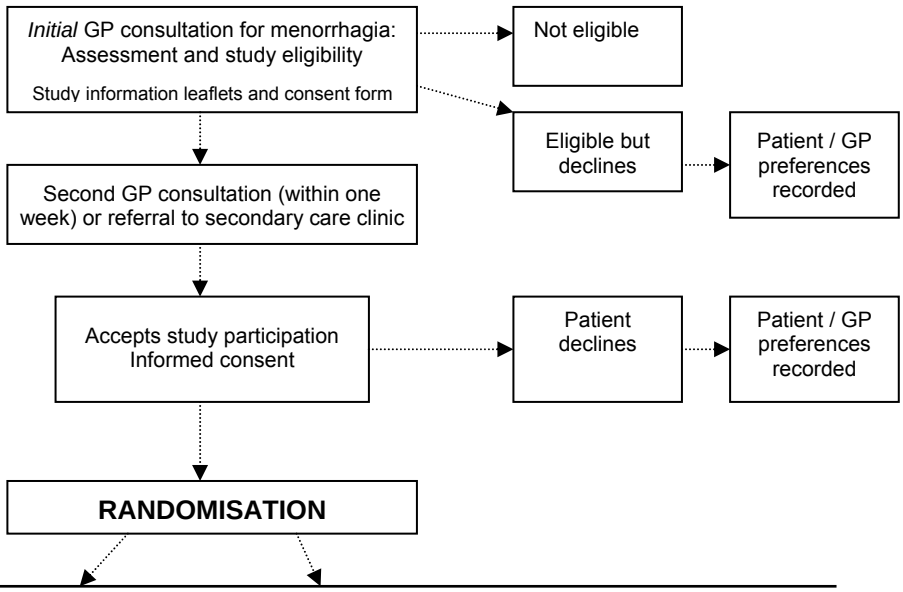


ECLIPSE TRIAL SCHEMA

ELIGIBILITY

- Any women between the ages of 25-50 presenting to her General Practitioner with menorrhagia
- Initial or subsequent presentation and not intending to become pregnant in the next 5 years

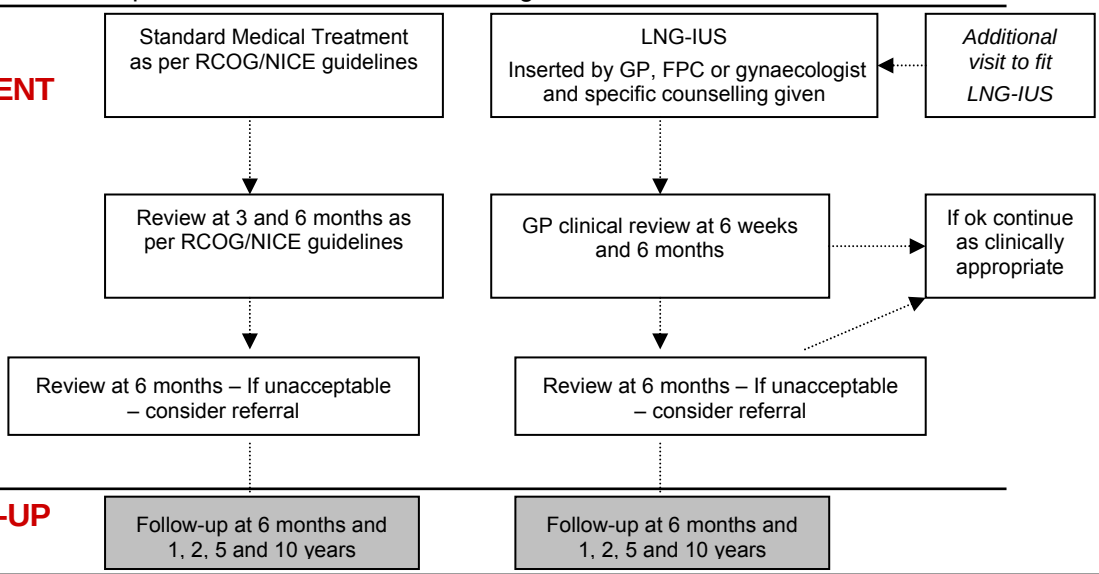
RANDOMISATION



TELEPHONE RANDOMISATION

- Obtain patient's consent.
- Prepare for telephone questions using the randomisation notepad.
- Telephone the randomisation service on 0800 953 0274.
- When all the relevant questions on the randomisation notepad have been answered, treatment allocation and patient reference number will be given.

TREATMENT



FOLLOW-UP

Follow-up at 6 months and 1, 2, 5 and 10 years

Follow-up at 6 months and 1, 2, 5 and 10 years

FOR **RANDOMISATION**

TELEPHONE 0800 953 0274 OR FAX 0121 415 9136

WEBSITE: https://www.trials.bham.ac.uk/eclipse

Also for urgent medical queries. For administrative queries and trial supplies, contact the ECLIPSE Trial Office, Division of Medical Sciences, Robert Aitken Institute, University of Birmingham, Bham B15 2TT

FREEPOST RRKR-JUZR-HZJG, BCTU, Div of Med Sciences, Uni of Bham, B15 2TT. Tel: 0121 415 9109