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The UCON Trial:

Ulipristal acetate versus conventional management of heavy menstrual bleeding (HMB; including uterine fibroids): a randomised controlled trial and exploration of mechanism of action

PROTOCOL



**National Institute for
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Protocol Versions

Version No - Date	Amendment Type	Summary of Changes Made
2.0 – 15 th April 2015	Substantial Amendment (AM2)	<p>Admin changes - trial logo added, TSC/ UCON Trials Office Updated, trial registration numbers updated.</p> <p>Trial Summary – eligibility updated.</p> <p>'2.2 - RCT Outcomes' section updated with surgical intervention. '3.1 Design' clarified. '4.1 number of participants' clarified. '4.2 – Eligibility' clarified. '5 Participant Selection and enrolment'. Figure 1 updated. '5.2 Consenting for Screening for Eligibility' clarified. '5.5 Randomisation' clarified. Figure summarising patient pathway for Edinburgh patients inserted. '6 – Investigational Medicinal Products' clarified. '7 Study Assessments Overview' clarified. '8 – Data Collection' clarified. '9 – Statistics and Data Analysis'. '10 – Adverse Events and Pharmacovigilance'. '11 - Trial Management and Oversight Arrangements' admin changes.</p>
1.1 – 10 th November 2014	N/A - Response to NRES	Points of clarification – Study Population (Section 4), Participant Selection and Enrolment (5), Investigational Medicinal Product (6), Study Assessments (7)

Trial Registration Numbers

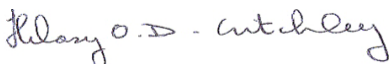
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PROTOCOL APPROVAL SIGNATURES

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

This protocol was written in accordance with the sponsor's procedures available at:
<http://www.accord.ed.ac.uk/standardopprocs/CRSOPs.html>

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Professor Hilary Critchley  22nd June 2015

University of Edinburgh	Signature	Date
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Mr Lee Middleton  23rd June 2015

University of Birmingham	Signature	Date
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Dr Vikki Young  22 JUNE 2015

University of Edinburgh	Signature	Date
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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LNG-IUS	Levonorgestrel releasing intra-uterine system
MHRA	Medicines and Healthcare Products Regularity Authority
MRI	Magnetic Resonance Imaging
NIHR	National Institute for Health Research
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UPA	Ulipristal Acetate
UFS-QoL	Uterine Fibroid Symptom-Quality of Life

CONTENTS

CONTENTS	x
TRIAL SUMMARY	1
1 INTRODUCTION	5
1.1 BACKGROUND	5
1.2 RISKS AND BENEFITS	6
1.3 RATIONALE FOR STUDY	6
2 STUDY OBJECTIVES.....	6
2.1 OBJECTIVES	6
2.2 OUTCOMES	7
3 STUDY DESIGN	8
3.1 DESIGN	8
4 STUDY POPULATION	8
4.1 NUMBER OF PARTICIPANTS	8
4.2 ELIGIBILITY.....	9
4.3 CO-ENROLMENT.....	10
5 PARTICIPANT SELECTION AND ENROLMENT	11
5.1 IDENTIFYING PARTICIPANTS	11
5.2 CONSENTING FOR SCREENING FOR ELIGIBILITY	12
5.3 CONFIRMATION OF ELIGIBILITY BEFORE RANDOMISATION.....	13
5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS	13
5.5 RANDOMISATION.....	14
6 INVESTIGATIONAL MEDICINAL PRODUCT(S)	18
6.1 STUDY DRUG	18
6.2 DOSE AND DELIVERY OF IMPS	19
6.3 DOSE CHANGES.....	20
6.4 PARTICIPANT COMPLIANCE	21
6.5 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for ulipristal acetate	21
6.6 KNOWN ADVERSE REACTIONS FOR ULIPRISTAL ACETATE.....	22
6.7 SPECIAL WARNINGS AND PRECAUTIONS FOR USE FOR LEVONORGESTREL.....	22
6.8 KNOWN ADVERSE REACTIONS FOR LEVONORGESTREL.....	23
6.9 OTHER MEDICATIONS	23
7 STUDY ASSESSMENTS.....	24
7.1 STUDY ASSESSMENTS OVERVIEW	24
7.2 TIMING OF STUDY ASSESSMENTS.....	24
7.3 OUTCOMES COLLECTED AT STUDY ASSESSMENTS	25

8	DATA COLLECTION	26
8.1	DATA COLLECTION FORMS	26
8.2	SOURCE DATA	28
8.3	DATA MANAGEMENT.....	29
8.4	QUALITY ASSURANCE OF ENDOMETRIAL BIOPSY ASSESSMENTS.....	29
8.5	MECHANISTIC SUB-STUDY	29
9	STATISTICS AND DATA ANALYSIS	31
9.1	SAMPLE SIZE CALCULATION	31
9.2	PROPOSED ANALYSES	31
9.3	PROPOSED ANALYSES - MECHANISTIC STUDY	26
10	ADVERSE EVENTS AND PHARMACOVIGILANCE.....	33
10.1	DEFINITIONS.....	33
10.2	IDENTIFYING AEs AND SAEs	34
10.3	RECORDING AEs AND SAEs	34
10.4	ASSESSMENT OF AEs AND SAEs	36
10.5	REPORTING OF SAEs/SARs/SUSARs	37
10.6	REGULATORY REPORTING REQUIREMENTS.....	38
10.7	FOLLOW UP PROCEDURES	38
10.8	PREGNANCY	39
11	TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS.....	39
11.1	TRIAL MANAGEMENT GROUP	39
11.2	The UCON TRIAL OFFICE	39
11.3	TRIAL STEERING COMMITTEE	39
11.4	DATA MONITORING COMMITTEE	40
11.5	INSPECTION OF RECORDS	40
11.6	RISK ASSESSMENT	40
11.7	STUDY MONITORING AND AUDIT	41
12	GOOD CLINICAL PRACTICE	41
12.1	ETHICAL CONDUCT.....	41
12.2	REGULATORY COMPLIANCE.....	41
12.3	INVESTIGATOR RESPONSIBILITIES.....	41
13	STUDY CONDUCT RESPONSIBILITIES	44
13.1	PROTOCOL AMENDMENTS	44
13.2	PROTOCOL VIOLATIONS AND DEVIATIONS.....	44
13.3	SERIOUS BREACH REQUIREMENTS	44
13.4	STUDY RECORD RETENTION.....	44
13.5	END OF STUDY	45

13.6	CONTINUATION OF DRUG FOLLOWING THE END OF STUDY	45
13.7	INSURANCE AND INDEMNITY	45
14	REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS.....	46
14.1	AUTHORSHIP POLICY.....	46
14.2	PUBLICATION	46
15	REFERENCES.....	38
	APPENDIX 1: TRIAL SCHEMA	40

TRIAL SUMMARY

DESIGN:	A multicentre, randomised controlled trial with an embedded mechanistic evaluation of UPA compared to LNG-IUS.
SETTING:	5 NHS hospitals within the United Kingdom
TARGET POPULATION:	<p>Women aged over 18 years or over , who are presenting to primary and/or secondary care with HMB.</p> <p>Exclusion criteria:</p> <p>Post-menopausal, a uterus >14 week fibroid uterus and/or cavity length >11cm, submucosal fibroids >2cm in diameter, contraindications to UPA or LNG-IUS; intention to continue current use of CYP3A4 inhibitors (e.g. erythromycin propionate; ketoconazole); intention to continue current use of CYP3A4 inducers (Phenytoin, carbamazepine, rifampicin, St John's Wort), intention to continue current use of P-glycoprotein substrate (e.g. digoxin); past, current or suspected diagnosis of endometrial hyperplasia or neoplasia, severe hepatic impairment; Epilepsy managed with carbamazepine, phenytoin; significant renal impairment; pregnant; current plans to become pregnant within 12 months; currently breastfeeding, severe asthma that is not sufficiently controlled by oral glucocorticoids; past or current known history of uterine, cervical, ovarian or breast cancer; receiving P-glycoprotein substrates; current use progestagen-releasing intrauterine device (except if allocated within UCON), intention to continue continued regular use of Mefenamic acid, intention to continue intention to continue regular use of Mefenamic acid, intention to continue regular use of GnRH analogues, continued regular use of Progestagen-only contraceptive, intention to continue continued regular use of combined oral contraceptive pills, intention to continue hormonal replacement therapy.</p>

<p>HEALTH TECHNOLOGIES</p> <p>ASSESSED:</p>	<p>Those allocated to UPA will receive proprietary ulipristal acetate 5mg, orally, once daily. The participant should start taking UPA within the first five days of starting menstrual bleeding.</p> <p>Women will be instructed to take UPA in 3 courses according to the following cyclical regime:</p> <ol style="list-style-type: none"> 1. One 5mg tablet of UPA to be taken daily for 12 weeks then stopped for 4 weeks, when light vaginal bleeding may occur (withdrawal bleed). 2. After 4 weeks off treatment, regardless of whether they experience a withdrawal bleed, they should recommence UPA 5mg daily for another 12 weeks, then stop for 4 weeks, when they will expect to have a withdrawal bleed. 3. Repeat as for treatment course (2). <p>Where contraception is required, the woman will be asked to use a barrier method.</p> <p>OR</p> <p>Levonorgestrel-releasing intra-uterine system, retained for up to 5 years.</p>
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OUTCOME MEASURES:	<p>Primary Outcome:</p> <p>The primary outcome measure is the condition-specific Menorrhagia Multi-Attribute Scale (MMAS) designed and validated to capture the impact of HMB on women's day-to-day life (1). HMB 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 menorrhagia multi-attribute utility assessment (MMAS) questionnaire attempts to capture the consequences of HMB on these domains with 6 questions each with 4 levels of response. Summary scores range from 0 (not affected) to 100 (worst affected). The primary time point for analysis will be at 12 months.</p> <p>Secondary Outcome measures:</p> <ul style="list-style-type: none"> • Menstrual bleeding will be captured by validated Pictorial Blood Loss Assessment Chart (PBAC) (14). The standard PBAC is a validated and well used assessment of menstrual blood loss in women. The PBAC will be supplemented by visual analogue scales for menstruation duration, regularity and pelvic pain. • Uterine Fibroid Symptom and Quality of Life (UFS-QoL) instrument, which contains a health related quality of life (HRQoL) domain and a symptom domain (15). This instrument will be only given to women diagnosed with fibroids. • Sexual Activity Questionnaire (16), a measure of sexual functioning, used in other HMB trials. The sexual activity questionnaire is a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort. It is quick and easy to administer and has good face validity delineating between the sexual functioning of pre and post-menopausal women. • Satisfaction with treatment outcome measured on a 5-point Likert scale. Specific statements about the experience and the acceptability of the treatment and the beliefs about the value of the treatment will be elicited from the participants. • Surgical intervention (hysterectomy or endometrial ablation) • Adherence to trial treatments, as reported by the participant. • Serious adverse events and reactions reported by participants, principally those that are serious and detailed in the respective Summary of Product Characteristics (SmPC) and those that are unexpected. • Clinical measurements to assess safety and efficacy will include pelvic ultrasound (endometrial appearance; fibroid volume, presence of fibroids) and endometrial biopsies (reported according to pre-agreed criteria by independent pathologists blinded to treatment allocations). Blood samples will be taken to assess serum haemoglobin and oestradiol levels.
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	<p>Functional and mechanistic outcomes</p> <ul style="list-style-type: none"> • Impact on endometrial tissue architecture including regulation of the vascular compartment • Impact on endometrial steroid responsiveness, proliferation, cell survival and inflammatory processes • Expression of genes implicated in pre-malignant change including tumour suppressors • Effects on uterine/ fibroid structure and vascularity as determined by MRI-DCE and high resolution structural MRI
ANALYSIS:	<p>Analysis of the primary outcome will be performed using a linear regression model to estimate differences in MMAS responses between groups at each time-point, including baseline score and the minimisation variables as covariates. Twelve months will be considered the primary outcome time. Point estimates, 95% confidence intervals and p-values from two-sided tests will be calculated for all main outcome measures.</p> <p>The mechanistic sub-study will investigate possible changes in defined histological, immunological and molecular/ cellular parameters within treatment groups over time and will be analysed using paired t-tests following an appropriate transformation and also by using non-parametric methods (Wilcoxon signed rank test) for confirmation.</p>
SAMPLE SIZE:	<p>The trial has been designed to detect a 13 points difference in MMAS score between the two groups at 12 months. To detect this size of difference (approximately 0.5 standard deviations) with 90% power ($p=0.05$) will require 86 women per group, 172 in total. To allow for a 20% loss to follow-up or pregnancy, the sample size has been inflated to 220 women in total.</p> <p>In the mechanistic evaluation (performed at the Royal Infirmary of Edinburgh only), a sample size of 20 would give >90% power ($p=0.05$) to detect a change from baseline – for example in PH3 immunoscore in the endometrium of >1 standard deviation.</p>

1 INTRODUCTION

1.1 BACKGROUND

Menstrual bleeding complaints affect quality of life and comprise a substantial societal burden, including major impact on health care use and costs. In the UK, 1 million women annually seek help for heavy menstrual bleeding (HMB; Clinical Guideline 44; <http://www.nice.org.uk/guidance/cg44>) and reported treatment costs exceed £65m; an estimated 3.5 million work-days are lost annually (1).

Current commonly prescribed medical treatments for HMB include COX-inhibitors, anti-fibrinolytic therapy, and the levonorgestrel-releasing intra-uterine system (LNG-IUS; Mirena®). NICE recommends LNG-IUS as the first line medical treatment. The LNG-IUS significantly reduces the burden of heavy menstrual bleed compared to non-hormonal treatments, substantially reduces menstrual blood loss, often resulting in amenorrhoea, but the unpredictable unscheduled bleeding may be problematic, with up to a third ceasing use within 2 years (2, 3).

An exciting new group of pharmacological agents, called selective progesterone receptor modulators (SPRMs) are in development and have the potential to provide effective oral treatment for HMB. These SPRMs impart a tissue-specific partial progesterone antagonist effect, acting on progesterone receptors in both endometrial and underlying myometrial tissue. Ulipristal Acetate (UPA) is the only SPRM to have been licensed for use in clinical practice albeit restricted to two cycles of 3 month pre-treatment of fibroids prior to surgical removal. The introduction of this drug followed evaluation in two concurrent randomised controlled trials (RCTs) (4); 'PEARL I' assessed the efficacy of UPA 5mg and 10 mg daily on uterine bleeding and fibroid volume against placebo and 'PEARL II' assessed the efficacy and side effects of UPA versus the gonadotrophin-releasing hormone analogue (GnRHa) leuprolide acetate for treating symptomatic uterine fibroids prior to surgery (4). Both trials demonstrated control of HMB in over 90% of women and amenorrhoea in over 70% women. Control of HMB was achieved significantly more quickly in the UPA group. There was a statistically significant reduction in uterine fibroid size (-21% in the 5mg and -12% in the 10mg groups). Compliance with treatment over 3 months was high in both studies (96% and 98%) and reported side-effects were limited to minor complaints, of which headache (4%) and breast complaints (4%) were the most common, with no difference between active drug and placebo.

Different classes of SPRM induce distinct endometrial morphology, which can be confused with complex hyperplasia. To date detailed analysis of endometrial histology has been limited to treatment with UPA for 3 months (5, 6); detailed histological evaluation showed altered architectural glandular features including extensive cystic dilatation. The glandular epithelium appeared inactive or contained abortive subnuclear vacuolization, occasional mitoses, and apoptosis. Histology returned to normal after discontinuation of treatment (6). Treatment of monkeys for 39 weeks revealed similar endometrial histology to that in women (7).

PTEN is a tumour suppressor gene product, described as a gatekeeper for initiation of carcinogenesis in the endometrium (8, 10). Loss of PTEN function occurs as an early event in endometrial carcinogenesis and has been proposed as a biomarker for premalignant disease even in histologically normal endometrium (8, 10). Progesterone plays an important role in eliminating PTEN-deficient endometrial cells when administered via a progestin-releasing intrauterine device (11) or systemically (12). A compound with progesterone antagonist activity, such as UPA, may raise concerns of an unfavourable effect on PTEN expression and thus on the potential to influence predisposition to latent endometrial precancerous lesions. Hence study of PTEN in women administered UPA is important.

1.2 RISKS AND BENEFITS

Whilst short term use of UPA has been shown to be effective in treating HMB associated with uterine fibroids (3-10cm in size), UPA has the potential to provide a safe, fertility preserving, rapidly effective and convenient oral medical treatment, suitable for women with HMB throughout reproductive age whether associated with fibroids or not. However, whilst UPA has the potential to revolutionise the treatment of HMB, our understanding of the mechanism and location of action of UPA is unclear, as is its longer term safety and effectiveness. As with earlier SPRMs, UPA induces non-physiological endometrial changes known as progesterone-receptor modulator-associated endometrial changes (PAECs) in 62% of participants receiving 5mg UPA, although there is no evidence these are premalignant. Whilst these changes are reported to be reversed in all women after 6 months of ceasing treatment, the mechanisms underlying these changes and their clinical significance remain uncertain. More recent unpublished data provide further reassurance of the reversibility of PAEC - if endometrial biopsy is performed after one normal menstrual shedding after treatment withdrawal, the incidence of PAEC is reduced to around 30%, a rate that remains similar after up to 4 UPA treatment cycles (Personal communication A Williams).

1.3 RATIONALE FOR STUDY

The rationale for using UPA to control HMB is because HMB is a clinical area of unmet need, with a community prevalence of 25%, and can significantly impact on women's lives and burden individuals and healthcare systems. HMB often co-exists with uterine fibroids, benign tumours of uterine muscle present in up to 80% of women of reproductive age. Medical therapy for HMB, particularly when fibroids are present, may be either ineffective or associated with unacceptable side effects. Preservation of fertility is an issue for many women, given the trend for later births.

It is clear that there is an urgent need to develop safe, simple, acceptable, fertility-sparing medical treatments for HMB. SPRMs may provide a solution in light of the mounting evidence that progesterone and the progesterone receptor play a pivotal role in both menstruation and fibroid growth and development. The PEARL studies demonstrated control of HMB in over 90% of women and amenorrhoea in over 70% women. There were no serious side effects or complications associated with UPA; adverse events were limited to minor complaints. However despite profound therapeutic potential, robust data on long term effectiveness and the mechanisms of action of SPRMs in women with HMB remain to be elucidated. There is an urgent need to evaluate the use of UPA against current best medical treatment for all women with HMB.

2 STUDY OBJECTIVES

2.1 RCT OBJECTIVES

2.1.1 Primary Objective

- Determine if UPA is more effective at reducing the burden of HMB symptoms than LNG-IUS after 12 months of treatment.

2.1.2 Secondary Objectives

- Ascertain whether UPA use beyond 3 months and up to 12 months duration is associated with histological changes to the endometrium, and if so, whether this compromises safety.

- Ascertain whether UPA is more effective than LNG-IUS in relation to menstrual blood loss, sexual activity, generic quality of life, satisfaction with treatment, patient reported adverse events, and compliance at 3, 6 and 12 months.
- Determine the response to UPA and LNG-IUS treatment difference in the presence of uterine fibroids in terms of (i) alleviation of HMB and (ii) change in uterine/fibroid volume.

2.1.3 Mechanistic Sub-study Objectives

To understand how UPA causes a reduction in menstrual bleeding and uterine/ fibroid volume in women with HMB, we will determine whether:

- Administration of UPA alters endometrial cell function (proliferation, apoptosis, expression of steroid receptors, tumour suppressors or inflammatory mediators).
- UPA reduces blood flow and blood volume in the endometrium, junctional zone, outer myometrium and fibroid tissue.
- UPA alters the volume fraction of the extracellular matrix in the above tissues.
- UPA reduces uterine and fibroid volume.

2.2 RCT OUTCOMES

2.2.1 Primary outcome

The primary outcome measure is the condition-specific Menorrhagia Multi-Attribute Scale (MMAS) designed and validated to capture the impact of HMB on women's day-to-day life (1). HMB 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 menorrhagia multi-attribute utility assessment (MMAS) questionnaire attempts to capture the consequences of HMB on these domains with 6 questions each with 4 levels of response. Summary scores range from 0 (not affected) to 100 (worst affected). The primary time point for analysis will be at 12 months.

2.2.2 Secondary outcome

- Menstrual bleeding will be captured by validated Pictorial Blood Loss Assessment Chart (PBAC) (14). The standard PBAC is a validated and well used assessment of menstrual blood loss in women. The PBAC will be supplemented by visual analogue scales for menstruation duration, regularity and pelvic pain
- Uterine Fibroid Symptom and Quality of Life (UFS-QoL) instrument, which contains a health related quality of life (HRQoL) domain and a symptom domain (15). This instrument will be only given to women diagnosed with fibroids.
- Sexual Activity Questionnaire (16), a measure of sexual functioning, used in other HMB trials (3). The sexual activity questionnaire is a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort. It is quick and easy to administer and has good face validity delineating between the sexual functioning of pre and post-menopausal women.
- Satisfaction with treatment outcome measured on a 5-point Likert scale. Specific statements about the experience and the acceptability of the treatment and the beliefs about the value of the treatment will be elicited from the participants.

- Surgical intervention (hysterectomy or endometrial ablation)
- Adherence to trial treatments, as reported by the participant.
- Serious adverse events and reactions reported by participants, principally those that are serious and detailed in the respective Summary of Product Characteristics (SmPC) and those that are unexpected.
- Clinical measurements to assess safety and efficacy will include serum haemoglobin as appropriate, oestradiol, pelvic ultrasound (endometrial appearance; fibroid volume) and endometrial biopsies (reported according to pre-agreed criteria by independent pathologists blinded to treatment allocations).

2.2.3 Functional and mechanistic outcomes

- Impact on endometrial tissue architecture including regulation of the vascular compartment
- Impact on endometrial steroid responsiveness, proliferation, survival and inflammatory processes
- Expression of genes implicated in pre-malignant change including tumour suppressors
- Effects on uterine/ fibroid structure and vascularity as determined by MRI-DCE and high resolution structural MRI

3 STUDY DESIGN

3.1 DESIGN

A multicentre, randomised controlled trial of UPA compared to LNG-IUS with a concurrent mechanistic evaluation of UPA. A trial schema is shown in Appendix 1.

4 STUDY POPULATION

The target population is women who present to primary and secondary care with HMB. Participants will be recruited from the gynaecological, out-patient clinics of participating centres, fitting around their current service provision. Recruitment will be supported by dedicated research nurses, who will work with local gynaecology leads. A flowchart of the recruitment process is shown in Figure 1.

4.1 NUMBER OF PARTICIPANTS

UCON will aim to recruit a minimum of 220 women into the randomised controlled trial and from those, approximately 20 women will be required to undergo more detailed evaluation to contribute to the mechanistic study which is conducted at the Royal Infirmary of Edinburgh. The statistical basis of the sample size calculation is detailed in Section 9.1.

Recruitment will take place over 24 months from 5 centres (i.e. 2 participants/ centre/month).

4.2 ELIGIBILITY

In order to be randomised into the UCON trial, all eligibility criteria must be satisfied. Investigators will be asked to confirm each eligibility criteria at randomisation.

4.2.1 Inclusion Criteria

- Aged 18 years or over
- Menstrual bleeding at intervals of 21-42 days that she perceives to be heavy and troublesome
- Willing to receive medical treatment with either UPA or LNG-IUS
- Willing to undergo two pelvic ultrasounds
- If allocated to UPA, willing and eligible to undergo two endometrial biopsies with the possibility of a third and fourth (i.e. up to four biopsies)
- If allocated to UPA mechanistic sub-study, willing and eligible to undergo three endometrial biopsies with the possibility of a fourth and fifth (i.e. up to five biopsies). If 'No' may be randomised to RCT if UPA endometrial biopsy consent given
- Willing to use barrier contraception if allocated to UPA
- Given written informed consent
- Willing and eligible to undergo up to three magnetic resonance imaging scans? If allocated to UPA, mechanistic sub-study only. If 'No' may still be randomised to RCT

4.2.2 Exclusion Criteria

- Post-menopausal
- A >14 week fibroid uterus and/or cavity length >11 cm confirmed by ultrasound scan
- Submucosal fibroids >2cm diameter confirmed by ultrasound scan
- Contraindications to UPA or LNG-IUS
- Intention to continue current use of Cytochrome P450 (CYP3A4) inhibitors
- Intention to continue current use of Cytochrome P450 (CYP3A4) inducers (e.g. Phenytoin, carbamazepine, rifampicin, St John's Wort)
- Intention to continue current use of P-glycoprotein substrates (e.g. digoxin)
- A past, current or suspected diagnosis of endometrial hyperplasia or neoplasia
- Severe hepatic impairment
- Epilepsy managed with carbamazepine, phenytoin
- Significant renal impairment
- Pregnant
- Current plans to become pregnant within 12 months
- Currently breastfeeding

- Severe asthma that is not sufficiently controlled by oral glucocorticoids
- Past or current known history of with uterine, cervical, ovarian or breast cancer.
- Current use of progestagen-releasing intrauterine device (except if allocated within UCON)
- Intention to continue regular use of Mefenamic acid
- Intention to continue regular use of Tranexamic acid
- Intention to continue regular use of GnRH analogues
- Intention to continue regular use of Progestagen-only contraceptive
- Intention to continue regular use of any combined oral contraceptive pills
- Intention to continue regular use of hormonal replacement therapy

4.2.3 Exclusion of particular populations

Renal impairment is not expected to significantly alter the elimination of UPA. In the absence of specific studies, UPA is not recommended for patients with severe renal impairment unless the patient is closely monitored.

There is no therapeutic experience with UPA in patients with hepatic impairment, which is expected to alter the elimination of UPA, resulting in increased exposure. This is considered not to be clinically relevant for patients with mildly impaired liver function. UPA is not recommended for use in patients with moderate or severe hepatic impairment unless the patient is closely monitored.

Use in women with severe asthma insufficiently controlled by oral glucocorticoids is not recommended.

4.3 CO-ENROLMENT

Women randomised to the UCON trial should be excluded from participation in any further trial of investigational medicinal products (IMPs) for the treatment of gynaecological disorders or infertility. If the woman has withdrawn from the trial treatment but is still contributing to data collection, any further treatments within trials for her HMB should be noted, for example if she chooses to participate in a trial of surgery for HMB.

Women already participating in another trial of an IMP for a non-gynaecological reason are able to participate in UCON, provided careful consideration of the interactions between that IMP and the UCON trial treatments is undertaken. Arrangements for co-enrolment with another CTIMP will be bound by a written agreement between the Chief Investigator and Co-Sponsors of both/all CTIMPs implicated. This agreement will include special safety reporting measures if required; a minimum wash-out period between last dose in one study and first dose in another; a statement to indicate that the chairs of the TSC/DMC from each study and statisticians from each study that they have no objections to the proposals for co-enrolment; and a statement that arrangements for attribution of liability for co-enrolled participants have been put in place agreed between the sponsors of both/all CTIMPs implicated.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Patients will be recruited from the gynaecological, outpatient clinics of participating centres (identified in both primary and secondary care), fitting around their current service provision. Figure 1 shows the different routes by which women may be identified and approached.

5.1.1 Identification from GP databases

Patients with a recent history of HMB problems may be identified within GP practices. Databases will be screened using the HMB related read codes, with access to these patient identification centres negotiated via the local Primary Care Network. The hospital will send potentially eligible women a patient invitation letter, a copy of the participant information sheet and be invited to contact the UCON research nurse to discuss the trial and/or make a hospital appointment.

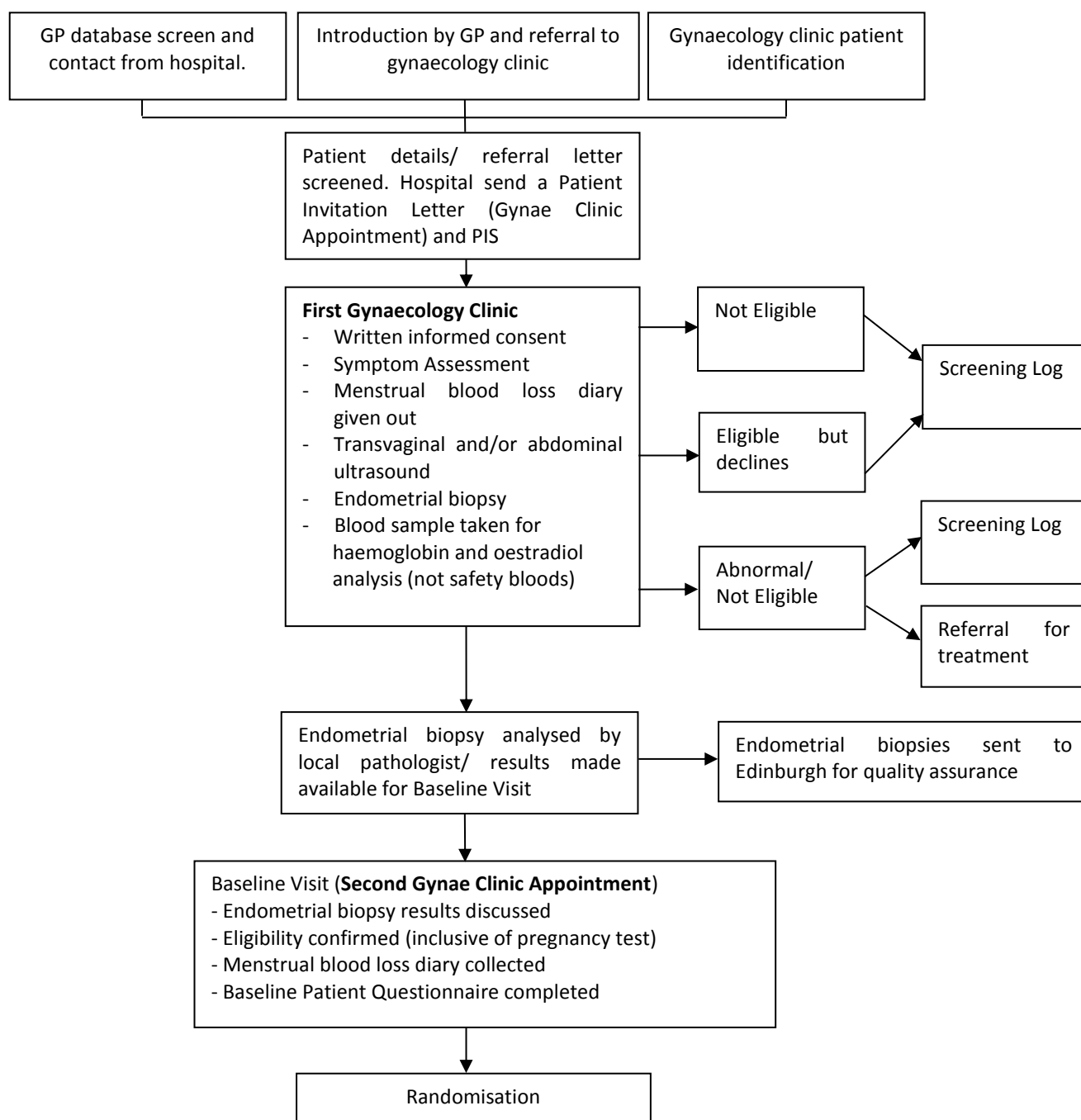
5.1.2 GP Referral to Secondary Care

Patients with existing HMB problems who present to a GP may then be referred to a participating hospital. GP practices in the catchment area of the participating centres will be made aware of the study and will be encouraged to discuss the trial with the woman, explaining a referral will be necessary. The UCON research nurse(s) will screen all patient referral letters to identify referred participants who have been introduced to the trial and arrange a gynaecology clinic appointment.

5.1.3 Gynaecology Clinic Patient Identification

The UCON research nurses will screen the patient referral letters who have been referred by their GP to secondary care but who have not been introduced to the trial. Eligible patients will then receive a patient invitation letter along with a copy of the participant information sheet and be invited to contact the UCON research nurse to discuss the trial and/or make a hospital appointment.

Figure 1: Identification and screening of participants for the UCON trial



5.2 CONSENTING FOR SCREENING FOR ELIGIBILITY

All women who are referred to secondary care with HMB will be identified by the UCON research nurse(s) in each centre as a potential participant, prior to her outpatient appointment. The gynaecologist who will be providing her clinical care will discuss treatment options and establish eligibility based on history and preferences. The option to contribute to the mechanistic sub-study will instead be discussed in those centres able to contribute to the sub-study. Women who are confirmed pregnant are not eligible for the trial and participants would need to be prepared to avoid pregnancy for one year, so a discussion must be held about intentions to conceive.

Consent to participate in UCON will be sought by the gynaecologist, and/ or by a research nurse. Women will be asked to consent to the UCON Trial in order that trial specific procedures, namely endometrial assessment using transabdominal and/ or transvaginal ultrasound and outpatient endometrial biopsy, can be undertaken. Women will be asked to confirm their consent by initialling the appropriate boxes on the consent form and signing in the presence of the person taking consent. Multiple copies will be available to ensure a copy is given to the women, one is kept in the patient notes, one in the local site file and one is sent to the UCON Trial Office.

Women who consent at this point should have the ultrasound(s) performed and biopsy taken at the same clinic appointment if at all possible. All women should be given a menstrual blood loss diary containing the PBAC to take away and complete during their next period, which ideally will occur before the next gynaecology clinic appointment. The completed blood loss diary will need to be returned at the baseline visit prior to randomisation.

At the Royal Infirmary of Edinburgh the option of participating in addition in the mechanistic sub-study and undergoing additional endometrial biopsies and/ or MRI scans should be discussed. Women should be advised that these additional assessments are only applicable if they are randomly allocated to UPA.

All women approached should be recorded on the screening log(s), available in the investigator site file. This information will only be passed to the coordinating centre as an anonymous screening log.

5.3 CONFIRMATION OF ELIGIBILITY BEFORE RANDOMISATION/ ENTRY INTO THE MECHANISTIC SUB-STUDY

The participant should be invited to a baseline (second) gynaecology clinic appointment by which time the results of the endometrial biopsy must be available. Normal findings from the local histopathology service will confirm eligibility for UCON, which should be relayed to the woman and continued consent established. At this point, the menstrual diary should be collected, if the woman has had a period in between appointments, and the other baseline questionnaires should be completed in clinic at this time.

Any pathological or suspicious findings from the biopsy should be investigated thoroughly and treated as appropriate outside of the UCON trial.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

If a woman is screened but is not eligible for the trial due to a preference, contraindication or pathological reason for their HMB, or consent for randomisation is not given, an anonymous record of the case should be kept in the screening log. The screening log will include, age group, ethnic group, and the reason each patient not eligible for the trial. Women who consent and have an ultrasound and endometrial biopsy but are then found to be ineligible will be noted. The screening log should be kept in the site file and a copy sent to the UCON Trial Office, who will be unable to identify women based on the information provided. This screening log information will inform updates to the funder regarding recruitment targets for UCON.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Immediately after eligibility has been established, baseline questionnaires have been completed, and once written informed consent has been obtained, the women may be randomised into the trial.

The Birmingham Clinical Trials Unit will provide third part web-based randomisation with telephone back-up. Patients are entered and randomised into the trial by logging into secure online randomisation available at <https://www.trials.bham.ac.uk/UCON>. Each centre and each randomiser will be provided with a unique log-in username and password in order to randomise a patient online. The online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems. Alternatively, investigators can make one Freephone telephone call (Tel - 0800 953 0274) to the randomisation service. Telephone randomisations are available Monday-Friday, 09:00-17:00.

Randomisation Forms will be provided to investigators and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form will need to be answered before a trial number can be given. Only when all eligibility criteria and baseline data items have been provided will a trial number and treatment allocation be given followed by a confirmatory email sent to the randomising investigator, local Principal Investigator, local pharmacist and the research nurse.

A minimisation procedure using a computer based algorithm will be used to avoid chance imbalances in treatment allocation and the following potentially important variables:

Age: ≤ 35 yrs or > 35 yrs

BMI: ≤ 25 kg/m² or > 25 kg/m²

Presence of any fibroid > 2 cm, as determined by the ultrasound scans

Duration of symptoms: < 1 year or ≥ 1 year

Site: Individual Site

Agreement to enter sub-study: Both/ MRI only/ Biopsy Only/ Neither and N/A

In addition, to avoid any possibility of the treatment allocation becoming too predictable, we will include a random factor within the algorithm in which for a proportion of the allocations (1 in 5) true randomisation will be implemented rather than by using the minimised allocation.

5.5.2 Treatment Allocation

Participants will be randomised individually into the UCON trial in an equal ratio to either ulipristal acetate (UPA) or levonorgestrel releasing intrauterine system (LNG-IUS).

Figure 2: Patient pathway (Sites except Royal Infirmary of Edinburgh)

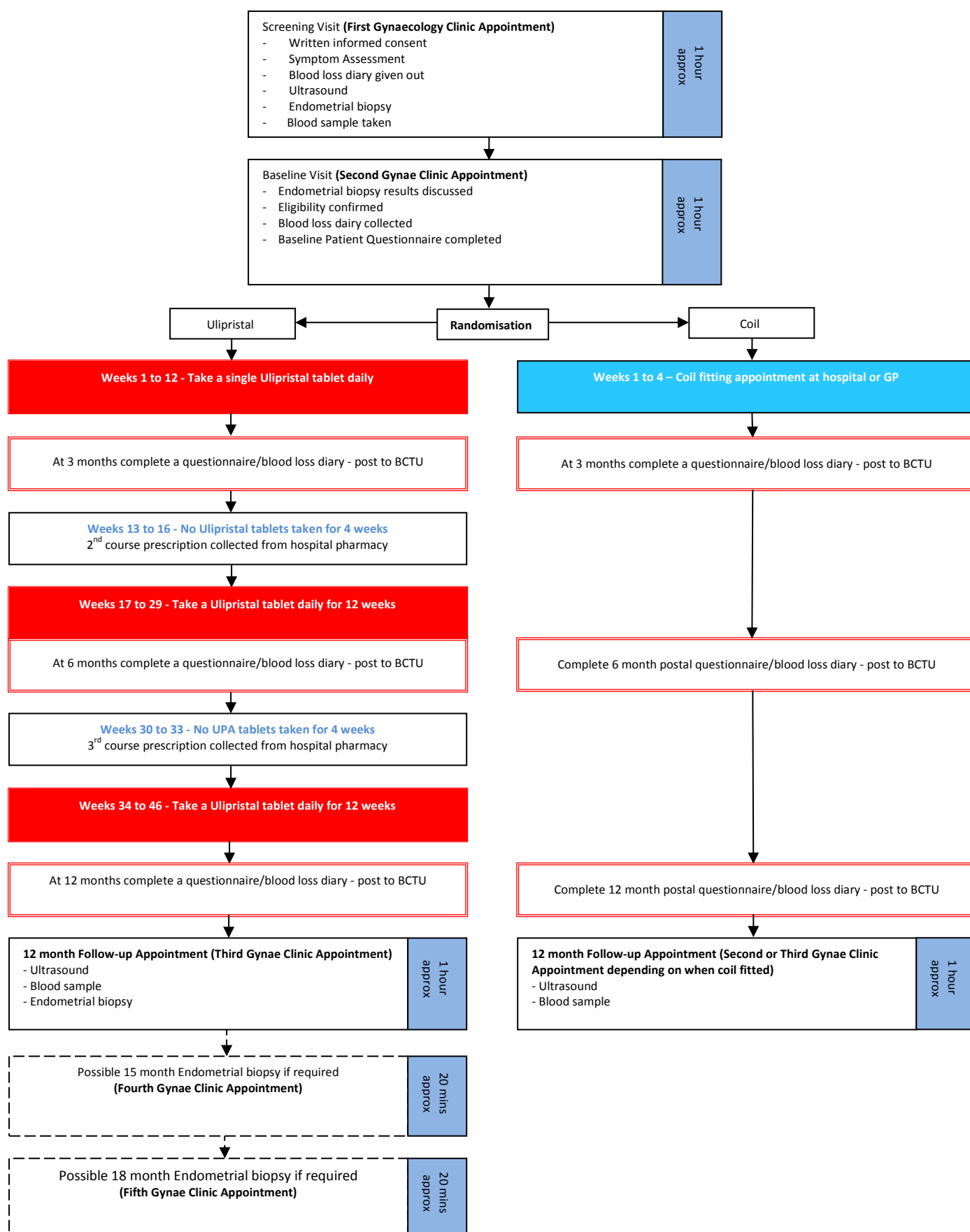
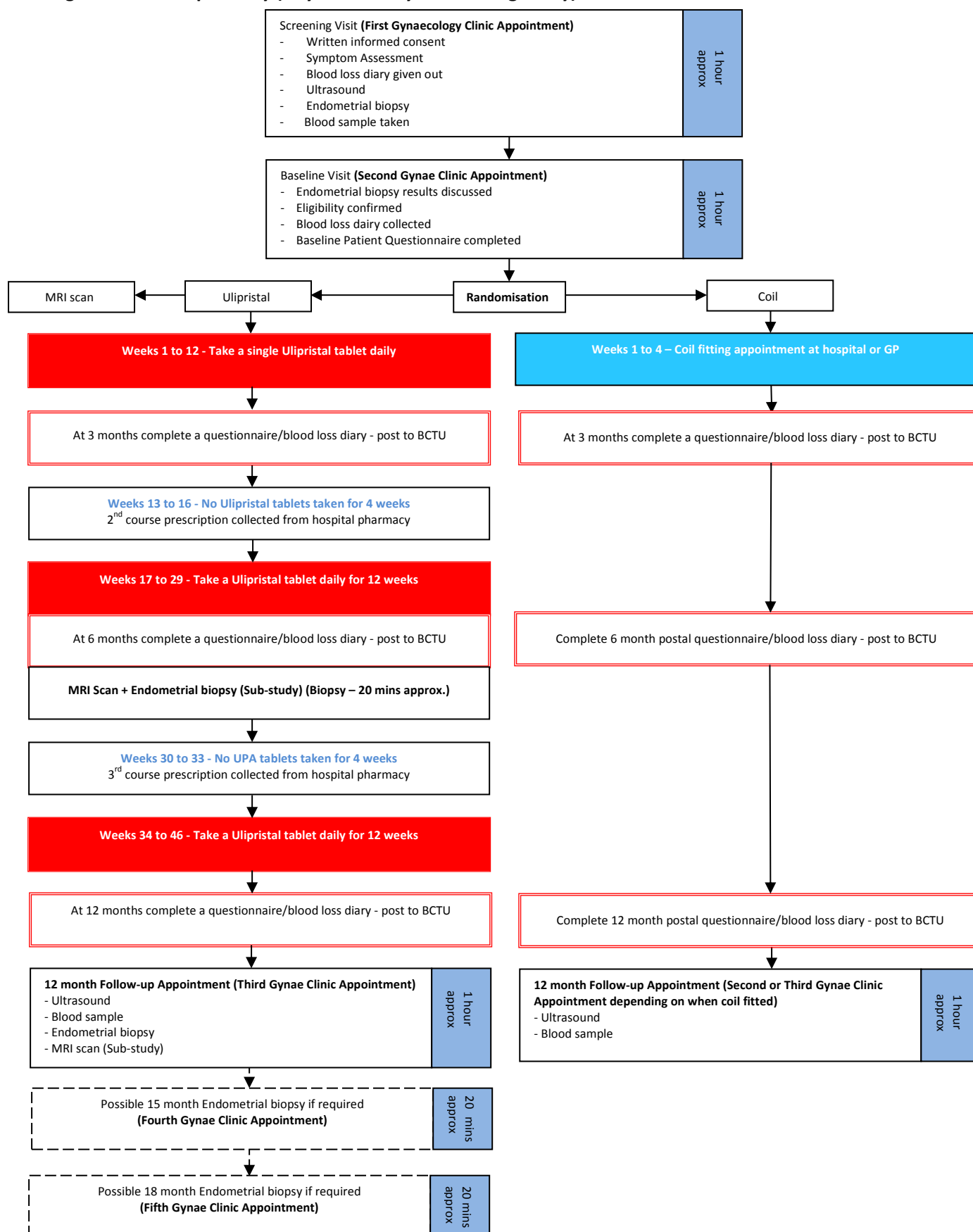


Figure 3: Patient pathway (Royal Infirmary of Edinburgh only)



5.5.3 Baseline MRI for women in mechanistic sub-study (UPA)

Women opting for the mechanistic sub-study at the Royal Infirmary of Edinburgh will, have additional assessments that relate to this study only, but will otherwise complete the same study outcome as those randomised to the UPA group and be followed up in exactly the same manner. As part of the additional assessments will, where possible undergo an MRI scan during the secretory phase (second half of her cycle) of her menstrual cycle before commencing UPA (see Figure 3).

5.5.4 Blinding and Emergency Unblinding Procedures

As the treatments are so different in route of administration, the participants, investigators, research nurses and other attending clinicians cannot be blinded to the treatment allocation.

5.5.5 Withdrawal of Study Participants

Trial treatment should continue until a woman has reached the 12 month post-randomisation unless:

- A known serious adverse reaction to UPA occurs and in the opinion of the investigator or clinical that it is medically necessary to withdraw the woman from trial treatment.
- A suspected unexpected serious adverse reaction occurs
- A participant changes mind and wishes to become pregnant
- The participant refuses to take the trial drug
- Women allocated LNG-IUS can retain the coil *in situ* for up to 5 years if they wish, and can have the coil replaced after this

With premature cessation of trial treatment, the trial staff will make every responsible effort to obtain, and record, information about the reasons for discontinuation, any adverse events and to follow-up the women for all safety and efficacy outcomes, as appropriate. A second endometrial biopsy for women ceasing UPA treatment should be arranged.

A participant may voluntarily withdraw participation in this study at any time. If a participant does not return for a scheduled visit or return a postal questionnaire, responsible attempts will be made to contact her and where possible, complete the patient reported outcome measures, and review compliance and adverse events. If a woman decides, after randomisation, she does not wish to take UPA, or wishes to have the LNG-IUS removed or wishes to withdraw from the trial for any reason (e.g. wishes to conceive or no longer interested in the research) then the woman should be strongly advised to have a second endometrial biopsy taken, four weeks after cessation of UPA. All participants wishing to withdraw from the trial will have the option of withdrawing from all aspects of the trial but may allow for continued use of data collected up to that point.

Where possible, the centre and study team will aim to document the reason for withdrawing from the trial. Clear distinction will be made as to whether a participant is withdrawing from trial treatments whilst allowing further follow-up, or whether the participant refuses any follow-up. If a participant explicitly withdraws consent to have any further data recorded their decision will be respected and recorded. All communication surrounding the withdrawal will be noted in the patient's hospital records and in the trial database and no further data will be collected for that participant.

The target sample size of 220 patients includes a 20% loss to follow-up rate. Rates will be monitored to detect differential drop-out, which can bias clinical trial results and reduce the power of the trial to detect important differences.

6 INVESTIGATIONAL MEDICINAL PRODUCT(S)

6.1 STUDY DRUG

6.1.1 Study Drug Identification

The investigation medicinal products (IMPs) are ulipristal acetate and levonorgestrel-releasing intrauterine system will be used as a reference in its authorised form.

6.1.2 Ulipristal acetate (Comparator)

UPA is provided as a 5mg tablet. The trade name for UPA in the European Union is Esmya™ for treatment of uterine fibroids, and is marketed by Gedeon Richter.

6.1.3 Levonorgestrel (Reference)

The LNG-IUS is a contraceptive device that slowly releases a daily dose of 20 µg levonorgestrel into the uterine endometrium. It is a long acting reversible contraceptive preparation that requires removal and reinsertion every five years. LNG-IUS is approved for use as a contraceptive and for HMB and is marketed under the name of Mirena™ by Bayer Pharma AG.

6.1.4 Study Drug Manufacturer and Supply

Each centre pharmacy will arrange an initial and continuing supply of ulipristal acetate and LNG-IUS through normal procurement procedures.

6.1.5 Marketing Authorisation Holder

The marketing authorisation holder for UPA (Esmya™) is Gedeon Richter (Hungary) Plc and the marketing authorisation number(s) is EU/1/12/750/001. The ATC code is G03XB02.

The marketing authorisation holder for LNG-IUS (Mirena™) is Bayer Plc and the marketing authorisation number(s) is PL00010/0547. The ATC code is G02BA03.

6.1.6 Labelling and Packaging

All details of trial drug supply; labelling, storage and preparation are as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and are detailed in the UCON Pharmacy Manual which is supplied to pharmacy at the time of site approval.

UPA dispensed by the pharmacy will require a trial specific label, complying with the Annex 13 of the EU Directive on Clinical Trials, 2004. Supplies of labels will be provided to the pharmacy at each participating hospital.

As LNG-IUS is not dispensed and is fitted according to the manufacturer's recommendations, so it will therefore not require trial specific labelling.

6.1.7 Storage

The UPA tablets must be kept in the blisters in the outer carton in order to protect from light. The blister packs are Alu-PVC/PE/PVDC blister and a pack may contain 28 or 84 tablets. There are no recommendations regarding temperature control of UPA, and so no specific temperature monitoring measures are required for the UCON Trial. The shelf life of UPA is 3 years.

Storage considerations are not applicable for LNG-IUS.

6.1.8 Dispensing and accountability

At randomisation, the first packet of tablets will be dispensed to the woman. The pharmacist will receive notification of the name and trial number of the randomised woman and will prepare the trial treatment tablets for labelling and dispensing. The packet of UPA will contain 12 weeks' supply for use by one participant. An accountability log will be provided to record the dispensing of trial treatment.

6.1.9 Summary of Product Characteristics

The Summary of Product Characteristics (SmPC) will be provided in the site file.

The up-to-date Summary of Product Characteristics for ulipristal acetate can be found at <http://www.medicines.org.uk/emc/medicine/26068>

The up-to-date Summary of Product Characteristics for LNG-IUS can be found at <http://www.medicines.org.uk/emc/medicine/1829/SPC/mirena/>

6.2 DOSE AND DELIVERY OF IMPS

6.2.1 UPA

Those allocated to UPA will receive proprietary ulipristal acetate 5mg, orally, once daily.

A single tablet must be taken orally once daily with or without food, at approximately/ or as close as possible to the same time each day. The participant should start taking UPA within the first five days of starting their menstrual bleeding.

If a participant misses a dose, she should take UPA as soon as possible. If the dose was missed by more than 12 hours, the participant should not take the missed dose and simply resume the usual dosing schedule.

Women will be instructed to take UPA in 3 courses according to the following cyclical regime:

4. One 5mg tablet of UPA to be taken daily for 12 weeks then stopped for 4 weeks, when light vaginal bleeding may occur (withdrawal bleed).
5. After 4 weeks off treatment, regardless of whether they experience a withdrawal bleed, they should recommence UPA 5mg daily for another 12 weeks, then stop for 4 weeks, when they will expect to have a withdrawal bleed.
6. Repeat as for treatment courses (2).

We have chosen this regime as women and their clinicians will likely prefer a regime that has only one menstrual bleed between treatment courses and thus our study will be able to provide valuable data on this aspect of UPA treatment.

6.2.2 LNG-IUS

The fitting of the LNG-IUS should be performed by the gynaecologist during outpatient visit, or later by a GP or at a sexual/ reproductive health clinic. If LNG-IUS is fitted within seven days of the onset of menstruation or withdrawal bleeding it will provide immediate contraceptive cover, otherwise barrier methods must be used for 14 days. The LNG-IUS can remain *in situ* up to for 5 years and should be removed by a competent practitioner, with immediate replacement if desired.

6.3 DOSE CHANGES

Each women randomised to UPA will take UPA 5mg, orally, once daily in 3 courses according to the following cyclical regime:

- (1) Take one 5mg tablet of UPA daily for 12 weeks then stop for 4 weeks
- (2) After 4 weeks off treatment, recommence UPA 5mg daily for another 12 weeks then stop for 4 weeks
- (3) Repeat as for treatment course (2).

The participant should start taking UPA within the first five days of starting their menstrual bleeding.

6.4 PARTICIPANT COMPLIANCE

6.4.1 Maximising adherence of women to their allocated treatment.

We will try to avoid women not commencing the allocated treatment firstly by careful counselling with respect to childbearing intentions. Randomised women will either be provided with their UPA prescription immediately, or we will encourage women to have the LNG-IUS fitted promptly by the gynaecologist at the second clinic visit. To maintain adherence, women in the LNG-IUS group will be counselled to expect some disturbance to their menstrual cycle, but encouraged to persist. In the UPA group, women will receive a reminder to remind them to collect their repeat prescriptions from the hospital pharmacy.

6.4.2 Monitoring compliance

Follow-up questionnaires will ask for self-reported compliance to the allocated treatment. We may also collect data on adherence via a text message or email to women in the UPA group, asking for number of tablets remaining at various time points in between gynaecology clinic appointments. Compliance may also be evaluated by 'pill-counting'. Women will be asked to bring completed, partially used and unused drug packets to the trial centre at follow up visits. The research nurse may verify the empty/partially used/unused treatment drug packets and will document this in the database for each trial participant.

6.5 SPECIAL WARNINGS AND PRECAUTIONS FOR USE FOR ULIPRISTAL ACETATE

There is the potential for other medicinal products to affect ulipristal acetate and conversely the potential for ulipristal acetate to affect other medicinal products. For further details regarding guidance on prohibited and permitted medications please see sections 6.9.1 and 6.9.2. For guidance regarding the potential interactions with other medications please see section 6.5.3

6.5.1 Overdose

Experience with ulipristal acetate overdose is limited. Single doses up to 200 mg and daily doses of 50 mg for 10 consecutive days were administered to a limited number of subjects, and no severe or serious adverse reactions were reported (for up to date information please see <http://www.medicines.org.uk/emc/medicine/26068>).

6.5.2 Contraception

Concomitant use of UPA with progestagen-only pills, a progestagen-releasing intrauterine device or combined oral contraceptive pills is not recommended. Although a majority of women taking a therapeutic dose of ulipristal acetate are anovulatory, where contraception is required, the woman will be asked to use a barrier method with spermicidal foam/gel/film/cream/suppository, in line with MHRA contraception guidelines.

6.5.3 Potential drug interactions

Ulipristal acetate is not recommended for patients receiving P-glycoprotein (P-gp) substrates (e.g. dabigatran etexilate, digoxin).

Co-administration of moderate or potent Cytochrome P450 (CYP3A4) inhibitors (e.g. erythromycin propionate, ketoconazole, ritonavir, nefazodone) may lead to significant changes in plasma levels of ulipristal acetate and so women requiring potent drugs are not eligible for UCON and the use of UPA in those requiring moderate potency CYP should be reviewed carefully. Concomitant use of mild CYP3A4 inhibitors is acceptable and no dose adjustment of UPA is considered necessary.

Patients receiving concomitant Cytochrome P450 (CYP3A4) inducers may have reduced plasma levels of UPA and so concomitant use of potent CYP3A4 inducer, such as anti-convulsants (e.g. carbamazepine, phenytoin) or anti-infectives (e.g. rifampicin, nevirapine) or St John's Wort is not recommended.

6.6 KNOWN ADVERSE REACTIONS FOR ULIPRISTAL ACETATE

A full list of known adverse reactions for UPA is given in Table 3, whilst specific issues of concern are detailed here.

6.6.1 Endometrial changes

In 10-15% of women, thickening (> 16 mm by ultrasound or MRI at end of treatment) of the endometrium may occur. In addition, changes in the histology of the endometrium (PAECs) may be observed, that are different to endometrial hyperplasia. These changes are reversible after treatment cessation. More evidence regarding PAEC is discussed in Section 1.2.

6.6.2 Bleeding pattern

Participants should be informed that treatment with ulipristal acetate usually leads to a significant reduction in menstrual blood loss or amenorrhea within the first 10 days of treatment. Should the excessive bleeding persist, participants should notify their GP. Menstrual periods will generally return within 4 weeks after the end of the treatment course.

6.6.3 Other hormonal adverse events

Hot flushes were reported by 12.7% patients on average but the rates varied across trials. In PEARL II, the rates were 24% (10.5% moderate or severe) for UPA and 60.4% (39.6% moderate or severe) for leuporelin-treated patients. In PEARL I, the rate of hot flushes was 1.0% for UPA and 0% for placebo.

Functional ovarian cysts were observed during and after treatment in 1.5% of patients and in most of the cases spontaneously disappeared within a few weeks.

6.7 SPECIAL WARNINGS AND PRECAUTIONS FOR USE FOR LEVONORGESTREL

6.7.1 Fitting of the LNG-IUS

LNG-IUS fitting should ideally be performed by an experienced gynaecologist at the second clinic appointment. If this is not possible, a prescription can be given to enable the woman to go to a sexual health clinic or her GP, for the coil to be fitted by a clinician.

Perforation of the uterine corpus or cervix may occur, most commonly during insertion. This may be associated with severe pain and continued bleeding. If perforation is suspected the system should be removed as soon as possible and reported as a trial treatment withdrawal to the UCON Trial Office.

The insertion tube for LNG-IUS has been designed to minimise the risk of infections. Women should be told to be aware of symptoms and signs suggestive of pelvic infection and to go to her GP if at all concerned.

The RCOG guidelines suggest a women should be re-examined six weeks after insertion and further examinations should be performed where clinically indicated, but this will be left to the discretion of the gynaecologist to advise.

6.7.2 Potential drug interaction

The metabolism of progestogens may be increased by concomitant use of CYP3A4 inducers but the influence on these drugs on the contraceptive efficacy of the LNG-IUS has not been studied. However, it is not believed that CYP3A4 inducers will have a major importance, due to local mechanism of action of LNG-IUS.

6.8 KNOWN ADVERSE REACTIONS TO LEVONORGESTREL

Undesirable effects are more common during the first months after the insertion, and subside during prolonged use. A full list of known adverse reactions for LNG-IUS is given in

Table 4, whilst specific issues of concern are detailed here.

6.8.1 Bleeding irregularities

LNG-IUS usually achieves a significant reduction in menstrual blood loss in 3 to 6 months of treatment. Irregular bleeding/spotting may occur during the first months of therapy in pre-menopausal women. Some women's periods may even stop completely. Increased menstrual flow or unexpected bleeding may be indicative of expulsion.

6.8.2 Possibility of pregnancy

The LNG-IUS, when inserted properly, is an extremely effective contraceptive. The possibility of pregnancy should be considered in amenorrhoeic women if there are other symptoms, and expulsion should be excluded.

The absolute risk of ectopic pregnancy in LNG-IUS users is low. However, when a woman becomes pregnant with the LNG-IUS in situ, the relative likelihood of ectopic pregnancy is increased. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding.

6.9 OTHER MEDICATIONS

6.9.1 Permitted Medications

Drugs not listed as prohibited or have potential to interact (see Sections 6.5.3 and 6.7.2) are allowed.

6.9.2 Prohibited Medications

In order not to confound the effects of the trial treatments, the following should not be prescribed or taken by any participants whilst on trial treatment. Should the women withdraw or be excluded from the trial treatment but continue to provide data, continued regular use of below drugs should be noted. For patients who are 'coming off' some medications pre-randomisation then please refer to the wash out times specified in section 6.9.3.

- Mefenamic acid
- Tranexamic acid
- GnRH analogues
- Progestagen-only contraceptive
- Any progestagen-releasing intrauterine device (except if allocated within UCON)
- Any combined oral contraceptive pills

6.9.3 Wash out times

- | | |
|--|--------|
| • GnRH agonist/ antagonist: 3 to 6 month sustained-release preparation | 52 wks |
| • Immediate or monthly sustained-release GnRH agonist preparation | 26 wks |
| • Sex steroid: Progestins (systemic/ progestin-releasing intra-uterine system) | 4 wks |
| • Oral contraceptive, | 4 wks |
| • Mefenamic acid or antifibrinolytic drugs such as tranexamic acid | 1 wk |

7 STUDY ASSESSMENTS

Due to the different nature of the IMPs, the timing and format of the study assessments will differ slightly between the groups.

7.1 STUDY ASSESSMENTS OVERVIEW

A summary of actions and assessments undertaken, and data collected, at each time point is shown in **the Trial Schema (Appendix 1)**. Women who have consented and randomised to the mechanistic sub-study will have additional assessments that relate to this study only, but will otherwise complete the same study outcome as those randomised to the UPA group and be followed up in exactly the same manner.

7.2 TIMING OF STUDY ASSESSMENTS

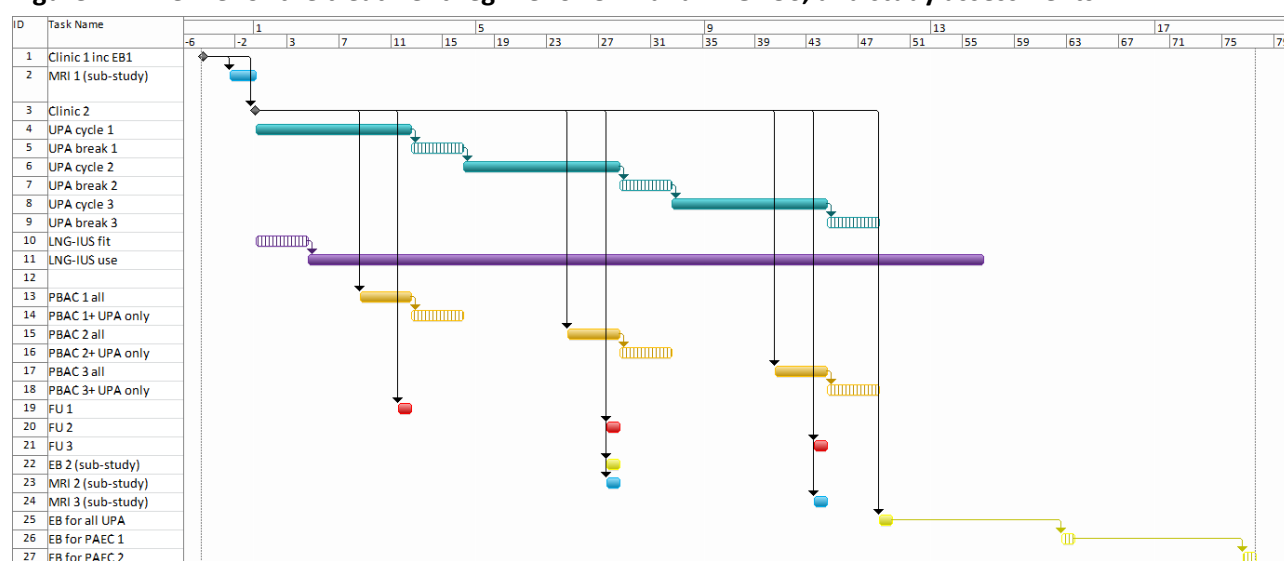
The overriding principles for the timing of the follow-up study assessments are:

1. The patient completed questionnaires should ideally be completed in the final week of each on-treatment cycle for the UPA group, and at an equivalent time for the LNG-IUS group.

2. The menstrual blood loss diary whilst on treatment should be completed over the final four weeks of each treatment cycle in the UPA group, and at an equivalent time for the LNG-IUS group. The UPA group will also be asked to complete the diary during the first 4 weeks off treatment before the start of the next treatment cycle (as per the cyclical regime stated in section 6.2.1).
3. The post-treatment endometrial biopsy should be completed after 4 weeks off treatment, which would be approximately 48 weeks after UPA was commenced.
4. Should PAECs be observed in the post-treatment biopsy specimen in the UPA group, a repeat endometrial biopsy should be taken around 13 weeks after the completion of treatment, and then again around 26 weeks post-treatment if PAECs persist.
5. The endometrial biopsy and MRI at time point 26 weeks in the sub-study should be in the final week of the second UPA cycle, to determine the features of the endometrium while receiving treatment.

A timeline for the treatment regimens and completion of the assessments is shown in Figure 4.

Figure 4: Timeline for the treatment regime for UPA and LNG-IUS, and study assessments.



Key: EB endometrial biopsy; FU patient questionnaire

7.3 OUTCOMES COLLECTED AT STUDY ASSESSMENTS

Table 1 shows the outcomes collected at each time point in the UCON trial and mechanistic sub-study

Table 1: Schedule of outcome assessment for UCON trial and mechanistic studies

(X) optional ((X)) dependent upon endometrial assessment at previous time point

Timepoint	Screening (1)	Baseline (2)	3 months (approx) (3)	6 months (approx) (4)	12 months (approx) (5)	Post- treatment 1 (6)	Post- treatment 2 (7)
Written informed consent	X						
Patient questionnaires (MMAS, UFS-QOL, SAQ, other patient reported outcomes, compliance and adverse events)		X	X	X	X		
Menstrual bleeding diary	X		X	X	X		
Blood sample, for haemoglobin and oestradiol analysis (not safety bloods)	X				X		
Ultrasound pelvic assessment	X				X		
Endometrial biopsy	X				X UPA only		
Endometrial biopsy – additional for women in UPA group who exhibit PAEC						((X)) UPA only	((X)) UPA only
Follow up outpatient appointment to discuss post-trial treatment options						(X) UPA only	
Purposive samples 1 and 2 (Edinburgh sub-study only)							
Endometrial biopsy	X			X UPA only	X UPA only	((X)) UPA only	((X)) UPA only
MRI (DCEMRI and high resolution structural MRI)		X		X UPA only	X UPA only		

(X) optional ((X)) dependent upon endometrial assessment at previous time point

* Endometrial biopsies will be stored at the University of Edinburgh Female Reproductive Tract Tissue Resource (10/S1402/59)

8 DATA COLLECTION

8.1 DATA COLLECTION FORMS

Data for the purpose of assessing the efficacy and safety within the UCON trial will be collected from the women, her gynaecologist and the histopathologist on a number of data collection (case report) forms.

8.1.1 Participant Questionnaire

The participant questionnaire is a booklet containing a number of validated instruments and questions completely independently by the participant. The booklet at baseline will contain:

- Menorrhagia Multi-Attribute Scale (MMAS)
- Uterine Fibroid Symptom and Quality of Life (UFS-QoL)
- Sexual Activity Questionnaire (SAQ)

- Satisfaction with treatment outcome measured on a 5-point Likert scale. Specific statements about the experience and the acceptability of the treatment and the beliefs about the value of the treatment will be elicited from the participants.
- Visual analogue scales for menstruation duration, regularity and pelvic pain

At the three follow-up timepoints, the following additional data will be sought:

- Adherence to UPA dosing schedule, as subjectively reported on an ordinal scale by the participant (for those allocated to UPA).
- Discontinuation or changes in allocated treatment.
- Any hospitalisations, or further investigations or treatments from a gynaecologist.
- Any pregnancies.
- Serious adverse events reported by participants, principally those that are unexpected or are known and relevant to the trial treatments.

The booklet will either be sent out in paper form by post, be emailed as a data-form enabled attachment, be via a password protected web form or be presented to the woman in an outpatient clinic. Various ways in which to contact women (land line and mobile telephone, email, address) will be collected and all may be used in the process of collecting the data.

8.1.2 Menstrual Diary

The standard pictorial blood assessment chart (PBAC) (14) will be given to the woman at the first clinic visit to allow her to complete during her next menstruation and return it at the second clinic visit, which should be scheduled to be at least 4 weeks after the first.

Both UPA and LNG-IUS may induce amenorrhea (absence of bleeding) in some women, so whilst on treatment, the concept of a regular cycle is problematic. A modified menstrual diary, with ordinal questions regarding bleeding each day, will be used to establish the degree of menstrual bleeding. This will be completed for 28 days from week 8 for women in the LNG-IUS group and for 56 days from week 8 in the UPA group, then again at week 24 and week 40, for 28 and 56 days for the LNG-IUS and UPA groups, respectively.

8.1.3 Clinical Assessment and Randomisation Form

At the first clinic visit, the gynaecological clinical history of the woman will be taken and details of duration of HMB symptoms, previous gynaecological treatment for HMB, and the contraceptive use and needs of the woman will be collected alongside basic demographic details. A blood sample to observe haemoglobin and oestradiol levels will be taken and results recorded in the clinical assessment form.

8.1.4 Ultrasound Form

A pelvic examination by transabdominal and/or transvaginal ultrasound will be undertaken and cardinal features noted as possible presence of fibroids and uterine size and size of largest fibroid to make the comparison between baseline and 12 month follow-up possible.

8.1.5 Clinical Assessment and Randomisation Form and Screening Logs

The Clinical assessment and Randomisation Form is a checklist for eligibility and key prognostic details needed for minimisation within the randomisation. This is completed by the investigator or UCON research nurse before randomisation.

The Screening Logs, described in Section 5.4, will record basic details of all women approached, including those who are found to be ineligible and those that decline to participate. This should be kept up to date by the UCON research nurse.

8.1.6 Endometrial Biopsy Report Form

The local consultant histopathologist will report on the morphology and cellular architecture of the endometrial biopsy sample on a local report form. The baseline biopsy and the 48 week post treatment biopsy in the UPA group will be assessed using standard techniques to identify PAECs. Independent analysis of the slides taken from the samples by the Lead Pathologist at the University of Edinburgh will be recorded on a standardised report form.

8.1.7 Serious Adverse Event Form

This will collect details of all SAEs are defined and description in Section 10.5.

8.1.8 Mechanistic Study Data Forms

Data forms pertinent to the assays and analyses being undertaken on the endometrial biopsy and MRI scans taken for the sub-study will be used to standardise data collected.

8.2 SOURCE DATA

For the purposes of the UCON trial, source data comprises of:

- Clinical Assessment and Randomisation Form
- Patient questionnaire and menstrual diary
- Clinical notes
- Blood sample for haemoglobin and oestradiol analysis
- Ultrasound
- Endometrial biopsy sample for standard histopathological analysis.

8.3 DATA MANAGEMENT

Data from the Clinical Assessment and Randomisation Form and Endometrial Biopsy Report Form and should be entered on to the secure online UCON database as soon as possible after collection by the research nurse, investigator or histopathologist, who will be allocated personal usernames and passwords that restrict access to participants at their centre. Alternatively, paper forms can be sent to the UCON Trial Office for central input. Patient completed forms will be returned directly to the UCON Trial Office for data entry.

Data validation is built into the online database, so that range, date and logic checks are performed at the point of data entry. Email, text message and letter reminders will be sent to the research nurses or participants for missing data forms, missing data or data inconsistencies.

8.4 QUALITY ASSURANCE OF ENDOMETRIAL BIOPSY ASSESSMENTS

The assessment of endometrial biopsies should be undertaken by a consultant histopathologist with expertise in endometrial analysis. For quality assurance, a second assessment will be undertaken by the lead pathologist for UCON, Dr Alistair Williams at the University of Edinburgh. Slides taken from the samples will be labelled with the trial number and send for second reading in secure shipping containers provided by the UCON Trial Office.

For the baseline endometrial biopsy, the second assessment in Edinburgh will not be used to confirm eligibility for the trial and therefore slides may be sent in batches.

For the final post-treatment biopsy in the UPA group, a local assessment will be under taken and the slides sent promptly to Edinburgh. Whilst the local assessment will be noted, the second Edinburgh review of the slides, undertaken without knowledge of the local assessment, will determine the presence or absence of PAEC for the purpose of the trial. Those women with PAECs as confirmed by Edinburgh will be asked to return for endometrial biopsies at 13 weeks, and if necessary 26 weeks after completion of the final UPA course.

All slides will be returned to their originating hospitals after the second assessment.

8.5 MECHANISTIC SUB-STUDY

8.5.1 Endometrial tissue function

An overview of approach to analysis of tissue-specific impacts of UPA on endometrial tissue function are summarised in Table 2 below. The choice of target endpoints has been informed by studies in our own laboratory that have highlighted the impact(s) of progestins, progestin receptor antagonists and receptor modulators (levonorgestrel, mifepristone, asoprisnil) on endometrial tissue function, *examples given but not limited to those end points identified in Table 2* (17-19).

Table 2: An overview of approach to analysis of tissue-specific impacts of UPA on endometrial tissue function

Process	Endpoint	Details of analytical method
Tissue morphology	H&E stain histology, number of mitoses and mitochondria	Analysis by expert pathologist qRT-PCR mitochondrial markers
Vascular morphology	Endothelial and perivascular cell function/morphology	Double staining for CD31 (endothelial cells) and smooth muscle actin Masson Trichrome staining for collagen
Regulation of cell number	Cell proliferation, apoptosis and autophagy	Immunostaining for Ki67, PH3(proliferation) or cleaved caspase 3, microtubule-associated protein 1 light chain 3 alpha (death/survival), gamma H2AX (senescence)
Steroid hormone signalling	Cell-specific pattern of expression of steroid hormone receptors and steroid metabolizing enzymes	Single and double immunostaining for PR, ERalpha, ERbeta, AR, GR
Inflammation	Immune cell complement and inflammatory mediators	qRT-PCR IL15. Immunostaining for CD56, CD68, neutrophil elastase, mast cell tryptase and pan leucocyte marker CD45
Pre-malignant change	Comparison with normal endometrium and endometrial hyperplasia	qRT-PCR, double fluorescent immunohistochemistry PTEN, E-Cadherin, Snail 1, vimentin, PAX2, telomerase (hTERT)

8.5.2 Uterine and fibroid function

The aim of the MRI sub-study is to investigate the hypothesis that UPA will reduce blood flow and blood volume in the endometrium and myometrium in women with HMB. In particular, dynamic contrast enhanced MRI (DCEMRI) and high spatial resolution structural MRI will be obtained in a subgroup of 20 women treated with UPA. DCEMRI, combined with pharmacokinetic modelling, yields quantitative estimates of physiological parameters, including tissue blood flow, blood volume fraction and endothelial permeability, as well as volume fraction of the extracellular extravascular space. Structural MRI provides high resolution images suitable for structural segmentation and radiological evaluation that, when combined with design based stereological analysis (20), yield accurate and precise measurements of uterine and fibroid volume for early assessment of treatment response.

Scanning will be performed at baseline, and at 6 and 12 months following commencement of treatment. Scans will take place during the secretory phase of the menstrual cycle at baseline and in the week prior to the end of the second and third cycles of UPA, weeks 27 and 43 respectively.

Structural images will be evaluated clinically by an experienced radiologist, and stereological analysis performed to determine the volumes of the uterus and of any fibroids. Modern design based stereological methods will measure total volume of endo- and myo-metrial compartments, and volume, type and location of individual fibroids, with mathematically predicted precision, on high resolution MR images.

Dynamic Contrast Enhanced (DCE)-MRI will be used to measure uterine tissue perfusion. Contrast agent concentration is modelled as exchange between the blood plasma and extracellular interstitial spaces, providing maps of tissue blood flow, blood and interstitial volume fraction and artery to tissue delay (i.e. lag) time. DCEMRI data will be analysed using the well-established adiabatic

approximation to tissue homogeneity (AAHT) model, to generate pharmacokinetic maps of blood flow, blood volume and extracellular extravascular volume fraction; these will be used to extract representative values for endometrium, junctional zone, outer myometrium and fibroid tissue.

Both MRI approaches are novel in the context of SPRM administration, so will be piloted in the first patients, who may require repeat scans with a refined protocol.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

9.1.1 RCT

The trial has been designed to be able to detect a clinically useful difference in MMAS score between the two groups at twelve months with high power. The ECLIPSE Trial, which evaluated the effectiveness of LNG-IUS against Standard treatment for HMB (21) using MMAS as the primary outcome, demonstrated a difference of 13 points between the groups with a standard deviation of 24 points. This difference considered to be clinically meaningful (22) and is equivalent to approximately 0.5 standard deviations. To detect a difference of this size with 90% power ($p=0.05$) would require 86 women in each group (172 in total). To allow for a 20% loss to follow-up or pregnancy, the sample size has been inflated to 220 women in total.

9.1.2 Mechanistic sub-study

For the mechanistic evaluation 20 samples would give >90% power ($p=0.05$) to detect a change from baseline in for example, PH3 immuno-score, in the endometrium assuming similar effect sizes (>1 standard deviation) as to those seen in previous studies of other PRMs (19).

9.1.3 Anticipated recruitment period

Recruitment will take place over a minimum of 24 months from at least 5 centres, with a target of 2patients/centre/month. All centres have large HMB clinics, are experienced in recruiting to RCTs and the BCTU has a track record of completing RCTs in women's health.

9.2 PROPOSED ANALYSES - RCT

The analysis will be by intention to treat. Every attempt will be made to gather data on all women randomised, irrespective of compliance with the treatment protocol. Appropriate baseline characteristics, split by treatment group, will be presented for each outcome. Point estimates, 95% confidence intervals and p-values from two-sided tests will be reported. A full Statistical Analysis Plan will be drafted prior to any analysis and provided to independent Data Monitoring Committee for review.

9.2.1 Primary analysis

A linear regression model will be used to estimate differences in MMAS responses between the two groups at each time point. Baseline score and the minimisation variables (listed in section 5.5.1) will

be included in the model as covariates. The statistical significance of the treatment group variable will be determined by an associated chi-squared test.

9.2.2 Secondary analysis

MMAS scores at three and six months follow-up will be analysed as per the primary analysis. Data from the other continuous measures (UFS-QOL, VAS and SAQ) will be analysed in a similar fashion to the MMAS scores. Further exploratory analysis using a repeated measures model will also be used for these continuous measures to examine differences over all time-points. Bleeding diary scores will be converted into categories including the proportion with amenorrhoea ($=0$) and heavy bleeding (≥ 100). They will be analysed using relative risks and chi-squared tests. Time from randomisation to surgery (hysterectomy or endometrial ablation) will be analysed by log-rank test with a Cox Proportional Hazard (PH) model also built if the assumptions of proportionality are met. Other outcome measures (Likert responses, Likert ordinal responses, satisfaction) will be analysed using standard methods (tests for trend, absolute and relative risks). Paired t-tests will be used to examine differences within groups over time.

9.2.3 Sub-group analysis

Subgroup analyses will be limited to the same variables which were used as minimisation variables (see Section 5.5.1). Tests for statistical heterogeneity (e.g. by including treatment group by subgroup interaction parameter in the linear regression model) will be performed prior to any examination of effect estimate within subgroups. Our hypothesis is that UPA may be more effective in older (>35 years) and heavier ($\text{BMI} > 25$) women and those who have a presence of fibroid or have experienced symptoms for longer than a year.

9.2.4 Handling missing data and other sensitivity analysis

Every attempt will be used to collect full follow up data on all women. In particular, participants will continue to be followed up even after protocol treatment violation. It is thus anticipated that missing data will be minimal. Patients with missing primary outcome data will not be included in the primary analysis. This presents a risk of bias. Thus, secondary sensitivity analyses will be performed to investigate the impact of any missing data for the primary, as well as any important secondary outcome. This will include worst (for those randomly missing) and best case assumptions (for those not able to complete the primary outcome as they no longer can have menstrual bleeding, i.e. because they have had a hysterectomy). We will also simulate missing responses using a multiple imputation approach. To explore the sensitivity of the primary MMAS analysis to any ceiling effects (i.e. a high proportion returning a maximum responses, i.e. no problems with bleeding), a Tobit regression model will also be implemented.

9.2.5 Timing of assessments

An interim report including the analysis of major endpoints will be provided in strict confidence to a Data Monitoring Committee at intervals of at least 12 months, or as to a timetable agreed by the DMC prior to study commencement (see Section 11.4 for further details on trial data monitoring including the use of pragmatic stopping criteria). Final analysis will be performed once all women have completed twelve months follow-up.

9.3 PROPOSED ANALYSES – MECHANISTIC STUDY

Outcomes for the n=20 prospectively studied women biopsied at 6 and 12 months will be compared to each participant's own baseline biopsy as a control. Outcomes (e.g. PH3 immunoscore changes within groups over time) will be analysed using paired t-tests following an appropriate transformation and also by using non-parametric methods (e.g. Wilcoxon signed rank test) for confirmation.

10 ADVERSE EVENTS AND PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. These tasks may also be delegated to a qualified member(s) of the research team. Assessment of events may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting adverse events.

Participants will be instructed to contact their investigator at any time after consenting to join the trial if any symptoms develop. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation[^] or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant 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.

[^]Any hospitalisation that was planned prior to randomisation will not meet SAE criteria.

A **suspected unexpected serious adverse reaction** (SUSAR) is any AR that is classified as serious and is suspected to be caused by either IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC).

10.2 IDENTIFYING AES AND SAES

There may be expected and unexpected adverse reactions, which may be minor or serious, associated with UPA and LNG-IUS when used in women affected by HMB. The adverse event profile for LNG-IUS is well defined, as the system has been licenced for over a decade, and hence the collection of expected adverse events is not required. For example, elective admission for LNG-IUS insertion or elective admission for hysterectomy would not need to be classified as a serious adverse event. The focus for safety reporting of UPA is on changes to the endometrium.

Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence during each study visit and in postal questionnaires. Participants will also be asked if they have been admitted to hospital, had any gynaecological treatments, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an SAE, the event will be recorded and reported.

AEs and SAEs may also be identified via information from the endometrial biopsy, which will be recorded on the histopathology report form and SAE form if necessary. Untoward findings may incidentally be found in women in the mechanistic study, for example unexpected pelvic masses seen on by MR imaging. These will be reported to the local Principal Investigator who will assess whether they constitute an AE or SAE and the appropriate clinical management will be determined. If any untoward findings meet seriousness criteria they will be subject to onward reporting.

All diagnoses of endometrial cancer, ovarian cancer, cervical cancer, breast cancer or ductal carcinoma must be reported as a SAE.

10.3 RECORDING AES AND SAES

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The investigator will then record all relevant information regarding SAEs on the SAE form (if the AE meets the criteria of serious) and record all unexpected AEs in both groups on the AE log. Expected AEs that do not need to be recorded, unless they meet seriousness criteria, are listed in Table 3 for UPA and

Table 4 for LNG-IUS.

Table 3: List of known adverse reaction for UPA

System Organ Class	Very common	Common	Uncommon
Psychiatric disorders		Emotional disorder	Anxiety
Nervous system disorders		Headache	Dizziness
Ear and labyrinth disorders		Vertigo	
Respiratory, thoracic and mediastinal disorders			Epistaxis
Gastrointestinal disorders		Abdominal pain Nausea	Dyspepsia Dry mouth Flatulence Constipation
Skin and subcutaneous tissue disorders		Acne Hyperhidrosis	Skin lesion
Musculoskeletal and connective tissue disorders		Musculoskeletal pain	Back pain
Renal and urinary disorders			Urinary incontinence
Reproductive system and breast disorders	Amenorrhea Endometrial thickening Hot flush	Uterine haemorrhage* Ovarian cyst Breast tenderness/pain Pelvic pain	Metrorrhagia Ovarian cyst ruptured Genital discharge Breast swelling Breast discomfort
General disorders and administration site conditions		Oedema Fatigue	Asthenia

Table 4: List of known undesirable effects for LNG-IUS

System Organ Class	Common	Uncommon	Rare	Unknown
Immune system disorders				Hypersensitivity including rash, urticaria and angioedema
Psychiatric disorders	Depressed mood/Depression Nervousness Decreased libido			
Nervous system disorders	Headache Migraine			
Gastrointestinal disorders	Abdominal pain Nausea	Abdominal distension		
Skin and subcutaneous tissue disorders	Acne Hirsutism	Alopecia Pruritus Eczema Chloasma/Skin Hyperpigmentation	Rash	
Musculoskeletal, connective tissue and bone disorders	Back pain			

Reproductive system and breast disorders	Ovarian cysts Pelvic pain Dysmenorrhoea Vaginal discharge Vulvovaginitis Breast tenderness Breast pain	Pelvic inflammatory disease Endometritis Cervicitis/ Papanicolaou smear normal, class II	Uterine perforation	
General disorders and administration site conditions	Intrauterine contraceptive device expelled	Oedema		
Investigations	Weight increase			Blood pressure increased

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from available data).

Information to be collected includes dose, type of event, onset date, investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.4 ASSESSMENT OF AES AND SAES

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator or another suitably qualified physician in the research team. Cases that are considered serious, possibly, probably or definitely related to either IMP and unexpected (i.e. SUSARs) will be thoroughly investigated.

The Investigator is responsible for assessing each AE. This may be delegated to other suitably qualified physicians in the research team who are trained in recording AEs and recording and reporting SAEs.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.

- **Possibly Related:** The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the Section 4.8 of the relevant Summary of Product Characteristics.

The reference safety information i.e. known undesirable effects are detailed in the relevant SmPCs and are also referred to in Section 6.1.9.

Where there are concomitant medications, if the AE is considered to be related to an interaction between the IMP and the other medication, or where the AE might be linked to either the IMP or the other medication but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as nature of the HMB, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

10.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC, and summarised in Table 3 and Table 4.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SmPC.

Unexpected: the AR is not consistent with the toxicity in the SmPC.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.5 REPORTING OF SAES/SARS/SUSARS

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated

when the additional information is received. Elective admission for LNG-IUS insertion or elective admission for hysterectomy would not need to be classified as a serious adverse event.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF). Details received by ACCORD will be passed on to BCTU in their capacity as Coordinating Centre.

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs.

10.7 FOLLOW UP PROCEDURES

After initially recording an unexpected AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported. The Investigator should follow each unexpected AE or SAE until the event has resolved, the event is assessed as stable by the Investigator, the participant is lost to follow up, or the participant withdraws consent. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded.

In the case of PAECs observed at 12 months in those allocated UPA, the women should be reassessed until an endometrial biopsy confirms the restoration of a normal endometrium.

10.8 PREGNANCY

Pregnancy will be considered an AE if women are compliant with either trial treatment. If a woman withdraws from trial treatment and conceives within 12 months of randomisation, this **will not** be considered an AE. However, the investigator will collect pregnancy information for any female participants while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the UCON Trial Office within 14 days of being made aware of the pregnancy. BCTU will follow-up any self-reported pregnancies with the women's GP or gynaecologist. All pregnant female participants will be followed up until the outcome of the pregnancy is known. Details received by the UCON Trial Office will be passed on to ACCORD.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group (TMG), consisting of the Chief Investigator, all other grant holders, the Trial Manager and Edinburgh based research nurse. The TMG will meet regularly, by teleconference or face to face.

11.2 THE UCON TRIAL OFFICE

The Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for the day to day management of the UCON Trial. The Trial Manager, based at BCTU, will oversee the study and will be accountable to the Chief Investigator. The Data Manager will be responsible for checking the data forms for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

The UCON Trial Office will also be responsible for providing all trial materials, including an Investigator Site File (ISF), with copies of all essential documents, and a trial stationary folders containing all required printed materials e.g. participant information sheets, consent forms. These will be supplied to each collaborating centre, after relevant local research governance approval has been obtained. Additional supplies of any printed material can be obtained on request. 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), The Trial Office will help resolve any local problems that may be encountered in trial participation.

11.3 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. Names and contact details are given on page iii.

The Trial Steering Committee (TSC) provides independent supervision for the trial, providing advice to the Chief and Co- Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the International Committee on Harmonisation Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman 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.

The BCTU Trial office will forward TSC meeting minutes to the Sponsor and funder. Terms of reference of the Trial Steering Committee and the draft template for reporting will be agreed at the inaugural meeting.

11.4 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. Names and contact details are given on page iii.

If one treatment really is substantially better or worse than any other with respect to the primary outcome, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that any one treatment is definitely more, or less, effective than any other. To protect against this, during the main period of recruitment to the study, interim analyses of the primary outcome and adverse events will be supplied, in strict confidence, to the independent DMC, along with updates on results of other related studies, and any other analyses that the DMC may request. The DMC will advise the chair of the TSC if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt”¹ 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 TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

The BCTU Trial office will forward DMC open meeting minutes to the Sponsor and funder. Terms of reference of the Trial Steering Committee and the draft template for reporting will be agreed at the inaugural meeting.

11.5 INSPECTION OF RECORDS

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

11.6 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also

1 Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $p < 0.001$ (similar to a Haybittle-Peto stopping boundary) 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.

be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before, during or after the study and if so, at what locations and at what frequency.

11.7 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor may visit the Investigator site prior to the start of the study and/or during the course of the study if required, in accordance with the central monitoring plan.

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by either the ACCORD Clinical Trials Monitor and/or Trial Coordinator as and when required who would require direct access to source data and documents as requested. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

The study will also adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the trial data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables.

Trusts may also be subject to inspection by the Medicines and Healthcare Products Regulatory Agency and/ or by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

12.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

12.3 INVESTIGATOR RESPONSIBILITIES

The local Principal Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of

ICH GCP, the following areas listed in this section are also the responsibility of each Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

12.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – UCON Participant Information and Informed Consent Forms will be provided, with variations for those sites participating in the mechanistic sub-study. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and with the original filed in the ISF and copies filed in the participant's medical notes and sent to the Trial Office.

12.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the trial treatments, protocol and their trial related duties.

Each participating centre should also designate at least one nurse as a UCON research nurse. This person would be responsible for ensuring that all eligible patients are considered for the study, that women are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse will be responsible for ensuring the baseline participant questionnaire is completed and for randomisation.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the clinician completed data forms at their site.

12.3.4 Investigator Documentation

The local Principal Investigator is responsible for maintenance of their site's Investigator Site File, including filing updates provided by the UCON Trial Office

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the BCTU, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents), detailing their commitment to accrual, compliance, GCP, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The UCON Trial Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

12.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

12.3.6 Confidentiality

All endometrial biopsy samples, data collection forms and patient questionnaires must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. All investigators and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the UCON Trial (clinical, academic, 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. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations.

12.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to designated staff at the UCON Trial Office, clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

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

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

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

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

13.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 24 hours of becoming aware of the violation.

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

13.3 SERIOUS BREACH REQUIREMENTS

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

1. the safety or physical or mental integrity of the participants of the trial; or
2. the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary. Details received by ACCORD will be passed on to BCTU in their capacity as Coordinating Centre.

13.4 STUDY RECORD RETENTION

In line with the Medicines for Human Use (Clinical Trials) Regulations, once data collection is complete on all participants, at the end of the study, all data will be stored for at least 15 years. This will allow adequate time for review and reappraisal, and form the basis for further follow-up research. Any queries or concerns about the data, conduct or conclusions of the trial can also be

resolved in this time. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.5 END OF STUDY

The end of study is defined as the completion of the last participant's 12-month follow-up assessment unless PAECs are detected at this time. Should PAECs be diagnosed at 12 months then the end of study is determined by an additional biopsy(ies) and the resolution of the PAECs at either 15 or 18 months. The funder and/or Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

13.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Although UPA is a licensed drug for the treatment of uterine fibroids, it is not routinely prescribed for the treatment of heavy menstrual bleeding. Justification for the use of UPA after the trial will have to be discussed at the centre on a case-by-case basis; this discussion will be outside the remit of the trial.

13.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out

of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the grant holders. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines. A writing committee may be established to prepare the report.

The main report of the trial will be published in the name of the UCON Collaborative Group, acknowledging the writing group as authors. Subsequent publications should also be published in the UCON Collaborative Group name, but those academics who contribute to specific aspects may be listed as authors.

14.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, 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, who will be listed as members the UCON Collaborative Group in all publications. Centres will be permitted to publish data obtained from participants in the UCON Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

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APPENDIX 1: TRIAL SCHEMA

