TRIAL PROTOCOL

DEBi
DESOGESTREL FOR PROBLEM BLEEDING ON THE IMPLANT

Clinical and cost-effectiveness of desogestrel versus the combined oral contraceptive pill for problematic bleeding on the etonogestrel implant

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Chief Investigator and Sponsor Approval Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator (CI) agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

This protocol has been approved by:	
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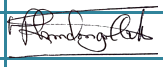
CI Name:	Kate Walker
Trial Role:	Chief Investigator
Signature and date:	
Date:	01 - 08 -20 25 (dd-mmm-yyyy)

Sponsor statement:
Where the University of Nottingham takes on the Sponsor role for oversight of protocol development, signing of the IRAS form by the Sponsor will serve as confirmation of approval of this protocol.

Statistical approval	
Statistician name:	Reuben Ogollah
Signature and date:	
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A full list of trial sites can be found on the Trial website www.DEBI.ac.uk

Abbreviations

Abbreviation	Term
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AR	Adverse Reaction
BMI	Body Mass Index
CACE	Complier Average Causal Effect
CEAC	Cost-effectiveness Acceptability Curves

CERT	Contraceptive Education and Reform Team
CHC	Combined hormonal contraceptive
CI	Chief Investigator
CIMC-GLRA	Contraceptive-induced Menstrual Change- Global Research and Learning Agenda
COCP	Combined Oral Contraceptive Pill
COMET	Core outcome Measures in Effectiveness Trials
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
DOAC	Direct Oral Anticoagulants
DMC	Data Monitoring Committee
DMP	Data Management Plan
DMPA	Depot Medroxy-Progesterone Acetate
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol Group standard measure of health-related quality of life
EU	European Union
FSRH	Faculty of Sexual Reproductive Healthcare
FU	Follow Up
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
GP	General Practitioner
HRQL	Health-related Quality of Life
HSG	Health and Safety Guidance
ICECAP-A	ICEpop CAPability measure for Adults
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention To Treat
LARCS	Long-acting Reversible Contraceptives
LMWH	Low Molecular Weight Heparin
MHRA	Medicines and Healthcare Products Regulatory Agency
NAAT	Nucleic Amplification Test
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Care Research
NSAIDs	Non-steroidal Anti-inflammatory Drugs

PI	Principal Investigator
PIS	Patient Information Sheet
POP	Progesterone Only Pill
PP	Per-protocol
PPI	Patient and Public Involvement
PSS	Personal Social Services
QALY	Quality-Adjusted Life Years
RCOG	Royal College of Obstetricians and Gynaecologists
R&D	Research and Development
REC	Research Ethics Committee
RN	Research Nurse
RSI	Relevant Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Products Characteristics
SRH	Sexual and Reproductive Health Research
STI	Sexually Transmitted Infections
STM	Senior Trial Manager
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within a Trial
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VTE	Venous Thromboembolism
WHO	World Health Organisation

Trial Summary

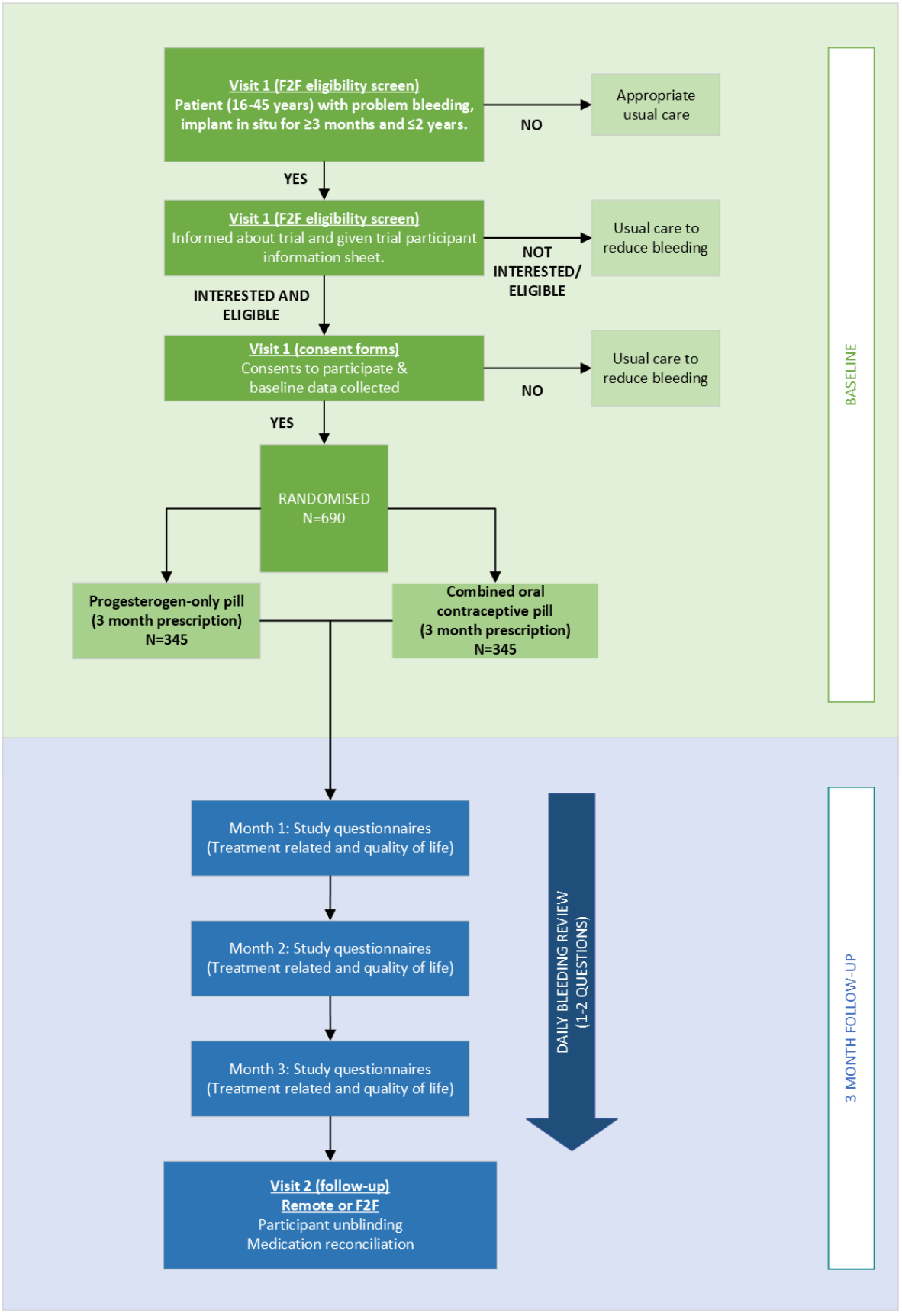
Trial Title	Clinical and cost-effectiveness of desogestrel versus the combined oral contraceptive pill for problem bleeding on the etonogestrel implant (DEBI)
Internal ref. no. (or short title)	DEBI trial
Clinical Phase	Clinical trial of investigational medicinal product (phase IV). Medicines and Healthcare Products Regulatory Agency (MHRA) category B.
Objectives	**Primary objective** To establish whether desogestrel is non-inferior to the combined oral contraceptive pill (COCP) in settling problem bleeding during a 90-day reference period for people with problem bleeding whilst using the etonogestrel implant. Resolution of problem bleeding is defined as people self-reporting significant improvement in the bleeding pattern during the 90-day reference period. **Secondary Objectives** For people with problem bleeding whilst using the etonogestrel implant, to compare between desogestrel and COCP the: 1. Effectiveness in terms of improving other bleeding related outcomes (longest duration of consecutive non-bleeding whole days, total number of non-bleeding, spotting and bleeding days, number and duration of bleeding episodes, time to the longest consecutive non-bleeding days. 2. Acceptability, adherence to treatment, and discontinuation of allocated treatment and of implant. 3. Health related quality of life and health care resource use.
Trial Design	Two-arm, parallel-group, clinician and participant blinded, non-inferiority, randomised controlled trial with an internal pilot phase.
Trial Participant Population	Menstruating people aged 16-45 with self-reported problem bleeding whilst using the etonogestrel implant. Problem bleeding is defined as bleeding of any type (e.g. spotting/heavy) considered problematic by the person.
Setting	UK integrated sexual health clinics and primary care practices offering implant services.
Key Eligibility Criteria	**Inclusion Criteria:** • 16-45 years. • Etonogestrel implant user, with current implant in situ for 3-24 months. • Female, or trans-male and non-binary people with a uterus, ovary/ovaries and vagina not using hormones other than etonogestrel implant. • Sexually transmitted infection (STI) screening and high sensitivity pregnancy test negative at time of recruitment. • Willing to complete daily bleeding diary for the trial duration • Self-reported problem bleeding. • Informed consent given.

	Exclusion criteria: • Current use or use within the last 3 months of hormones (except Depot Medroxy-Progesterone Acetate (DMPA), see section 4.2) or medications known to affect menstrual bleeding (see section 4.2) • Current use or use within the last 6 weeks of liver enzyme inducing medicines which induce the cytochrome CYP3A4 • Current use or use within the last 9 months of DMPA • Postpartum < 6 weeks (UKMEC Category 3 or 4) [1] • Surgery to genital tract altering bleeding • Contraindication (UKMEC Category 3 or 4) [1] or allergy to desogestrel or COCP or excipients (including **soya bean oil**) • Established pathological reasons for abnormal uterine bleeding. • Current known sexually transmitted infection • Currently pregnant (positive urinary pregnancy test) • Declines screening, speculum exam and examination of implant • Previous participation in the trial
Sample size estimate	To establish the non-inferiority of desogestrel compared to the COCP in resolving problem bleeding, assuming a reference group proportion of 85% experiencing significant improvement in bleeding pattern, a sample size of 276 per arm (552 total) would be required to achieve 90% power to detect non-inferiority of desogestrel compared to COCP within an absolute non-inferiority margin of 10% based on one-sided 2.5% significance level, 1:1 allocation, and a likelihood score test statistic (Farrington and Manning). Allowing for 20% missing primary outcome data, the DEBI trial will randomise 690 participants.
Number of participants	690
Treatment duration	90 days
Follow up duration	90 days
Planned Trial Period	Overall trial duration is 40 months from 01/04/2024 to: 31/07/2027 with the trial recruitment and follow up period from March 2025-October 2026
Investigational Medicinal Product(s) And/or Intervention/Control	Intervention: desogestrel 75 micrograms, once daily by mouth. Active comparator: 30 microgram ethinylestradiol and 150 microgram levonorgestrel COCP, 1 tablet daily by mouth (without a hormone free interval).
Randomisation and blinding	Eligible patients will be individually randomised to desogestrel or COCP on a 1:1 ratio. Dynamic randomisation will use a minimisation algorithm with a random element to balance across groups by recruitment site, body mass index, smoking status (including cigarettes/hand-rolled cigarettes/nicotine replacement therapy/e-cigarettes/disposable vapes/cigars/pipes or shishas that contain tobacco or nicotine), and self-reported categorisation of problem bleeding in previous 90 days. Both COCP and desogestrel tablets will be similar oval, unmarked, white tablets to mask the allocation.
Outcome measures	**Primary outcome**

	Participant-reported resolution of problem bleeding, with resolution defined as self-reported significant improvement in the bleeding pattern during the 90-day reference period. Improvement in problem bleeding will be measured by participants' self-determination that their bleeding pattern has improved using a 5-point Likert scale. **Secondary outcomes** *Clinical effectiveness* • Longest duration of consecutive non-bleeding (no bleeding or spotting) whole days for each 30-day period within the 90 days. • Total number of non-bleeding, spotting and bleeding days during the 90-day treatment period • Number and duration of bleeding episodes (one or more consecutive days of bleeding, bounded by bleed-free days) within the 90 days • Time to the longest consecutive non-bleeding days *Treatment acceptability and adherence* • Acceptability of treatment (side effects) • Adherence to treatment *Safety* • Discontinuation of allocated treatment and of implant *Cost-effectiveness* • Quality of life (EQ-5D-5L and ICECAP-A) • Primary care, sexual health, and secondary care health resource use • Personal and out of pocket expenses arising from problem bleeding • Intention to continue the trial drug at 3 months
Statistical methods	For the primary outcome, a two-sided 95% confidence interval for the between-group difference in proportion of people reporting significant improvement will be constructed by fitting a mixed-effect logistic regression model, adjusting for site as a random effect and other minimisation factors as fixed effects. The model will include outcome data from all the 3 timepoints (30, 60, and 90 days) and will include treatment by time interaction to obtain the treatment effect at each timepoint with 90 days as the primary contrast. Non-inferiority of desogestrel will be inferred if the lower bound of this interval lies within the non-inferiority margin of 10%. Analysis will be performed on both the intention to treat (ITT) and per-protocol (PP) population, with ITT being the primary inference. Between-group comparison of secondary outcomes will be based on an appropriate regression model for the outcome, in the generalised linear mixed model framework adjusting for same variables as the primary analysis.
Health Economics	**Resource Use:** The main resources to be monitored include: 1. The costs associated with treatment (provision of desogestrel and COCP).

	2. Time and resource use incurred in sexual and reproductive health research (SRH) settings associated with clinical examination, additional treatments and monitoring during the follow up period and to treat any adverse events. 3. Costs associated with discontinuation of the implant. 4. Costs associated with general practitioner (GP) attendances, A&E visits and other National Health Service (NHS) secondary care. 5. Any other health and social care resource use. 6. Costs such as those incurred by implant users and their families (e.g. associated with problem bleeding), will also be captured to allow personal family costs ed as a secondary analysis. Information on unit costs or prices will be sourced to attach to each resource use item, to enable an overall cost per participant to be calculated (e.g. Unit Costs of Health and Social Care and NHS Reference Costs). **Economic analysis** The initial economic analysis will assess cost-effectiveness based on participant self-reported significant improvement in the bleeding pattern, reflecting the primary outcome of the trial. A secondary analysis of incremental cost per quality-adjusted life years (QALYs) gained will also be undertaken in line with National Institute for Health and Care Excellence (NICE) recommendations.

Figure 1-DEBI Trial flow chart



1. Background and Rationale

Safe and effective interventions for people with irregular bleeding whilst using long-acting reversible contraceptives (LARCs) has been identified as the number 5 priority by The James Lind Alliance Contraception Priority Setting Partnerships. The 68mg etonogestrel subdermal contraceptive implant (implant) is the most effective (failure rate 0.05%) and popular method of LARC in the UK accounting for 40% of LARC and 18% of overall contraception used [2, 3]. The implant is a small flexible tube, placed under the surface of a patient's skin in the upper arm, with each implant providing contraception for up to three years. Unfortunately, the etonogestrel implant has the least favourable bleeding pattern of all LARC methods with 24% of users experiencing problem or unscheduled bleeding once the implant has been inserted. Problem bleeding is the most commonly reported reason for discontinuation of the implant, with 25% of users choosing to have the implant removed early due to their problem bleeding [4-7].

Current evidence for the best treatment for problem bleeding whilst using the implant is limited. To date, research has explored the use of the COCP, non-steroidal anti-inflammatory drugs (NSAIDs), Doxycycline and Tamoxifen with mixed results, and several important contraindications excluding some implant users from the use of these agents. The COCP is the recommended first line treatment in UK national guidelines [8] for problem bleeding when using the implant. The COCP works by the estrogen component of COCP sustaining endometrial integrity which counteracts the progestin-induced decidualisation and endometrial atrophy that creates problem bleeding.

COCP is the most evidenced treatment for problem bleeding whilst using the implant. Two randomised controlled trials that compared COCP with placebo used a 30mcg ethinylestradiol/150mcg levonorgestrel COCP preparation [9, 10]. National guidelines advise this preparation of COCP for use in problem bleeding whilst using the implant [8] partly due to these trial results and partly as levonorgestrel COCP has a slightly lower venous thromboembolism (VTE) risk than desogestrel COCP [11]. However, COCP and NSAIDs have multiple contraindications. Approximately 10% of women and menstruating people of reproductive age in the UK have a contraindication to the COCP such as smokers aged over 35 and people with a body mass index over 35. NSAIDs are contraindicated in moderate to severe asthmatics, those with certain gastrointestinal or kidney diseases. There are safety concerns with long term tamoxifen and ulipristal use. As a result, clinicians often resort to non-evidenced strategies for these groups or do not offer treatment at all.
On the basis of this limited evidence, current national guidance for the management of problem bleeding whilst using the implant advises the use of COCP or NSAIDs after exclusion of pathological causes for the bleeding [8].

One popular but unevidenced treatment used in clinical practice is desogestrel, a licensed progestogen only pill (POP). Desogestrel is an inactive prodrug of etonogestrel (the same progestin in the implant), making it ideal for combating problem bleeding whilst using the implant as it avoids multiple progestins and theoretically reduces the risk of hormonal side effects of progestin polypharmacy. Desogestrel is a licensed contraceptive oral tablet, taken once daily at 75mcg by mouth. It works to prevent pregnancy via inducing anovulation, endometrial thinning and cervical mucus thickening and achieves higher serum etonogestrel concentrations than the implant (mean concentration 853pg/ml versus 200pg/ml), [12] which may work to stabilise the endometrium or alleviate the variable etonogestrel serum plasma concentration seen with the implant over its three-year life span [13-17]. Desogestrel has fewer contraindications than COCP, so can be used in most people where COCP is contraindicated.

As problem bleeding is the biggest reason for implant users to discontinue their implant early, and in our national survey of 208 implant users, 25% (8/32) planned early discontinuation without another contraceptive method whilst reporting being sexually active and not planning a pregnancy. There is an urgent need for robust evidence to answer if desogestrel can be used as an effective, acceptable, and safe alternative to COCP for implant users experiencing problem and unscheduled bleeding. Whilst a head-to-head comparison of desogestrel with the COCP will be limited to a younger, healthier population without certain co-morbidities (e.g. personal history Body Mass Index {BMI} over 35), it would provide direct comparative evidence for most implant users and data on desogestrel that can be considered by those with contraindications to the COCP.

1.1. Trial Design Justification

DEBI has been designed to assess whether desogestrel is a non-inferior treatment when compared to COCP for implant users with problem bleeding over a 90-day period.

Whilst desogestrel is effective anecdotally, it is unlikely to be more effective in treating problem and unscheduled bleeding than the COCP. However, desogestrel provides other advantages at individual and health service levels such as reduced polypharmacy (desogestrel increases a single dose of progestogen compared to COCP which provides estrogen and a further progestogen), fewer contraindications, lower cost per tablet, fewer additional clinic visits for patients and reduced burden on General Practice and Sexual Health services as desogestrel can be dispensed by a pharmacist without prescription. The identification of potentially slightly lower efficacy against a cheaper alternative with fewer side effects lead to a non-inferiority trial design.

The trial is pragmatic and reflective of a large simple trial to make the trial convenient to both participants and clinical staff and the recruitment timing and methods were informed by input from clinicians and the Patient and Public Involvement (PPI) group.

There is no core outcome set for contraceptive research created by the Core outcome Measures in Effectiveness Trials (COMET) approach, although the Pearl index is the universally accepted measure of efficacy. Guidance on data collection and analysis of self-reported bleeding and spotting has come from the World Health Organisation (WHO) [18], and further developed and standardised in the US in a consensus conference in 2005 [19]. The focus of both was on combined hormonal contraceptives (CHCs) where the concept of cycles is more evident than for LARCs. The emphasis was reporting incidences of unscheduled bleeding, and the number of days of bleeding and/or spotting, or of bleed-free days using daily diaries. More recently, an international stakeholder group, the authors of the Contraceptive-Induced Menstrual Changes Global Research and Learning Agenda (CIMC-GRLA) highlight the lack of standardised and validated measures for different aspects of contraception induced menstrual changes [20].

In the era of LARCs, it became evident that it is not just the number of days with or without bleeding, but the predictability that is problematic for contraception users. Irregular bleeding has been defined as between 3 and 5 bleeding episodes with fewer than three bleed-free intervals of ≥14 days, in a 90-day reference interval, [18] and this is used in Faculty of Sexual Reproductive Healthcare (FSRH) and Royal College of Obstetricians and Gynaecologists (RCOG) guidance. This definition doesn't reflect the bleeding patterns of many LARC users and fails to acknowledge the subjective experience. The Contraceptive-induced Menstrual Change- Global Research and Learning Agenda (CIMC-GLRA) have convened working groups to review the indicators and tools being used, assess their usefulness and develop and validate new measures. Until this work is complete, there is no consensus in how menstrual changes induced by hormonal contraception should be measured.

Both our PPI group members and a member of the CIMC-GLRA (Prof H Critchley, personal communication) agree it is the predictability of bleeding that is the key issue, with people prepared to tolerate heavier bleeding if any treatment concurrently improved bleeding patterns. In view of the absence of a definition of a problem bleeding pattern, a global impression of change of bleeding pattern from treatment will capture predictability and be easy to interpret.

This trial will randomise implant users aged 16-45 with self-reported problem bleeding to either COCP (levonorgestrel 150mcg/ethinylestradiol 30mcg) one tablet daily (without a hormone free interval) by mouth or desogestrel 75mcg one tablet daily by mouth in a participant and researcher blinded non-inferiority trial on a 1:1 ratio for a duration of 90 days. Recruitment will be via a single in person trial site visit which is the same as standard of care, and remote follow up with self-reported outcomes using a digital or paper-based diary.

2. Aims, Objectives and Outcome Measures

2.1. Aims

To determine if desogestrel, a progestogen only contraceptive pill, is as effective in the management of problem bleeding whilst using the etonogestrel implant, compared to the COCP. The trial will also assess how cost-effective desogestrel and COCP are as treatments for problem bleeding whilst using the implant.

2.2. Primary Objectives and Outcome Measures

Table 1-Primary Objectives

Objective	Outcome Measure	Time Point	Method of Collection
To establish if the proportion of participants reporting problem bleeding is not worse in participants treated with desogestrel compared to COCP.	Participant self-reported significant improvement in the bleeding pattern.	Day 90	Participant Questionnaire

2.3. Secondary Objectives and Outcome Measures

Table 2-Secondary Objectives

Objective	Outcome Measure	Time Point	Method of Collection
To establish if the proportion of participants reporting problem bleeding is not worse in participants treated with desogestrel compared to COCP.	Participant self-reported significant improvement in the bleeding pattern.	Day 30 and 60	Participant Questionnaire
	Longest duration of consecutive non-bleeding (no bleeding or spotting) whole	Daily	Daily bleeding diary

	days for each 30-day period within the 90 days.		
To determine the effect of desogestrel compared with COCP on total number of non-bleeding, spotting and bleeding days during the 90-day treatment period	Participant self-reported bleeding pattern.	Daily	Daily bleeding diary
To determine the effect of desogestrel compared with COCP on the number and duration of bleeding episodes (one or more consecutive days of bleeding, bounded by bleed-free days) within the 90 days	Participant self-reported bleeding pattern.	Daily	Daily bleeding diary
To determine the effect of desogestrel compared with COCP on the time to the longest consecutive non-bleeding days	Participant self-reported bleeding pattern.	Daily	Daily bleeding diary
To determine the acceptability with trial treatment	Participant-reported side effects	Day 30, 60 and 90	Participant Questionnaire
To establish participant adherence to treatment	Participant reported adherence to trial treatment	Daily	Daily bleeding diary
	Participant reported discontinuation/removal of their implant	Day 30, 60 and 90	Participant Questionnaire
To determine the effect of desogestrel and COCP on participant Quality of life	Participant reported EQ-5D-5L and ICECAP-A	Day 30, 60 and 90	Participant Questionnaire

To determine the cost of treating implant user problem bleeding with desogestrel or the COCP	Treatment and healthcare usage	Day 30, 60 and 90	Participant Questionnaire
To determine the proportion of participants who intend to continue their allocated treatment.	Participant reported	Day 90 or sooner if early withdrawal from trial	Participant Questionnaire

3. Trial Design and Setting

3.1. Trial Design

Phase IV, multicentre, clinician and participant blinded, randomised non-inferiority trial, with economic evaluation. Equal allocation (1:1) to receive either desogestrel (intervention) or COCP (usual care). Recruitment of 690 participants is required to achieve 90% power and conclude non-inferiority with respect to resolution of problem bleeding. Further information on sample size and randomisation can be found in section 6.2 and 14.1 respectively.

Details on the internal pilot phase and progression criteria can be found in 14.3.1 Planned Interim Analysis.

3.2. Trial Setting

Participants will be identified and recruited during appointments at integrated sexual health clinics and primary care practices offering implant services within the UK. A minimum of 17 sites will be opened to recruit a total of 690 participants over 17 months.
Figure 1-DEBI Trial flow chart can be found at the start of this protocol.

3.3. Type of Trial by Risk Category

Type B: risk somewhat higher than that of standard medical care.

Both COCP and desogestrel will be used outside of their licensed purpose for the trial. COCP is the recommended first line treatment in UK national guidelines for problem bleeding on the implant based on current limited evidence. Although desogestrel is used in clinical practice, there have been no clinical trials evaluating the safety and effectiveness of desogestrel on problem bleeding experienced by implant users.

4. Eligibility

4.1. Inclusion Criteria

- Female, or trans-male and non-binary people with a uterus, ovary/ovaries and vagina not using hormones other than etonogestrel implant
- 16 – 45 years old
- Etonogestrel implant user, with current implant in situ for at least 3 but no more than 24 months
- Self-reported problem bleeding
- Willing to complete daily bleeding diary for the trial duration
- Able to provide Informed Consent
- Sexually transmitted infection screening undertaken and high sensitivity pregnancy test negative at time of recruitment.

4.2. Exclusion Criteria

- Current **routine** use of **oral** NSAIDs
- Current use or use within the last 3 months of hormones or medications known to affect menstrual bleeding, including progestogens, estrogens, androgens, tranexamic acid, selective progestogen receptor modulators
- Current use or use within the last 6 weeks of liver enzyme inducing medicines which induce the cytochrome CYP3A4
- Postpartum < 6 weeks (UKMEC 3 or 4) [1]
- Current use or use within the last 6 months of gonadotrophin-releasing hormone analogues
- Current use or use within the last 9 months of DMPA
- Surgery to genital tract altering bleeding, including hysterectomy, bilateral-oophorectomy or endometrial ablation
- Contraindication (UKMEC Category 3 or 4)[1] or allergy to desogestrel or excipients (including **soya bean oil**)
- Contraindication (UKMEC Category 3 or 4) [1] or allergy to COCP containing levonorgestrel and ethinylestradiol or excipients.
- Established pathological reasons for abnormal uterine bleeding, including malignancy or endometrial hyperplasia, fibroids, cervical polyps or lesions (seen on speculum examination), endometrial polyp(s), adenomyosis, coagulopathy, ovulation disorder (e.g. polycystic ovary syndrome)
- Current known sexually transmitted infection (If STI screening comes back positive then the participant will remain in the trial)
- Currently pregnant (positive urinary pregnancy test)
- Previous participation in this trial
- Declines screening for sexually transmitted infection dual nucleic amplification test (NAAT) for Neisseria Gonorrhoea and Chlamydia Trachomatis at the time of presentation
- Declines a speculum examination to assess the cervix for abnormality or other cause for problem bleeding at the time of presentation
- Declines examination of the implant insertion site to ensure palpable and present at the time of presentation

4.3. Participant Identification

Potentially eligible participants will be identified and approached by appropriately trained clinic staff at each recruiting site (including both clinical and non-clinical team members). Potential participants will be identified at the time of booking or during their clinic consultation and will be screened, consented and randomised during this one visit. Participants will be issued their trial medication during their consultation and will not be required to attend another clinical visit as part of the trial participation. The clinical care team will review personal patient information to identify and screen potential participants for the trial.

Publicity materials will be used to raise awareness of the trial to potential participants. The trial will have a public facing website, social media pages (on platforms such as Instagram/Facebook, X, TikTok) and posters will be used to share information regarding the trial and the active recruiting sites. Online publicity may include information on individual site activity such as date opening and recruitment. Members of the trial team may also share details of the trial at relevant events and conferences.

A medically qualified doctor will confirm participant eligibility. If non-medically qualified staff (who possess the experience, knowledge and ability to determine a potential participant's eligibility) are delegated by the PI to assess eligibility, then oversight by a medically qualified doctor at the site will be evidenced by a signature and date within 48 hours. If the PI is not a medically qualified doctor, then they must ensure sufficient medically qualified doctors are delegated to roles that require medical decisions. More details on the eligibility process for the trial can be found above in section 4.2 and appendix **Error! Reference source not found.**.

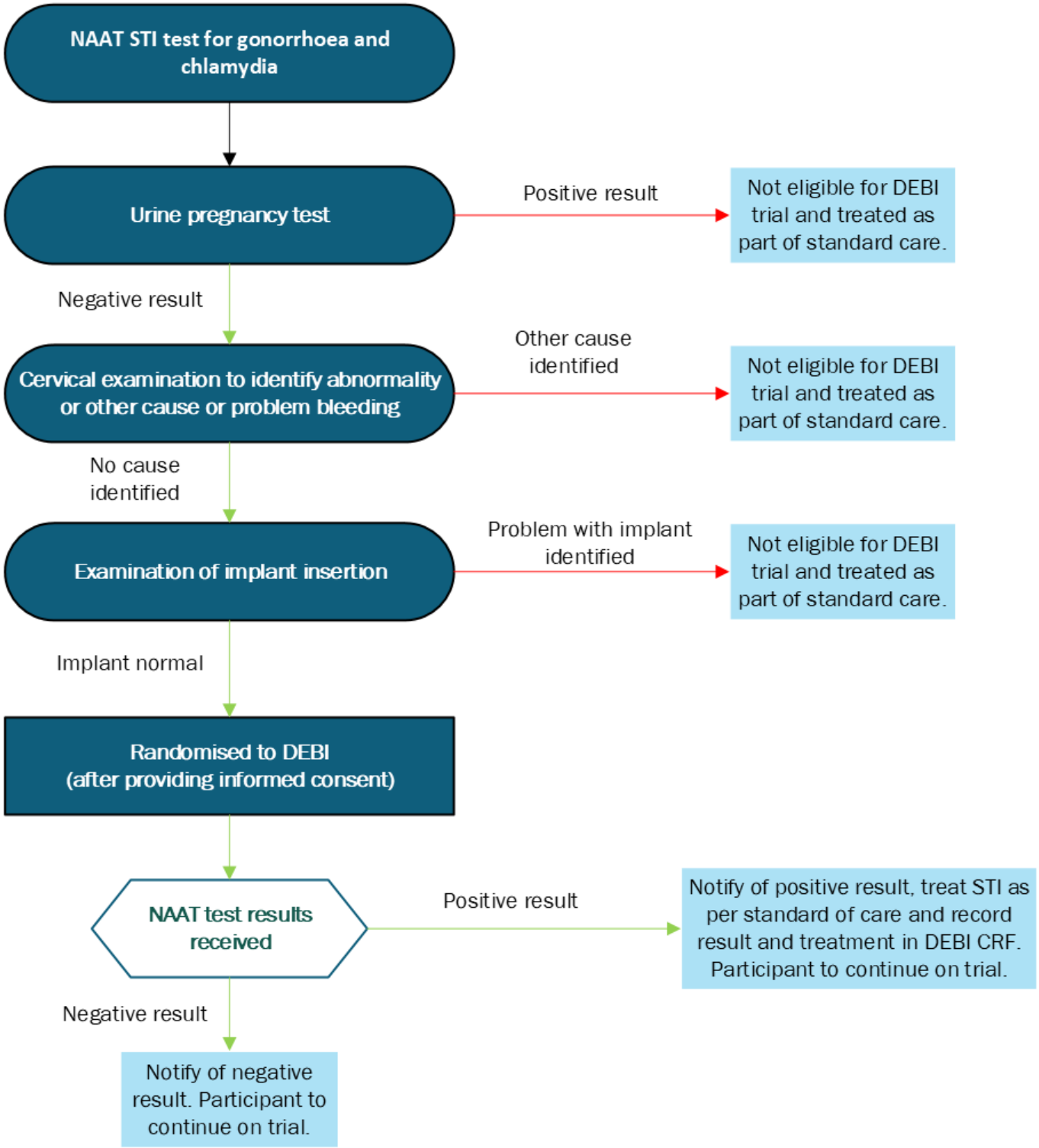
4.4. Screening

Potential participants will be approached by a member of their usual care team during a clinical consultation for problem bleeding on the implant. During this consultation they will be offered the following routine clinical assessments:

- Sexually transmitted infection NAAT for Neisseria Gonorrhoea and Chlamydia Trachomatis
- A high sensitivity urine pregnancy test
- A speculum examination to assess the cervix for abnormality or other cause for problem bleeding.
- Examination of the implant insertion site to ensure palpable and present

In keeping with SRH guidelines [21], pelvic ultrasound and hysteroscopy is not required as part of standard of care on the DEBI trial unless there is suspicion of structural abnormalities (e.g. endometrial polyp, endometrial hyperplasia, intrauterine fibroids).

Figure 2-Routine clinical assessment outcome flowchart



These routine clinical assessments are expected to be performed as part of standard care for people presenting with problem bleeding whilst using the implant. They are required to exclude other causes of problem bleeding, and the results will be reviewed in order to determine eligibility. Any potential participant who declines a pregnancy test or speculum examination will not be able to participate in the trial because some exclusion criteria cannot be verified.

Once other causes of problem bleeding have been ruled out, the participant can be invited to participate in the trial. Enrolment and randomisation will take place at the time of the single trial visit, as the speculum examination and urine pregnancy test results are immediately available. The NAAT results will be available approximately 5 working days after the swab has been taken. Those requiring pelvic ultrasound and/or hysteroscopy cannot be enrolled at the first trial visit.

Details of all participants approached about the trial will be recorded by sites on the Participant Screening Log, including date approached, initials, DOB, whether they consented, reason if they did not consent, whether they randomised and reason they did not randomise. Summary info (no identifiers) will be transferred to REDCap by site staff. Those who do not meet eligibility criteria will have the reason explained to them and that it will not impact on their care. They will then continue to have routine care without delay.

5. Participant Information and Consent

5.1. Participant Information

A Participant Information Sheet (PIS) will be provided to all eligible participants who have expressed an initial interest in participating in the trial. Investigators or delegate(s) will ensure that they adequately explain the aim, trial treatment, anticipated benefits, and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and so the potential participant is free to decline participation and may withdraw from the trial at any time. The DEBI trial PIS will be available in English and Polish, Romanian and Punjabi.

To best mirror standard care, participants will be provided with the trial information during the same visit that they enrol, however they will be given time to read the PIS and to discuss their participation with others if they wish (e.g. family members, GP or other healthcare professionals outside of the site research team) and return to provide consent at a subsequent visit.
As part of the DEBI trial Study Within a Trial (SWAT), potential participants at certain recruiting sites will be asked to watch a trial information video in addition to the PIS and discussion with the investigator or delegate. More information on the SWAT can be found in Section 10.

5.2. Consent and electronic consent

Table 3-Consent forms

Consent Forms in DEBI	***Method (e-consent or written informed consent)***	***Person taking consent (Principal Investigator {PI}, Research Nurse {RN}, PI or delegate, etc)***	*Use of legal representatives (Y/N)*
Main Trial (adults)	*Face to face- e-consent or written informed consent*	*Delegate or research nurse*	*N*

Written informed consent (electronic consent or paper-based where access to a personal electronic device is unavailable) for each participant must be obtained prior to performing any trial related procedure. The potential participant will be given the opportunity to ask questions throughout the process. Consent will be obtained face to face by a member of the clinical team at the recruiting site, in accordance with the responsibilities delegated by the Principal Investigator as captured on the Site Delegation Log. It remains the responsibility of the Principal Investigator to ensure informed consent or e-consent is obtained appropriately. Eligibility for the trial must always be confirmed by a medically qualified doctor (or delegated staff with oversight by a medically qualified doctor at the site as per section 4.3) using the eligibility checklist**.**

If a participant is 16 or 17 years of age, the Clinical Trials Regulation allows them to consent for themselves, provided they have the capacity to do so.

Potential participants will consent electronically via REDCap (where access to an electronic device is not possible, a paper written consent form will be used). Once signed by both parties, a copy of the complete consent from will be saved in REDCap and sent via email to the participant, along with an electronic copy of the PIS for their records. Where the consent form is completed on paper, the participant's unique trial identification number will be written onto the form, a copy will be made so that both the investigator and participant have a copy each. The investigator copy will be scanned and uploaded to REDCap where all consent forms (electronic and paper) will be available to the NCTU for central review. The investigator copy will then be filed within the patient medical records (for electronic consent this can be downloaded as a PDF by the site and saved within the electronic patient records or printed for paper records.)

The participant must give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to be given direct access to the participant's medical records.

Optional consent will be sought for a separately funded long-term follow-up of randomised participants continued prescription of COCP, desogestrel or other treatments for problem bleeding, and change/removal of the implant. This information will be obtained from routinely collected data. This will be submitted as an amendment once trial funding is known. The initial trial data would be reported in line with the current grant and one data capture would be performed at +2 years to collect all the relevant data at each site. It is to be noted that 2-year follow up will not be possible if such funding cannot be secured.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date and time of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of the ICF signed and date consent received.

Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue may be re-consented. A copy of the new consent form will be filed in the patient medical records and re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

6. Enrolment and Randomisation

6.1. Enrolment

Eligible participants will be enrolled at the single face to face visit and randomised at this time if all eligibility criteria (other than STI test results) can be ascertained. Participants may choose to take away trial information and return at a subsequent visit for enrolment.

Prior to enrolment of a participant, trial eligibility must be confirmed by the investigator or delegate and informed consent must be provided and signed by both the potential participant and the investigator or delegate. Baseline data will then be collected and recorded in the electronic Case Report Form (eCRF) and the participant enrolled using the online trial randomisation system. The participant will be required to categorise their problem bleeding in terms of number and duration of bleeding episodes in the previous 90 days: infrequent bleeding (<3 episodes); normal (3– 5 episodes); frequent (>5 episodes); prolonged (≥1 episode(s) lasting ≥14 days). See section 8.2.3 for further information on baseline data collection requirements.

6.2. Randomisation

Randomisation will be provided by REDCap, a secure online randomisation system at the NCTU. Unique log-in usernames and passwords will be provided to those who have been delegated the role of randomising participants into the trial as detailed on the DEBI Delegation Log. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

After participant eligibility has been confirmed, informed consent has been received, baseline data items have been provided the participant can be randomised into the trial and a trial number allocated. Following randomisation, a confirmatory email will be sent to the randomising clinician, local Principal Investigator, and the local pharmacy. A randomisation notification will be sent to the Chief Investigator and NCTU.

Participants will be randomised at the level of the individual in a 1:1 ratio to either desogestrel or COCP.

A minimisation algorithm will be used to ensure balance in the allocation over the following variables:

- Recruitment site
- Body mass index (BMI < 25 kg/m^2, BMI ≥ 25 to < 30 kg/m^2, BMI ≥ 30 kg/m^2)
- Smoking status (current smoker, non-smoker-by smoking we mean cigarettes, hand-rolled cigarettes, e-cigarettes, disposable vapes, cigars, pipes or shishas that contain tobacco or nicotine.)
- Self-reported categorisation of problem bleeding in previous 90 days (infrequent bleeding (<3 episodes); normal (3‑ 5 episodes); frequent (>5 episodes); prolonged (≥1 episode(s) lasting ≥14 days))

A ‘random element’ will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. The trial statistician will provide a detailed randomisation specification document to the database programmers.

6.3. Blinding and concealment

Trial treatment allocation will be concealed to participants, the site research team and most members of the Trial Management Group (TMG) as outlined in Table 4. Participants will be told the trial intervention at the end of the 90-day trial period.

Table 4 provides an overview of the blinding status of all individuals involved in the management and delivery of the trial.

Table 4 The blinding status of individuals involved in the trial

Trial role	Blinding status	Comments
Participant	Blinded during trial participation.	Blinded to their treatment allocation for the duration of their participation in the trial to minimise the chance of treatment bias when completing bleeding pattern diary or trial questionnaires. Participants will be unblinded following completion of their 90-day follow-up.
Principal Investigator and other site staff	Blinded	Blinded to treatment allocation to minimise the chance of unconscious treatment bias. At the end of an individual participant's participation (90 day follow up FU), a nurse (or other team member) will be unblinded to the treatment allocation to allow for continued prescription of the trial treatment as part of standard care.
Clinical assessor at site	Blinded	Blinded to treatment allocation to minimise the chance of unconscious treatment bias.
Chief Investigator(s)	Blinded	The CIs will remain blinded to treatment allocation overall, except for in their role as medical monitor if there is a SUSAR.
Database Programmer	Not blinded	The database programmer will be responsible for the management of the

		randomisation system and Investigational Medicinal Product (IMP) pack system and will have access to unblinded datasets within the trial database.
DEBI Trial Management staff within NCTU	Blinded	DEBI Trial Management staff within NCTU will remain blinded to treatment allocation.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the trial database to ensure data quality and undertake central monitoring activities
Trial Statistician and Senior Trial Statistician	Blinded	The trial and senior trial statistician will not have access to treatment allocations or data which has the potential to unblind until after the first database lock for the analysis
Independent Statistician	Not blinded	A statistician, independent to the trial team, will be responsible for the generation of closed reports for the Data Monitoring Committee (DMC) and other potentially unblinding data and will therefore be unblinded to trial treatments

6.4. Unblinding procedure

Unblinding is the process that relates to revealing the intervention that was allocated to a participant during their randomisation onto the trial. For the DEBI trial, unblinding of each participant will occur routinely at the end of their participation, or unblinding prior to the end of the trial may occur if the participant experiences a medical emergency or Suspected Unexpected Serious Adverse Event (SUSARs). Site staff who have been delegated the responsibility to reveal a participant's treatment allocation will be able to do this via the REDCap database. Unblinding is done on an individual basis to allow the participant to continue on their treatment as part of their usual care if they feel that the treatment has been effective in treating their problem bleeding. As both the participant and medical team are blinded this must be done to ensure that the correct medication can be provided.

6.4.1. Emergency unblinding

In order to protect the safety and well-being of the participants during a medical emergency, unblinding will be performed within the REDCap trial database. Emergency unblinding will be performed by a member of the participants research team via REDCap. Unblinding via REDCap will be available and readily accessible at time of need. The use of REDCap, an electronic platform will ensure they are kept securely but accessible (including remotely) if required with full audit trail recorded. This process will be used to unblind the participant during the emergency, where knowledge of DEBI treatment is absolutely essential for further management.

The NCTU and CI will be notified automatically by email that the blind has been broken but will not be made aware of the participant's allocation. The NCTU will notify the Sponsor as soon as possible after the event. Once notified, the NCTU should send the Emergency Unblinding Form to the site research team for completion. Once returned this should be reviewed by the Trial Manager (TM)/Senior Trial Manager (STM), PI, CI and Sponsor and the completed form filed in the Investigator Site File (ISF) and Trial Master File (TMF).

The decision to continue treatment for participants whose treatment allocation has been revealed will be decided by the recruiting site/participant clinical care team. The participant will remain in the trial unless they choose to withdraw.

6.4.2. Unblinding for SUSAR

In the event of a SUSAR unblinding will be initiated centrally through REDCap. As a minimum this will include the STM, and to ensure medical oversight, the Chief investigator and/or Deputy Medical Expert will be unblinded as necessary as per section 9.3.2. We would also inform the participant or site, as needed; to allow the participant to receive informed treatment for the SUSAR and the patient could be informed which treatment they had to potentially avoid recurrence of the SUSAR in the future.

7. Trial treatment

Table 5-Participants will be randomised to one of the following interventions

ARM	TREATMENT	FORMULATION, ROUTE OF ADMINISTRATION AND DOSE
INTERVENTION	Desogestrel (75 microgram)	1 daily oral tablet (approximately the same time each day)
CONTROL	Combined oral contraceptive pill (containing Levonorgestrel 150microgram and ethinylestradiol 30microgram)	1 daily oral tablet (approximately the same time each day)

The investigational medicinal product is desogestrel 75mcg (Distributed by Lupin Healthcare Ltd, manufactured by the MA holder-Laboratorios Leaon Farma) and is a licensed oral contraceptive taken once daily by mouth. Its use when used in addition to the implant for problem bleeding is not within its current licence.

The comparator investigational medicinal product is the COCP (as Levest (Morningside Healthcare Ltd)) containing Levonorgestrel 150mcg/ethinylestradiol 30mcg. It is a licensed oral contraceptive

pill, taken once daily for 21 days with a 7-day pill free interval. The COCP is recommended under national guidance for the use alongside the implant for the treatment of problem bleeding outside its licenced indications.

7.1. Name and Description of IMP

Table 6-Name and description of IMPs

TREATMENT	BRAND NAME	MANUFACTURER
Desogestrel (75 microgram) PL 34518/0015	Desogestrel	Laboratorios Leaon Farma- distributed by Lupin Healthcare Ltd
Combined oral contraceptive pill (containing Levonorgestrel 150microgram and ethinylestradiol 30microgram) PL 20117/0044	Levest	Morningside Healthcare Ltd

To maintain the blind throughout participation in the trial desogestrel and COCP will be packaged in an identical manner. Tablets will both be oval, white and unmarked and dispensed to the participant in opaque numbered blister packs. Although the tablets are subtly different in appearance, unless directly compared to known Levest and Desogestrel tablets, participants will be unaware of their allocation. Participants will be advised that their trial drugs may be different in shape, size and colour to any previous COCP/ POP they have used before.

IPS Pharma will de-blister tablets from their branded packaging and repackage them into 10 pill numbered blister strips and supply as nine strips in a sealed box with trial specific labelling. A unique pack ID will be used to identify each pack and its content. Neither participants nor site staff will be able to identify the intervention from the packaging alone.

7.2. Regulatory Status of Drug

Both desogestrel and the COCP have marketing authorisation in the UK, but their use in this trial is outside the indications listed on the Summary of Product Characteristics (SmPC's) and therefore outside of their respective marketing authorisation.

7.3. Product Characteristics

The product characteristics for each treatment is listed within the relevant SmPC. Section 4 provides information on the clinical particulars of each treatment. The reference safety information is detailed in section 4.8.

Known drug interactions are listed in section 7.8 of the protocol.

7.4. Drug Storage and Supply

All IMP stock will be managed via the trial REDCap database. IMP will be delivered directly to site from the IMP supplier on behalf on the NCTU, following instruction from a member of the DEBI trial team. IMP will be delivered in batches of individually sealed boxes, identifiable only with the batch number and IMP pack code. On delivery IMP should be stored below 25°C in accordance with the

instructions on the IMP label following local processes (e.g. clinic onsite storage, pharmacy storage etc).

The initial bulk shipment of IMP will be ordered once the site greenlight checklist has been completed. IMP is required to be onsite, with receipt of IMP confirmed, prior to the start of recruitment. The trial database will notify the NCTU trial team when individual sites require additional stock. The NCTU will liaise with both the site and IMP supplier when resupplying sites with batches of IMP.

Sites will not be required to return unused IMP back to the NCTU, Sponsor or IMP supplier. Expired stock can be destroyed in accordance with local processes. Once all trial recruitment and follow-up has concluded, unused stock can be destroyed. If the site closes early, with in date but unused stock, the site should contact the NCTU to confirm whether the stock can be destroyed.

Participants who require replacement IMP (e.g. lose trial supply etc) can be resupplied their allocated treatment via REDCap. The NCTU can be contacted should replacement IMP be required.

All participants will be provided with a copy of the current version of the DEBI Participant Information Leaflet when dispensed their trial treatment. This provides them with information on the medicine, including possible side effects and storage conditions.

If IMP recall is required at any point during the trial, the site will be notified of this by the NCTU and provided with guidance on identifying affected stocks and how to manage the recall process at the site. The current version of the DEBI IMP guidelines will include information on contacts for IMP supplier and NCTU as well as guidance on the processes outlined above (e.g. ordering IMP through REDCap).

7.5. Preparation and Labelling of IMP

In accordance with the MHRA risk-adapted approach to the management of Clinical Trials of Investigational Medicinal Products (CTIMPs) DEBI is categorised as a medium risk Type B trial as the IMPs are being used outside their licenced indication. As the trial is blinded, all trial medications will be supplied by NCTU and will be delivered to recruiting sites and/or pharmacies by a third-party supplier in blinded packaging with Annex 13 compliant labelling (in line with paragraph 32, which remains applicable until UK legislation replaces it). Site staff will not be required to make any modifications to the IMPs prior to dispensing. More detailed information on IMP handling and management can be found in the current version of the trial IMP guidelines.

7.6. Dosing Schedules

Both trial treatments desogestrel 75mcg and COCP (levonorgestrel 150mcg/ethinylestradiol 30mcg) are to be taken orally, once a day, at the same time each day for the 90-day duration of a persons participation in the trial.

In the case of any missed doses, participants will be advised to take the dose as soon as they have remembered if less than 24 hours late. If a dose is more than 24 hours late the dose should be disregarded and the next dose taken. Participants will be asked to confirm they have taken their pill when they complete the daily bleeding diary. No participant will be removed from the trial for non-adherence to treatment schedule.

7.7. Dose Modifications

Dose modifications are not permitted on the trial. Should the participant experience a suspected adverse reaction to the treatment, the treatment should be stopped immediately in line with guidance from their clinical care team.

7.8. Known Drug Interactions and other Therapies

Liver enzyme inducing medicines which induce the cytochrome CYP3A4 should not be co-administered for 6 weeks prior to recruitment onto the trial, commencement of the trial treatment or any time during the 90-day trial participation. Liver enzyme inducing medications will reduce the plasma concentration of both desogestrel and COCP. To check for drug interactions please visit https://bnf.nice.org.uk/interactions/.

Treatments include but are not limited to:

- Antibiotics – rifampicin and rifabutin
- Antiseizure medications- carbamazepine, eslicarbazepine acetate, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, topiramate.
- Antiretrovirals – ritonavir, efavirenz and nevirapine
- St John's Wort
- Lamotrigine

Further details can be found in section 4.5 of the SmPCs.

7.9. Concomitant Medications

The following concomitant use or use within the last 3 months of hormones (except DMPA) or medications known to affect menstrual bleeding, including progestogens, estrogens, androgens, tranexamic acid, routine use of oral NSAIDs, anticoagulants, selective progestogen receptor modulators **are not** permitted. Current use or use within the last 6 months of gonadotrophin-releasing hormone analogues and 9 months of DMPA is not permitted.

A full list of concomitant medications can be found in appendix Table 12-Concomitant medicationsTable 12-Concomitant medications.

Other medication (not included in Table 12) is permitted but should be recorded at baseline or self-reported by participant if started during participation in the trial.

The following medications do not need recording/self-reporting: paracetamol, proton pump inhibitors, vitamins, opioids, H1 receptor antagonists (e.g. cyclizine, loratadine, chlorphenamine), H2 receptor antagonists (e.g. ranitidine), laxatives (osmotic or stimulant), anti-depressants – selective serotonin re-uptake inhibitors or tricyclic or venlafaxine, inhaled or topical corticosteroids, insulin, biguanides e.g. metformin, anti-fungal drugs, emollients, iron, anti-emetics – dopamine D2 receptor antagonists e.g. metoclopramide, domperidone, anti-psychotics (1st or 2nd generation), loperamide, aciclovir, nicotine.

7.10. Trial Restrictions

Potential participants will have their eligibility assessed prior to recruitment in the trial, this includes a review of potential contraindications to both treatments as per exclusion criteria section 4.2

There are no additional trial specific restrictions. All sites will be provided with an information card to share with randomised participants with details on the trial and the two treatments that the participant may have been allocated. It is at the investigator or delegates discretion as to whether they provide the cards to participants in addition to the GP notification.

7.11. Assessment of compliance with Treatment

Participants will be asked to complete a daily bleed and medicine adherence diary which will include a question as to whether they have taken their pill. Participants will be prompted (MyCap, email or text message) to complete missing data for 5 days following the scheduled data collection point. Where a participant has multiple episodes of treatment non-compliance on self-reporting, either the NCTU and/or the recruiting site will contact the participant to provide support and to confirm the information is correct and to ascertain the reason for not treatment non-compliance, as well as a welfare check to determine if there are any Serious Adverse Events (SAEs) leading to compliance challenges as per the current trial monitoring plan.

Participants will be asked to return their blister packs to their recruiting clinic at the end of their participation so that self-reported adherence can be confirmed. It is acknowledged that a limitation of this is that participants may have thrown the empty blister packs away.

7.12. Name and description of each Non-IMP

There are no Non-Investigational Medicinal Products in the trial.

8. Trial procedures and assessments

8.1. Summary of assessments

Table 7-Trial Assessments

Activity	**Timepoint**				
	Baseline	**Randomisation**	**Follow-up (days)**		
			30	**60**	**90**
Informed consent	X				
Baseline demographic data	X				
Perception of bleeding pattern			X	X	X
Bleeding status	X (recall over previous 90 days)		Once daily		
Randomisation		X			
Intervention: Desogestrel or COCP			Once daily		
Health Related Quality of life (EQ-5D-5L)	X		X	X	X
Capacity-wellbeing (ICECAP-A)	X		X	X	X
Acceptability			X	X	X
Global impression of treatment					X
Adverse effects of treatment			X	X	X
Adherence to treatment			Once daily		
Adherence to treatment return of blister packs					At the end of individual participation in the trial
Healthcare resource use	X		X	X	X
Gratitude voucher			X	X	X

Intention to continue treatment					X

8.2. Trial Procedures and Schedule of Assessments

8.2.1. Baseline Visit

Screening data for patients entering the trial will be collected by each site and recorded within the trial database.

8.2.2. Informed consent

Informed consent will be obtained as described in section 5.2.

8.2.3. Baseline data collection

After informed consent and eligibility assessments are complete, baseline visit data will be collected. This will include participant demographic, baseline questionnaire data and bleeding status information. The full list of baseline data collected for this trial is listed in the current version of the Data Management Plan (DMP).

8.2.4. Routine assessments and eligibility

Patients who attend a consultation for problem bleeding whilst using the implant will be examined to exclude other possible causes of bleeding as part of standard care. This will include an assessment of drug interactions, a speculum examination to assess the cervix for pathological causes of bleeding, a high sensitivity urine pregnancy test and Sexually Transmitted Infections (STI) screen for gonorrhoea and chlamydia. These will be performed by the clinic staff in line with standard practice.

Any potential participant who declines a pregnancy test or speculum examination will not be able to participate in the trial because some exclusion criteria cannot be verified. The STI results will be available in approximately 5 working days. Those requiring pelvic ultrasound and/or hysteroscopy cannot be enrolled at the first trial visit.

Once other causes have been excluded, they will be introduced to the trial and if interested provided with the trial PIS and asked to sign informed consent. Following consent, the patient will be assessed for eligibility and baseline data collected. Eligibility will be confirmed and signed off by the principal investigator (or delegated trial clinician as per section 4.3) on the eligibility checklist form once informed consent and baseline data have been obtained. This must be completed prior to randomisation.

Those who do not meet eligibility criteria will have the reason explained to them and that it will not impact on their care. They will then continue to have routine care without delay.

8.2.5. Randomisation

Participants will be randomised to receive either desogestrel or COCP using a minimisatation algorithm implemented in REDCap. Randomisation will be performed by a suitably delegated member of the recruiting site research team. As the trial is blinded, neither the participant nor the recruiting site staff will know which of the two treatments the participant has received.

There is a small chance that, at the end of the trial when stock is being run-down, only one of the trial IMPs will be available and the minimisation algorithm will be constrained to allocate to the

available IMP. However, the chance of this occurring will be minimised by constantly monitoring the IMP stock levels. If stock is not available for more than two weeks during the trial, the trial management may consider pausing the randomisation within the affected sites until after stock levels are back to normal to avoid any imbalance in treatment allocation.

8.2.6. IMP dispensing

An IMP pack code, assigned to the correct treatment arm will be linked to the participant at the point of randomisation to allow the recruiting site to dispense the allocated IMP to the participant. Participants will be dispensed their entire 90-day course of IMP at randomisation, in line with the treatment they would receive as part of routine clinical practice.

Participants will be advised to start their treatment **the day after** their clinic visit and randomisation.

8.2.7. Follow-up procedures

In accordance with standard clinical practice, participants will not be required to revisit their sexual health service or GP as part of their participation in this trial. Following randomisation, the majority of follow-up information will be obtained directly from the participants (via questionnaires) and coordinated by the NCTU without further involvement from the recruiting site. Following the participant's completion of the trial, the site staff will be asked to reveal the treatment allocation to the participant (either as part of their 3-month standard care visit or via telephone call), confirm the participant's adherence to treatment (where possible) and confirm whether the participant intends to continue on their allocated treatment to manage their problem bleeding. Follow-up timepoints for the trial are detailed in Figure 2-Routine clinical assessment outcome flowchart.

8.2.8. Daily bleeding status

Follow-up of participants will start the day after randomisation and will continue for the duration of their 90-day participation. Participants will be asked to complete a daily bleeding diary (MyCap or paper) recording their bleeding status in the previous 24hr period. Diaries need to be completed daily, with a tolerance window of 5 days to allow for retrospective completion where a day has been missed.

8.2.9. Treatment adherence

Participants will be asked daily (MyCap or paper) if they had taken their pill the previous day at the same time as they are asked about their bleeding status in the previous 24hrs.

Participants will be asked to save all treatment blister packs, for these to be returned to the recruiting clinic and adherence to be reviewed by a member of the clinical team. Participants will be asked to return these to their recruiting clinic during their 3-month standard care review, and where this does not take place the trial research team will facilitate the return of the blister packs.

8.2.10. 30- and 60-day Follow-up Questionnaires

Participants will complete a questionnaire (online, postal or telephone) at 30 and 60 days after randomisation which will collect information on the following:

- Bleeding days and episodes
- Perception of their bleeding pattern
- Treatment acceptability
- Reporting of symptoms and known treatment side effects
- Medications

- Use of health service resources relating to problem bleeding or contraceptive use
- Out of pocket expenses for treatments or products in relation to problem bleeding
- Health Related Quality of life (EQ-5D-5L)
- Capacity-wellbeing (ICECAP-A)
- Removal of implant

8.2.11. 90-day Follow-up Questionnaires

Participants will complete a questionnaire (online, postal or telephone) at 90 days after randomisation which will collect information on the following:

- Bleeding days and episodes
- Perception of their bleeding pattern
- Treatment acceptability
- Global impression of treatment
- Reporting of symptoms and known treatment side effects
- Medications
- Use of health service resources relating to problem bleeding or contraceptive use
- Out of pocket expenses for treatments or products in relation to problem bleeding
- Health Related Quality of life (EQ-5D-5L)
- Capacity-wellbeing (ICECAP-A)
- Intention to continue using implant and allocated trial treatment

At the end of the 90-day participation period, participants will be unblinded to their treatment allocation by their recruiting site. Unblinding will take place at the 3-month standard care visit, or for participants who are unable/unwilling to attend a clinic visit, the recruiting centre will call the participant to reveal their treatment allocation over the telephone. The recruiting centre will be asked to confirm whether the participant intends to continue with their implant and allocated trial treatment (as part of their standard care) once their participation in the trial has concluded.

Completion windows for 30-, 60- and 90-day questionnaires will be 10 days. Questionnaires will no longer be available for completion once outside of the specified completion window; therefore, no protocol deviations will be required for completion of data outside of the specified data collection windows.

8.3. Collection, Storage and Analysis of Clinical Samples

In line with standard clinical care, each potential participant will provide a urine sample to test for pregnancy and a vaginal swab to screen for the presence of sexually transmitted infections. Samples provided will be handled, tested and destroyed in accordance with local clinic guidelines. The results will be used to assess eligibility. If a participant is randomised into the trial and subsequently the STI result comes back positive they will be treated for the STI as per standard of care and the result and treatment will be recorded in the DEBI CRF. The participant will continue on the trial.

8.3.1. Return of unused trial medication

Participants will be asked to return their completed blister packs or unused medication to the recruiting clinic to confirm adherence to their treatment and for destruction of surplus trial drug. Blister packs should be returned in person at their standard review at 3 months after starting

treatment for problem bleeding. Where a participant is unable to attend a clinic in person, the NCTU will work with the participant to facilitate return of the IMP packs back to the recruiting site.

8.4. Withdrawal and discontinuation Procedures

8.4.1. Withdrawal prior to randomisation

Any patients that request to withdraw their consent **prior to randomisation** will be withdrawn completely from the trial; they will not be randomised, and follow-up questionnaires will not be issued.

8.4.2. Discontinuation and withdrawal post randomisation

Participants may withdraw from the trial for any reason. This will be made clear at recruitment. We will include a contact number for a member of staff at the recruiting clinic as a point of contact for participants to use in the event they are experiencing problems during the trial or considering early withdrawal.

The NCTU must be informed of all requests by participants to stop their involvement in the trial; appropriate action will be taken to ensure that the participant's wishes are followed promptly and safely.

Sites will be trained to determine which activities participants may wish to withdraw from.

Where a participant communicates their intention to withdraw from some or all of the main trial, the site must confirm whether they are also withdrawing consent for the long term follow-up.

Table 8-Withdrawal type and procedure post randomisation

Withdrawal type	Withdrawal procedure	Use of data
Withdrawal from trial treatment	Any participant that requests to discontinue trial treatment will be marked as withdrawn from treatment on the trial database but will be asked to continue to complete questionnaires if willing. Information on reason for stopping trial treatment will be recorded by the site if given, and patient care will continue as part of standard clinical practice.	Any data collected prior to participant withdrawal will be retained and used in the analysis.
Removal of implant	Any participant who notifies the trial or site team that their implant has been removed during their participation in the trial would be withdrawn from the trial and unblinded to their treatment allocation to	Any data collected prior to participant withdrawal will be retained and used in the analysis.

	inform their ongoing contraceptive care. Participants would not be required to complete any further questionnaires or daily diaries but would be followed up for safety outcomes for 7 days following stopping of their trial treatment.	
Withdrawal from daily bleed diary	Any participant that requests to discontinue from daily bleed diary will be marked as withdrawn from diary collection on the trial database and no further MyCap notifications will be sent. Withdrawal from the daily diary does not withdraw from questionnaire completion.	Any data collected prior to participant withdrawal will be retained and used in the analysis.
Withdrawal from follow up questionnaires	Any participant that requests to discontinue from trial questionnaires will be marked as withdrawn from questionnaire collection on the trial database and no further contact relating to questionnaires will be made. Withdrawal from questionnaires does not withdraw from daily diary completion.	Any data collected prior to participant withdrawal will be retained and used in the analysis.
Withdrawal from long-term follow-up	Any participant that withdraws consent for the long term follow-up will be recorded within the database and no long term follow-up data will be collected.	Any data collected prior to participant withdrawal will be retained and used in the analysis.
Complete withdrawal- from trial treatment, daily bleed diary, follow up questionnaires and long-term follow up	Any participant that requests complete withdrawal will be marked as withdrawn and no further contact will be made.	Any data collected prior to participant withdrawal will be retained and used but all participant information will be redacted (marked with xxs) and no further contact will be made.

8.5. Post Trial Care

Participants will be given a voucher on completion of the 30-, 60- and 90-day questionnaires as a thank you for their time.

Usual care will continue after trial completion and unblinding, treatment outside of the trial will not be funded by the trial sponsor as both trial medications are licensed and readily available via GP or sexual health clinics and not limited, unless for medical reasons e.g. a new contraindication to the treatment.

9. Adverse Event Reporting

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 (and subsequent amendments). Definitions of the different types of AEs are listed in Table 9 below. AEs will be reported by the participants to the NCTU on the 30, 60 and 90 day questionnaires. The Principal Investigator will assess the seriousness and causality (relatedness) of all SAEs experienced by the participant with reference to the Reference Safety Information when notified of a participant SAE at their site.

Table 9-Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that: • Results in death • Is life threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator** Comments:

	The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria. * Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
Serious Adverse Reaction (SAR)	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

9.2. Adverse Events and reporting requirements/procedures

AEs are commonly encountered in participants receiving either desogestrel or the COCP. As the safety profiles of the both the IMPs used in this trial are well characterised, only selected ARs experienced during treatment will be elicited from participants.

The following are regarded as expected for the purpose of this trial and will be collected on the 30-, 60- and 90-day follow-up questionnaires, completed by the participant:

- Headaches
- Nausea
- Breast tenderness
- Mood changes
- Increased blood pressure
- Hair thinning or loss
- Fluid retention in ankles/feet
- Bloating
- Weight change
- Acne

Only the presence (and severity) or absence of the above will be routinely collected for this trial.

The MedDRA medical coding dictionary will be used for the coding of serious adverse events is documented in this protocol.

9.3. Serious Adverse Events and reporting requirements/procedures

The 30, 60 and 90 follow-up questionnaires include questions to ascertain whether a participant has experienced an SAE since they consented to take part in the trial. Where participants have entered information to suggest a reportable SAE e.g. a hospital admission (unplanned), a review of the participants questionnaire will occur, and the recruiting site will be contacted by the NCTU and asked to obtain further information to determine whether an event has occurred that fulfils the SAE criteria. Where a SAE has been experienced, the Principal Investigator (or delegate) must report the SAE on an SAE form to the NCTU. The reporting procedure for an SAE is outlined later in this section.

In instances where a suspected SAE has been reported on the participant questionnaire but the recruiting site has been unsuccessful in contacting the participant to obtain further details, the PI will assess the event based on the information obtained by the research team using medical records and the participant questionnaire. Where the PI deems the event meets the trial SAE criteria, the recruiting site will be required to complete an SAE form and report this to the NCTU within 24 hours of assessment.

AE and potential SAE information will be primarily collected from participants on the 30-, 60- and 90-day questionnaires. Participants may contact the site directly to report a potential SAE that has occurred whilst participating in the trial or may report an SAE during their 3-month standard care review appointment or treatment unblinding phone call. Where a suspected SAE has been reported by a participant, an SAE form must be completed and submitted in line with the trial SAE reporting procedure.

Investigators will report AEs that meet the definition of an SAE. AEs defined as serious, and which require expedited reporting as an SAE, should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE.
Causality of an event will be categorised as one of the following:

- Definitely related
- Probably related
- Possibly related
- Unlikely to be related
- Unrelated

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be emailed to the NCTU as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, email a copy of the signed SAE form to NCTU-SAE@nottingham.ac.uk, copying in the DEBI trial inbox DEBI@nottingham.ac.uk.

On receipt NCTU will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt within 1 working day. If confirmation is not received within 1 working day please contact NCTU office. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the Site File and TMF.

9.3.1. Sites

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to NCTU and a copy kept in the Site File. Investigators should also report SAEs to their own Trust where required by local practice.

9.3.2. NCTU

On receipt of an SAE form, seriousness and causality will be reviewed independently by the medical monitor (Chief Investigator or Deputy Medical Expert) responsible for determining causality assessments. An SAE judged by the Investigator or medical monitor (Chief Investigator or Deputy Medical Expert) to have a reasonable* causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Chief Investigator or Deputy Medical Expert will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the current approved version of the Reference Safety Information (RSI)) it will be classified as a SUSAR (section 6.4.2). The Chief Investigator or Deputy Medical Expert will not downgrade an assessment of seriousness or causality made by the site PI, any changes to this assessment can only be an upgrade (unless the wrong category was selected in error when initially reported).

*reasonable equates to possible, probable or definitely related in the opinion of either the Investigator or Chief Investigator

9.3.3. Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should ideally be provided on a new SAE Form.

9.4. Reporting period

Details of all ARs will be documented and reported from the date of commencement of protocol defined treatment until 7 days after the scheduled last treatment (day 90 pill to be taken). SAEs that are judged to be at least possibly related to the IMP must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

9.5. Reporting to the Competent Authority and Research Ethics Committee

9.5.1. Suspected Unexpected Serious Adverse Reactions

The NCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

9.5.2. Serious Adverse Reactions

The NCTU will report details of all SAEs and SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

9.5.3. Adverse Reactions

Details of all ARs will be reported to the MHRA on request.

9.5.4. Other safety issues identified during the trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the trial.

9.6. Reporting to Investigators

Details of all SUSARs and any other safety issue which arises during the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

9.7. Reporting to Data Monitoring Committee

The independent DMC will review all SAEs.

9.8. Reporting to third parties

No reporting of adverse events to third parties is expected. Any safety issues identified during the trial will be notified to the MHRA.

10. Study Within A Trial (SWAT)

10.1. Background

Trial participant information sheets are often only provided in written English, which may limit trial participation for people who have difficulty understanding written English. It is important to make participation in clinical trials as inclusive as possible and researchers are exploring the best ways to do this. Media tools are increasingly used to engage potential participants, but there is limited data on how to best do this. Testimonies from previous participants show that media tools probably increase recruitment, as they provide potential participants with evidence that people like them engage with research [22]. No comparable data exists for use of video clips, which are ubiquitous on social media.

Our SWAT will investigate whether watching a patient testimony video clip, available in English, Polish, Romanian and Punjabi in addition to reading the written participant information sheet increases consent rates compared to written information alone.

10.2. Interventions

Group 1: Written participant information only
Group 2: Written participant information followed by patient video testimony

10.3. Method of allocation

Randomisation for the SWAT will occur at site level (cluster) to prevent contamination with the intervention. Sites will be randomised in 1:1 ratio to either use the video clip for recruitment or not using stratified block randomisation. Randomisation will be stratified by the size of the site (large vs small). An independent study statistician will generate the randomisation schedule. For sites randomised to use of the video clip, a link to the video clip will be given on the PIS and a QR code for the video clip that participants can scan using their phones, will be on the PIS. Participants would need to have the opportunity to watch the video clip prior to being randomised in the main trial.

10.4. Outcome measures

The primary outcome will be the proportion of eligible patients who consent to the trial.

The secondary outcome will be the proportion of randomised participants who provide primary outcome.

10.5. Sample size

The sample size for the SWAT will be predicated by that of the DEBI trial. We anticipate including at least 17 sites in the SWAT. More detailed information on the sample size will be detailed in the SWAT statistical analysis plan.

10.6. Analysis

Detailed analysis of this SWAT will be documented in the trial SWAT statistical analysis plan. Analysis will be based on cluster-level summaries. Unpaired t-test, with each cluster weighed by its sample size, will be used to provide 95% confidence intervals for the between-group effect measures.

10.7. Dissemination

The SWAT will be registered on the Northern Ireland MRC Trials Hub for Methodology Research SWAT registry. The findings will be made publicly available as soon as possible after the end of the SWAT and will be made available to researchers conducting meta-analysis in this field.

11. Data Handling and Record Keeping

11.1. Source Data

To allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained.

Source data is kept as part of the participant's medical notes generated and maintained at site. Each site will record the location of source data at their site using a source data location log prior to commencing recruitment. Data that are not routinely collected elsewhere may be entered directly onto the CRF; in such instances the CRF will act as source data and this will be clearly defined in the source data location log and recorded.

For this trial, source data refers to, though is not limited to, the participant's medical notes, laboratory results for tests recorded as part of the baseline visit data collection, data recorded directly into the CRF, and patient reported follow-up data (bleeding diary, adherence and follow-up questionnaires).

All data collected directly from participants will be considered as source data within the CRF. Where paper questionnaires are issued to participants these will be returned to the NCTU for data entry and will be considered source data. Where questionnaire data is obtained via telephone, this data will be entered directly into the CRF by a member of the NCTU and will be considered source data.

11.2. CRF Completion

Data for the trial will be captured directly into a REDCap CRF. Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete CRFs will be GCP trained and receive trial-specific training from the NCTU team on how to complete

these correctly.

In all cases it remains the responsibility of the site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Where applicable for the trial this will be evidenced by the signature of the site's Principal Investigator on the CRF. It is the responsibility of the Principal Investigator to ensure there are site staff in place locally to complete data entry into the eCRF in a timely manner.

Site staff are only required to complete the CRF for the baseline visit and standard follow up review at 90 days. This must be done within 7 days of the visit date.

Bleeding diary, treatment adherence and participant questionnaire data will be captured directly into the eCRF where possible using the MyCap application or other electronic responses (e.g. email containing link to questionnaire). Where information is completed by the participant on paper, the completed originals will be sent to the Trials Office to be entered by a member of the NCTU.

11.3. Data Management

All trial data will be entered into REDCap with each participant assigned an enrolment and randomisation number for use on CRFs and other trial documents. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth.

Participant contact details will be logged separately to the trial CRF data, to ensure participant identifiable data is separate to data used for analysis. Participant contact details may also be used by the trial team to send out trial related questionnaires and correspondence limited to the duration of the participant's participation in the trial or to share the trial results once the trial has been published.

The database will have in-built validation to ensure that the identifiers used all match with the allocated participant ID number. CRFs will be treated as confidential documents and held securely in accordance with regulations. Access to REDCap will be restricted and secure and CRFs will be restricted to those personnel approved by the CI or local PI and recorded on the trial delegation log. Missing or ambiguous data will be queried with the site via the CRF and sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised. Errors will be corrected and recorded on the CRFs on the audit log. The CI or local PI (or their designee) will sign a declaration ensuring accuracy of data recorded in the CRF.

The CRF will only collect the minimum required information for the purposes of the trial. Access to the information will be limited to the trial staff, investigators, authorised sponsor representatives and relevant regulatory authorities (see above). Electronic data including the trial database will be held securely and password protected restricted to those approved requiring access for the trial.

For the electronic daily bleed and treatment adherence diary, a MyCap push notification will be sent to each participant. For questionnaire data collected electronically (30-, 60- and 90-day questionnaires), a secure link to an online questionnaire will be sent. Where paper copies of diaries or questionnaires are used, a paper version of the questionnaire will be sent by NCTU to the contact address provided by the participant at their baseline visit, with a pre-paid return envelope.

Questionnaires returned to NCTU will be entered by a member of NCTU and a sample will be reviewed by a separate member of the NCTU. Further details will be documented in the current version of the DMP. Data obtained from participant reported outcomes will not be subject to data queries. Decisions on how to treat anomalous data will be made by members of the TMG blinded to allocations and documented in the current version of the DMP and/or Statistical Analysis Plan.

11.4. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, participants' medical records, copies of CRFs etc.) at their site are securely retained for at least 7 years to comply with The Medicines for Human Use (Clinical Trials) Regulations 2004and Sponsor requirements.

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

The Trial Master File and trial documents held by the CI on behalf of the Sponsor shall be finally archived securely in the Microsoft cloud which has multiple redundant systems and backup services. This archive shall include all trial databases and associated meta-data encryption codes. Access to files once archived (e.g. for inspection purposes), will be managed by the NCTU archivist and will only be accepted on approval of the University of Nottingham sponsor

11.5. Data Sharing

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Participants' contact details, including name, address, telephone/mobile number and email will be shared between participating sites, NCTU and third parties (where required) for the purposes of contacting participants relating to their participation in the trial (e.g. questionnaire reminders, data collect etc).

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU research team will have access to these data.

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

Data generated as a result of this trial will be available for inspection on request by the University of Nottingham, NCTU, the REC, local Research and Development departments and the regulatory authorities.

Anonymised participant data may be shared with researchers external to the trial research team in accordance with the NCTU's data sharing procedure and the National Institute for Health Care Research (NIHR) policy on the sharing of research data. All requests for data should be sent to the Nottingham Clinical Trials Unit.

12. Quality control and quality assurance

12.1. Site Set-up and Initiation

All participating PIs will be asked to sign the necessary agreements and supply a current CV to NCTU – this should be signed within the last 2 years. All members of the site research team will also be required to sign a site delegation and training log. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed any necessary training. Key members of the site research team will be required to watch a training session or attend either a meeting (virtual or in-person) covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documents, instructions, and other documentation required for the conduct and reconstruction of the trial. NCTU must be informed immediately of any change in the site research team.

12.2. Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the current version of the trial monitoring plan. NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial team will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, excessive number of participant withdrawals or deviations. If a monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow NCTU trial staff access to source documents as requested.

12.3. Audit and Inspection

The PI will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The PI will comply with these visits and any required follow up. Sites are also requested to notify NCTU of any MHRA inspections.

The Trial Master File and evidence of audits will be made available upon request for regulatory inspections.

12.4. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and its amendments) the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.
For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial. Sites are therefore requested to notify NCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Where NCTU is investigating whether a serious breach has occurred, sites are also requested to cooperate with NCTU in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment could potentially meet the criteria of a Serious Breach and sites may be

suspended from further recruitment. Any major problems identified during monitoring may be reported to TMG, Trial Steering Committee, Sponsor, the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

13. End of Trial Definition

The end of trial will be the final database lock. This will allow sufficient time for the completion of protocol procedures, data collection and data input. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. If the decision to terminate the trial early has been made, NCTU will inform the MHRA and REC within 15 days of that decision. NCTU will provide them with a summary of the clinical trial report within 12 months of the end of trial.

14. Statistical Considerations

14.1. Sample size calculation

We have powered the trial to establish the non-inferiority of desogestrel compared to the COCP in settling problem bleeding. Data from previous studies [10, 23] show that approximately 90% of implant users would experience significant improvement in bleeding pattern with COCP or ulipristal treatment within the 90 days reference period. To be conservative we have used a reference group proportion of 85%. There are no validated minimum clinically important differences for improvement in bleeding pattern, but our sexual health clinical experts and patient representatives advised that, due to its advantages, adoption of desogestrel would be recommended even if it has a slightly less improvement rate in bleeding pattern of at least 75%. This represents an absolute non-inferiority margin of 10% and was judged to be a clinically relevant margin. A sample size of 276 per arm (552 total) would be required to achieve 90% power to detect non-inferiority of desogestrel compared to COCP within a non-inferiority margin of 10% based on one-sided 2.5% significance level, 1:1 allocation, and a likelihood score test statistic (Farrington and Manning) assuming the actual between-group difference in improvement proportion is zero. Allowing for up to 20% missing primary outcome data, we plan to randomise 690 participants.

14.2. Definition of Outcome Measures

14.2.1. Primary outcome

Patient-reported resolution of problem bleeding will be measured by participants' self-determination that their bleeding pattern improved using a 5-point Likert scale (improved significantly, improved slightly, no change, worsened slightly, worsened significantly). The outcome will be dichotomised into a response of "significantly improved" versus any other response. Patient perception of their bleeding pattern will be measured every 30 days during a 90-day reference period, with the last measurement (asked at day 90) treated as the primary time-point.

14.2.2. Secondary outcomes

Table 10-Secondary outcomes

Outcome Measure	Definition or derivation
Participant's self-reported significant improvement in the bleeding pattern.	At day 30, 60 and 90 as for primary outcome

Participant's self-reported non-worsening of the bleeding pattern	The 5-point Likert scale will be dichotomised into a response of "improved significantly" or "improved slightly" or "no change" versus "worsened slightly" or "worsened significantly"
Participant self-reported bleeding pattern.	Total number of days, within the 90-day window, of: - no bleeding - spotting - bleeding
Longest duration of consecutive non-bleeding (no bleeding or spotting) whole days for each 30-day period within the 90 days.	Longest consecutive number of days with responses of no bleeding or spotting, in 90 days
Time to longest episode of consecutive non-bleeding whole days	Time to the first day of the longest consecutive number of days with responses of no bleeding or spotting, over the 90 days.
Number of bleeding episodes	Number of episodes with one or more consecutive days of reported bleeding, bounded by bleed-free days, within the 90 days
Duration of bleeding episodes	Number of episodes of 2, 3 (etc, to maximum reported) consecutive days with reported bleeding.
Participant-reported side effects	Measured at baseline and day 30, 60 and 90 to assess whether a participant has experienced the side effect and if so the extent of the side effects so that they can be compared to previous timepoints. (Using no/yes "mild", "moderate" or "severe"
Participant reported adherence to trial treatment	Responses will be categorised as all (90/90 pills), most (63-89/90), some (36-62/90), few (1-35/90) and none (0/90). 'Few' and 'None' categories would be classed as treatment non-adherence.
Participant reported discontinuation/removal of their implant	Proportion of participants who report removal of the implant and time to this event.
Participant reported EQ-5D-5L and ICECAP-A	Derived according to published scoring systems.

Participant reported treatment and healthcare usage	Participant Questionnaire
Intention to continue of their allocated treatment after unblinding	Participant Questionnaire

14.3. Analysis of Outcome Measures

The reporting of the trial will be in accordance with the CONSORT extension to reporting of non-inferiority and equivalence randomised trials [24]. Full details of the statistical analysis will be provided in the Statistical Analysis Plan, which will be finalised and approved by the Trial Steering Committee (TSC) prior to database lock.

Comparative analysis will be performed for the primary outcome on both the intention to treat (ITT) population and some version of the per-protocol (PP) population (preferably complier average causal effect (CACE) analysis, if feasible/identified), as a protection against the ITT's possible increased risk of falsely claiming noninferiority (type I error). Primary estimand will be the treatment policy estimand (i.e., ITT population- analysing data on all randomised participants according to the randomised groups irrespective of subsequent compliance with the treatment allocation) with CACE (or per-protocol) results used to check the consistency. Full definition and cut-off for compliance will be specified in the Statistical Analysis Plan (SAP).

For the primary outcome, a two-sided 95% confidence interval for the between-group difference in proportion of participants reporting significant improvement will be constructed by fitting a mixed-effect logistic regression model, adjusting for site as a random effect and other minimisation factors as fixed effects. The model will include outcome data from all the 3 timepoints (30, 60, and 90 days) and will include treatment by time interaction to obtain the treatment effect at each timepoint with 90 days as the primary contrast. Estimates of model-adjusted difference in proportions and 95% confidence intervals will be obtained by contrasts of average marginal predictions in the fitted model. Non-inferiority of desogestrel will be inferred if the lower bound of this interval lies within the non-inferiority margin of 10%. Missing data for primary outcome will be dealt with through maximum likelihood estimation using mixed-effect model which will use all available follow-up data. Intercurrent events such as discontinuation of assigned treatment or treatment switching, if any, will be dealt with through treatment policy strategy for the primary analysis.

Between-group comparison of secondary outcomes will be based on an appropriate regression model for the outcome, in the generalised linear mixed model framework adjusting for the minimisation factors and baseline outcome measure for continuous variables, if available. Adverse events will be presented descriptively and will be summarised according to the treatment received. All other planned sensitivity and exploratory analyses will be described in the SAP.

14.3.1. Planned Interim Analysis

There is no planned formal interim statistical analysis of treatment effectiveness. However, an integral internal pilot phase will allow a feasibility assessment, examining recruitment, and retention. As part of continuous oversight, the DMC will be provided with confidential reports by trial arm, containing information on recruitment, protocol compliance, safety, and interim

assessments of outcomes (between-group estimates of differences in efficacy and/or safety outcomes), as agreed.

14.4. Funder Feasibility Assessment

The funder feasibility assessment will take place 8 months after the planned start of recruitment (trial month 19). Site opening, recruitment, treatment adherence, diary completion and primary outcome completion will be assessed at this timepoint. Thresholds for the individual categories are outlined below.

Table 11 - Progression criteria

Progression criteria	Green – proceed	Amber – improve	Red – stop (Following discussions with TSC and Funder)
Site Opening	≥17 sites open to recruitment	12-16 sites open to recruitment	≤11 sites open to recruitment
Participant recruitment	≥248 participants recruited (≥100%)	186-247 participants recruited (75- <100%)	≤185 participants recruited (<75%)
Treatment adherence (Percentage of randomised participants reaching satisfactory adherence level)	≥100% of randomised participants	75- <100% of randomised participants	<75% of randomised participants
Bleeding diary adequate completion (Percentage of randomised participants adequately completing the diary)	≥100% of randomised participants	75- <100% of randomised participants	<75% of randomised participants
Perception of bleeding pattern questionnaire completed at 90 days (primary outcome)	100% of randomised participants who have reached 90 days follow-up	75- <100% of randomised participants who have reached 90 days follow-up	<75% of randomised participants who have reached 90 days follow-up

At trial month 19, when the Funder assessment is undertaken, if the trial progress falls into the green category then the trial will continue to recruit without adjustment. If the trial is assessed as amber, a recovery strategy would be implemented with the support of the trial oversight committees (TMG, DMC and TSC). If the trial is assessed as red, a recovery strategy or closure plan would need to be implemented, following consultation with oversight committee members and Funder input. If there is inconsistency in the scoring of the progression criteria then overall the trial will be categorised according to the criterion that is furthest from achieving the progression threshold (e.g. if two criteria are green but one is amber, the trial will be categorised as amber).

The progress of the trial will be continually monitored by the trial team and Funder. Recruitment and trial procedures will continue during the decision-making process.

14.4.1. Planned Final Analyses

Final analyses will be performed once the database has been locked.

14.4.2. Planned Subgroup Analyses

Subgroup analyses for the primary outcomes will be performed according to body mass index (BMI < 25 kg/m^2, BMI ≥ 25 to < 30 kg/m^2, BMI ≥ 30 kg/m^2), smoking status (currently smoking, non-smoker), and self-reported categorisation of problem bleeding in previous 90 days (infrequent bleeding (<3 episodes); normal (3– 5 episodes); frequent (>5 episodes); prolonged (≥1 episode(s) lasting ≥14 days)) by including appropriate interaction terms in the regression models. The trial is not powered to detect any interactions hence the subgroup analyses will be treated as exploratory.

14.4.3. Analysis of safety

For safety outcomes, data will be presented descriptively using frequency counts and percentages in each allocated group.

14.4.4. Procedures for missing, unused and spurious data

Every effort will be made to follow up all participants up to the primary endpoint, however, as missing data is inevitable, we will employ statistical techniques for handling missing data for the primary outcomes under the Missing At Random assumption such as further adjustment in the mixed model for variables predictive of missingness. For the primary analysis, only minimisation variables will be adjusted for as covariates and we do not expect any to be missing as they are required for the participant to be allocated.

14.4.5. Analysis sets

For the primary analysis, all randomised participants who receive at least one dose of the trial medication, will be analysed according to allocated treatment group regardless of adherence to the allocated treatment. This will be supplemented by analysing only the participants who would comply with their allocated intervention. Full definition and cut-off for compliance will be specified in the SAP.

For the secondary outcomes, participants will be analysed according to allocated treatment group regardless of adherence to the allocated treatment.
For the safety outcomes, all randomised participants who receive at least one dose of the trial medication will be analysed according to treatment received.

15. Health Economics

15.1. Aim

The economic component will analyse the costs and outcomes associated with desogestrel treatment, in comparison to the COCP, for people with problem bleeding whilst using the implant. If treatment with desogestrel is non-inferior to the COCP, there could still be important cost implications for the healthcare sector. The primary base case analysis will therefore adopt a NHS/PSS (Personal Social Services) perspective in line with NICE guidelines [25].

15.2. Outcome measurement

The primary outcome for the trial will be as described in Section 2 in terms of the non-inferiority of desogestrel to the COCP in treating problem bleeding during a 90-day reference period for people with problem bleeding whilst using the etonogestrel implant. We will use the data collected within the trial, so estimates of costs and benefits will relate to the initial 90-day period. Alongside the clinical outcomes collected in the trial and in line with recommendations from NICE, data will also be captured that will allow QALYs to be used as an outcome measure in the cost-effectiveness analysis [25, 26]. It is recommended that QALYs are calculated so that cost-effectiveness can be compared across disease areas. This will require changes in health-related quality of life (HRQL) to be captured for both trial arms. NICE recommends the use of EQ-5D-5L to measure HRQL. We will explore broader impacts on wellbeing as additional analyses using the ICECAP-A instrument. The ICECAP-A instrument has been widely used in a range of health areas, particularly where impacts on patients are anticipated to be broader than health alone [27]. These questionnaires will be administered to compare changes in health-related quality of life and wellbeing for the two trial arms, at baseline and at 30, 60 and 90 days.

15.3. Resource Use Measurement

Resource use data will be prospectively collected to estimate the costs associated with both desogestrel and COCP alongside the etonogestrel implant. The main resources to be monitored include:

1. The costs associated with treatment (provision of desogestrel and COCP)
2. Time and resource use incurred in SRH settings associated with clinical examination, additional treatments and monitoring during the follow up period and to treat any adverse events
3. Costs associated with discontinuation of the implant
4. Costs associated with GP attendances, A&E visits and other NHS secondary care.
5. Any other health and social care resource use
   Costs such as those incurred by implant users and their families (e.g. associated with problem bleeding), will also be captured to allow a societal perspective to be explored as a secondary analysis. Information on unit costs or prices will be sourced to attach to each resource use item, to enable an overall cost per participant to be calculated (e.g. Unit Costs of Health and Social Care [28] and NHS Reference Costs [29].

15.4. Analysis

The initial economic analysis will assess cost-effectiveness based on participant self-reported significant improvement in the bleeding pattern, reflecting the primary clinical outcome of the trial. A secondary analysis of incremental cost per QALY gained will also be undertaken in line with NICE recommendations. The economic evaluation will be conducted and reported in accordance with relevant guidelines [30, 31]. Initially, the base-case analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and the important consequences as assessed in the trial. An incremental economic analysis will then be conducted. Results will be presented using cost-effectiveness acceptability curves (CEACs) to show the uncertainty surrounding the cost-effectiveness of the intervention [32]. We shall also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions, especially around the costs associated with discontinuation and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results [33].

16. Trial Organisational Structure

16.1. Sponsor

The University of Nottingham will be the sponsor of the DEBI trial. The role and responsibilities of the Sponsor are outlined in the current version of the trial Delegation of Responsibilities (DoR).

16.2. Trials Unit

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU). The role and responsibilities of the Trials Unit are outlined in the current version of the trial Delegation of Responsibilities (DoR).

16.3. Trial Management Group

The TMG includes those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, Statistician, Trial Manager, Data Manager, with other members of the trial team attending as required. The role of the group is to ensure high quality trial conduct, to time and within budget, to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will report to the Independent Trial Steering Committee (TSC). The role of the TMG is outlined in the current version of the trial TMG terms of reference.

16.4. Trial Steering Committee

The role of the TSC is to provide overall supervision for the trial on behalf of the Sponsor and Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The TSC monitors trial progress and conduct. The TSC will consider and act, as appropriate, upon the recommendations of the DMC or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be modified or stopped on grounds of safety or efficacy.

The TSC includes members who are independent of the Investigators, their employing organisations, funder and Sponsor. The TSC will operate in accordance with a trial specific charter. The TSC will meet annually at a minimum but more frequently as requested by the committee, dependent on trial activity or phase. More information on the TSC can be found in the current version of the trial TSC charter.

16.5. Data Monitoring Committee

The role of the DMC is to monitor the unblinded trial data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should stop, or aspects of the trial design be amended. This is to safeguard the interest of the participants, investigators and Sponsor. Members of the DMC are independent of the trial (i.e. should not be involved with the trial in any other way or have any competing interest that could impact on the trial).

Reports will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet annually at a minimum but more frequently as requested by the committee, dependent on trial activity or phase.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Steering Committee (TSC) who will convey the findings of the DMC to Trial Steering Committee, funders, and Sponsors as applicable. More information on the DMC can be found in the current version of the trial DMC charter.

16.6. Finance

This trial is funded by the National Institute for Health Research Health Technology Assessment Programme, award ID: NIHR153258.

16.7. Participant gratitude and stipends

Participants will not receive payment to participate in the DEBI trial. Participants will be offered shopping vouchers to encourage responses to the trial questionnaires at 30-, 60- and 90-days post randomisation. On receipt of the completed questionnaires participants will receive a £15 gift voucher as a thank you for the time spent completing the questionnaires (3 x £15 = maximum total of £45 across the trial duration).

17. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: Declaration of Helsinki 1996 – WMA – The World Medical Association.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, 2017, the applicable UK Statutory Instruments, (which include the Medicines for Human Use (Clinical Trials) Regulations, 2004 and subsequent amendments and the Data Protection Act 2018) and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use (Clinical Trials) Regulations, 2004. The protocol will be submitted to and approved by the REC prior to circulation.

18. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using only their unique trial identification number on the CRF and correspondence between NCTU and the participating site. Participants will give their explicit consent for the movement of their consent form, giving permission for the NCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to NCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the

treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. Registries, laboratory staff, competent authority, Sponsor). Representatives of the DEBI trial, NCTU and Sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

19. Insurance and Indemnity

The University of Nottingham will act as sponsor for the trial. Delegated responsibilities will be assigned to the NHS Trusts taking part and NCTU. Third party suppliers, such as IPS Pharma will be contracted by NCTU. Insurance and indemnity for trial participants and NHS trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of Health and Safety Guidance HSG (96) 48. There are no special compensation arrangements, but trial participants may have recourse to the NHS complaints procedure.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity. The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

The University of Nottingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

20. Publication Policy

The dissemination of the DEBI trial results will be via publication in the NIHR Journals Library (threaded publication) and submitted for publication in a peer reviewed journal. The manuscripts will be prepared by the Chief Investigator and TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigator or delegate and NCTU. Manuscripts must be submitted to both parties in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Nottingham.

During the trial, press releases may be issues from the Sponsor or NCTU. Presentations or other material prepared by local investigators to publicise the trial must be reviewed by the Chief Investigator or delegate and NCTU. No party will be entitled to submit any publicity material without prior approval of the NCTU.

Trial results presented in a plain English summary which will be sent to the participants via their preferred communication method. Results will be presented in different medias (e.g. infographics or videos) to improve accessibility of the findings. The findings will be disseminated among people via our PPI groups (including groups such as Reproductive Justice Initiative and CERT) and social media.

Sites will be invited to a results meeting where the findings of the trial will be shared prior to publication.

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22. Appendices

22.1. Table 12 Concomitant medications

Table 12-Concomitant medications

Medication	Exclude from recruitment	Allow use during the trial	Action if used during the trial
Progestogens other than etonogestrel implant	Yes if used within 3 months prior to recruitment	No	Withdraw from trial, use data up to withdrawal
Estrogens within 3 months prior to recruitment	Yes	No	Withdraw from trial, use data up to withdrawal
Testosterone use within 3 months prior to recruitment	Yes	No	Withdraw from trial, use data up to withdrawal
Gonadotropin-releasing hormone (GnRH) analogues within 6 months prior to recruitment	Yes	No	Withdraw from trial, use data up to withdrawal
NSAIDs/mefenamic acid within 7 days of recruitment except Piroxicam use within 11 days	Yes	No	Do not withdraw. Record all use of NSAIDs/mefenamic acid for inclusion in the analysis
Tranexamic acid within 7 days prior to recruitment	Yes	No	Do not withdraw. Record all use of tranexamic acid for inclusion in the analysis
GLP-1 agonists (e.g. tirzepatide, semaglutide, exenatide, liraglutide, dulaglutide, lixisenatide) use within 3 months of recruitment	Yes	No	Withdraw from trial, use data up to withdrawal
Anticoagulants (e.g. warfarin, Low Molecular Weight Heparin {LMWH}, heparin or Direct Oral Anticoagulants {DOACs}) within 3 months of recruitment	Yes	No	Do not withdraw. Record all use of anticoagulants for inclusion in the analysis
Tamoxifen within 6 weeks of recruitment	Yes	No	Withdraw from trial, use data up to withdrawal

Ulipristal acetate within 6 weeks of trial	Yes	No	Withdraw from trial, use data up to withdrawal
Tetracycline antibiotics within 28 days prior to recruitment	Yes	No	Do not withdraw. Record all use of tetracycline antibiotics for inclusion in the analysis
Any use of CYP450 inducers within 6 weeks of trial recruitment • Anticonvulsants: phenytoin, fosphenytoin, primidone, rufinamide, carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbitone, cenobamate, topiramate, lamotrigine • Antibiotics: Rifampicin, rifabutin • Antifungals: griseofulvin • Systemic glucocorticosteriods: prednisolone, dexamethasone, hydrocortisone. • Antiretrovirals: efavirenz , ritonavir • Immunosuppressants : tacrolimus • Other: St John's wort, modafinil, bosentan, aprepitant, lumacaftor, statins	Yes	No	Do not withdraw. Record all use of CYP450 inducers for inclusion in the analysis

22.2. Summary of Changes

Version	Date	Changes
1.0	20 March 2025	Final version of approved protocol
2.0	06 June 2025	• IMP change from Feanolla to Desogestrel • Eligibility sign off • Randomisation algorithm clarified • Progestogenic and global side effects combined for reporting and analysis