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The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.

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Keywords: Infertility, In vitro fertilisation, adenomyosis, downregulation, randomised-controlled trial

WHO trial registration data

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03946722
Date of registration in primary registry	13th May 2019
Source of monetary or material support	Dimitrios Mavrelos (CI)
Primary sponsor	University College London
Contact for public queries	DM, SL (dimitrios.mavrelos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Contact for scientific queries	DM, SL (dimitrios.mavrelos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Scientific title	Modified downregulation for women with moderate/severe adenomyosis of the uterus prior to frozen-thawed embryo transfer.
Descriptive title	The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.
Public title	MODA
Countries of recruitment	UK
Health condition or problem studied	Adenomyosis
Intervention(s)	Active comparator: Prolonged downregulation for 6 weeks.
	Placebo comparator: Standard downregulation for one week.
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years <42 years Sexes eligible for study: female Accepts healthy volunteers: no
	Inclusion criteria: Women with moderate/severe adenomyosis undergoing IVF

Data category	Information
	treatment, BMI < 30, two out of three of the following criteria are met: AMH > 5.4, FSH < 8.9, antral follicle count > 4.
	Exclusion criteria: Previous open or laparoscopic myomectomy, uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids > 3 cm), use of GnRH analogues within previous 3 months, severe male factor infertility (sperm count < 2 x 10^6/ml, use of surgically retrieved spermatozoa)
Study type	Interventional
	Allocation: randomized intervention model. Parallel assignment masking: unblinded.
	Primary purpose: to determine effectiveness of modified downregulation.
	Phase III
Date of first enrolment	October 2020
Target sample size	162
Recruitment status	Recruiting
Primary outcome	Clinical pregnancy rate
Key secondary outcomes	Livebirth, pregnancy loss (biochemical pregnancy, miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication reaction, number of frozen embryos available for transfer, number of days to achieve optimal endometrial thickness.

Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1	3/4/2019	N/A	N/A
2	1/1/2020	Novin Fard	Hospital Trust formulary update; Triptorelin changed to Leuprorelin.

Trial personnel

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Abstract

Introduction: Adenomyosis can adversely reduce chances of pregnancy in couples undergoing assisted conception. We aim to evaluate the effect of two different downregulation protocols on the reproductive outcomes in women with moderate and severe adenomyosis undergoing frozen-thawed embryo transfer (FTET).

Methods and analysis: We will conduct a two-armed pragmatic randomised clinical trial comparing modified downregulation with gonadotrophin releasing hormone (GnRH) analogue for six weeks to standard downregulation with GnRH analogue for one week prior to FTET. Our primary outcome is clinical pregnancy, defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation, with other secondary reproductive, neonatal and safety outcomes. We aim to randomise 162 patients over 3 years to achieve 80% power for detecting a 20% difference in the primary outcome at 5% significance.

Ethics and dissemination: To date there is no consensus on the optimal protocol for management of subfertile women with adenomyosis. Modified downregulation could improve the clinical pregnancy rate by reducing the endometrial inflammatory reaction and/or myometrial contractility and their impact on uterine receptivity in women with moderate and severe adenomyosis of the uterus undergoing frozen thawed embryo transfer. The MODA trial is designed to offer pragmatic, real-life evaluation of the optimal protocol for downregulation for this population during assisted conception treatments. Our findings will be published in peer-reviewed journals and presented at national and international scientific meetings and congresses. Ethical approval was granted by the NHS Research Ethics Committees (19/LO/1567).

Trial registration number: NCT03946722

Article Summary

Strengths and limitations of this study

- The MODA trial offers a pragmatic evaluation of two different downregulation protocols used in current practice to optimise the reproductive outcomes of women with adenomyosis.
- We will report on established core outcomes of interest for stakeholders in assisted conception and will randomise a large number of women to achieve sufficient power to evaluate the treatments of interest across different participant subgroups.
- The intervention is unblinded.

Introduction

Adenomyosis is characterised by the presence of ectopic endometrial glands and stroma located within hypertrophic and hyperplastic myometrium, affecting up to 20.9% of women at reproductive age (1, 2). Recent advances in ultrasound and MRI technology have facilitated the diagnosis of adenomyosis with a reported accuracy of up to 81% using two and three dimensional ultrasound (2).

Two meta-analyses suggested that women with adenomyosis have lower implantation, pregnancy and livebirth rates with higher miscarriage rate, thus its impact on fertility is marked (3,4). This impact is directly linked to the severity of the adenomyosis with rate of clinical pregnancy decreasing from 42.7% (95% CI 37.1-48.3) in women with no adenomyosis on ultrasound to 22.9% (95% CI 13.4-32.6) for those with four features and 13.0% (95% CI 2.2-23.9) for those with all seven features (5). Several theories have been suggested to explain its negative impact on fertility, such as abnormal uterotubal transport due to anatomical distortion of the uterine cavity and disturbed uterine peristalsis (6). Ultrastructural myometrial abnormalities may cause hyperperistalsis and increase the intrauterine pressure due to a disturbance in normal myocyte contractility with subsequent loss of normal rhythmic contraction (7). Several molecular alterations have also been noted in the eutopic endometrium of women with adenomyosis. These include increased levels of inflammatory markers, increased oxidative stress, reduced expression of implantation markers, lack of expression of adhesion molecules and changes in the sex steroid hormone pathway, resulting in impaired impantation (6).

Treatment with gonadotrophin-releasing hormone (GnRH) analogues for prolonged periods could reduce the amount of inflammatory reaction in the eutopic endometrium of women with

adenomyosis (8). It is also possible that prolonged downregulation may improve abnormal uterine peristalsis seen in women with adenomyosis. Two retrospective studies suggested a significant benefit in the reproductive outcomes with prolonged downregulation prior to frozen embryo transfer, in contrast to one retrospective analysis that showed an adverse impact of prolonged downregulation on pregnancy rates (9, 10, 11). Therefore, the true benefit of prolonged versus standard downregulation remains imprecise in this population.

Objective: We aim to determine whether modified downregulation prior to frozen thawed embryo transfer (FTET) improves the chance of clinical pregnancy in women with moderate and severe adenomyosis.

Methods

Trial design

The MODA Trial is a pragmatic randomised controlled trial of two parallel arms comparing prolonged downregulation with GnRH analogue for six weeks to standard downregulation with GnRH analogue for one week prior to frozen-thawed embryo transfer, recruiting participants from fertility centres across the UK. Participants will be followed-up until six weeks after the pregnancy outcome is determined. The trial design is summarised in Figure 1.

Inclusion criteria

1. Couples who are undergoing a cycle of IVF/ICSI, where a cycle is defined as egg collection following ovarian stimulation.

2. The female partner is ≥18 and < 42 years of age.
3. The female partner has a BMI <30.
4. Two out of three of the following criteria are met: AMH >5.4, FSH <8.9, antral follicle count >4.
5. Moderate or severe adenomyosis of the uterus diagnosed on ultrasound scan.
6. Both partners are willing and able to provide written informed consent.

Exclusion criteria

1. Concurrent and/or recent involvement in other research that is likely to interfere with the intervention within the previous 3 months of study enrolment.
2. Previous open or laparoscopic myomectomy
3. Uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids > 3 cm)
4. Use of GnRH analogues within previous 3 months.
5. Severe male factor infertility (sperm count < 2 x 10^6/ml, use of surgically retrieved spermatozoa)
6. Couples who in the opinion of the researcher by virtue of language or learning impairment would be unable to give fully informed consent to the study.

Outcomes

The primary outcome of the study is clinical pregnancy, defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation.

Our secondary outcomes will include livebirth, pregnancy loss (biochemical pregnancy, miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication

reaction, number of frozen embryos available for transfer, number of days to achieve optimal endometrial thickness.

Enrolment

Enrolment of participants will involve coordinated registration and allocation of participant trial numbers by the trial co-ordinator. All participants will be asked by a member of the research team to complete a written consent at least 24 hours after providing the trial's participant information sheet (PIS). All consents will be recorded in the medical notes including signature from both partners undergoing the IVF/ICSI procedure. A member of the research team will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. No trial procedures will be conducted prior to the participant giving consent by signing the consent form.

Once consent has been granted a TVS will be performed by a member of the research team. The scan will be performed in a systematic fashion starting from the uterus in longitudinal plane with measurement of the endometrial thickness. The probe is then rotated to the transverse plane and the uterus scanned from the cervix to the fundus with any uterine pathologies noted and measured in 3 orthogonal planes. A 3D ultrasound volume is then obtained and saved starting with the uterus in longitudinal view making sure to include all uterine tissue in the 3D volume sweep. Any congenital or acquired uterine anomalies are diagnosed according to published diagnostic criteria. Adenomyosis is diagnosed according to a standardised diagnostic criteria (2) and graded for severity according to the number of adenomyosis features present (assign a score of 1 for each of: i) asymmetrical myometrial thickening, ii) parallel shadowing, iii) myometrial cysts, iv) irregular endometrial-myometrial

junction, v) linear striations, vi) hyperechoic islands, vii) adenomyoma). Patients with four or more features of adenomyosis are considered to have moderate or severe adenomyosis (5). Videosonography for a period of 5 minutes will be performed to assess uterine peristalsis. The operator will then sweep to the adnexae, starting from the left to identify and measure the ovaries in three orthogonal planes and document the antral follicle count. Each ovary is examined for the presence of cysts as well as for mobility and tenderness by gentle pressure with the ultrasound probe. Once the ovaries have been assessed the operator examines the pouch of Douglas for the presence of free fluid as well as any evidence of endometriosis such as obliteration, endometriotic nodules and endometriomas, as previously described (12). Once the ultrasound scan is concluded all information is added to the clinical database (RedCap, Vanderbilt University).

After the scan and once eligibility is confirmed participants will be asked to confirm if they want to participate in the trial. Those that confirm their consent will proceed with FTET preceded by the downregulation protocol allocated at randomisation. If an eligible participant undergoes a fresh transfer they will be followed through their cycle to determine pregnancy outcome and will be offered the opportunity to participate in MODA for their subsequent FTET.

Randomisation

Participants will be randomised using an online sequence generation and allocation system (www.sealedenvelope.com) in a ratio of 1:1, using stratified randomisation to adjust for age (age < 37, age ≥ 37), with permuted blocks of random sizes. The block sizes will not be disclosed to ensure concealment. Randomisation will be performed by a member of the UCLH Reproductive Medicine Unit administration team, independent to the research team. Participants will be informed of their assigned treatment group and this will be recorded on the

Trial Subject Enrolment Log. The principal investigator (PI) will hold the randomisation list. It is not feasible to perform blinding in our setting.

Procedures

Standard downregulation protocol: Participants allocated to the standard downregulation protocol will start Norethisterone on day 14 of downregulation cycle and continue for 11 days, followed by Buserelin 0.5ml subcutaneously from day 21. A baseline scan will be performed between days one to four of their bleed, Buserelin reduced to 0.2ml and they will commence Progynova 2mg three times daily orally. Serial scanning will be performed from day ten until an endometrial thickness of greater than 8mm is achieved, followed by luteal support with Cyclogest 400mg twice daily vaginally or rectally and Lubion 25mg twice daily subcutaneously. Embryo transfer will be performed on the appropriate day for embryo age (Figure 2 and 3).

Modified downregulation protocol: Participants allocated to the modified downregulation protocol will have a baseline scan between days one and four of their bleed and will administer Leuprorelin acetate 3.75 mg subcutaneously, followed by Leuprorelin acetate 1.875 mg subcutaneously 28 days later. They will commence Progynova 2mg three times daily orally 14 days later. Serial scanning will be performed from day ten until an endometrial thickness of greater than 8mm is achieved, followed by luteal support with Cyclogest 400mg twice daily vaginally or rectally and Lubion 25mg twice daily subcutaneously. Embryo transfer will be performed on the appropriate day for embryo age (Figure 2 and 3).

Discontinuation/withdrawal of participants:

In consenting to participate in the trial, participants are consenting to intervention, assessments, follow-up and data collection.

A participant may be withdrawn from the trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- Intercurrent illness
- Participants withdrawing consent
- Persistent non-compliance to protocol requirements.

The decision to withdraw a participant from treatment will be recorded in the electronic case report form (eCRF) and medical notes.

Patient and public involvement

Patients were involved as research partners in all aspects of the study including identifying the original research question, in revising study design, and in confirming acceptability of study monitoring methods and the intervention to be administered.

Modification of the protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the CI and research team. They will be approved by the Research Ethics Committee prior to implementation.

Data and trial management

Data will be collected on trial specific electronic case report forms (eCRFs). All eCRFs will be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF. The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679). Personal data will be held on the password protected database. We will adopt the NHS Code of Confidentiality and will allocate a unique participant identification number to ensure participant anonymity at data handling and analysis stage. Access to this will be restricted to the PI. Anonymised data will be stored for twenty years after completion of the trial, after which time data will be disposed of using confidential information trust destruction procedures.

MODA will have a Trial Management Group (TMG) that will include the Chief Investigator (CI) and trial staff to oversee the everyday trial's conduct. The TMG will meet regularly four times a year to review recruitment figures, serious adverse events (SAEs) and substantial amendments to the protocol prior to submission to the REC. We will identify an independent Trial Steering Committee, which has overall responsibility for the conduct of the study. The study will be supervised on a day-to-day basis by the TMG, who will report to the Trial Steering Committe (TSC). We will also identify an independent Data Monitoring Committee (DMC) to provide advice on data management and safety aspects of the trial. The DMC will meet six monthly to review interim analyses, or as necessary to address any issues.

Recording and reporting of adverse events

Each adverse event will be assessed for severity, causality, seriousness and expectedness. All adverse events (AEs) will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All serious adverse events (SAEs) will be recorded in the medical records and the eCRF, and the sponsor's AE log. The AE log of SAEs will be reported to the sponsor at least twice per year. SAEs will be reported to the Sponsor within five days of becoming aware of the event.

Sample size

Our previous observational studies suggest a clinical pregnancy rate of 22.9% in women with mild adenomyosis compared to 42.7% with moderate/severe adenomyosis (7). We theorise that the modified protocol will improve the chance of clinical pregnancy to similar levels in those with mild disease. We need to randomise 162 patients over 3 years to achieve 80% power for detecting a 20% difference in the primary outcome across those groups at 5% significance.

Adenomyosis has an estimated prevalence of 20.9% in benign gynaecology patients (2), we estimate higher prevalence among women seeking assisted conception with history of subfertility. Given our yearly 750 cycles of IVF/ICSI, we estimate a recruitment period of 3 years to achieve our target sample size.

Analysis

Participants with missing data and non-compliers, including participants who decide to withdraw from the study or do not follow their assigned protocol, will be excluded from our analysis. We will perform univariate and multivariate analyses to compare the primary outcome of both groups and report using risk ratio (RR) and 95% confidence intervals (CI) for

dichotomous outcomes as well as mean difference with standard deviation (SD) for continuous outcomes.

Discussion

Women with moderate/severe adenomyosis undergoing assisted conception are known to have a reduced clinical pregnancy rate; there is currently no consensus regarding their treatment. Retrospective studies have identified benefit in prolonged downregulation for these patients however these are subject to selection and publication bias and therefore may not offer a realistic assessment of this protocol modification. Others have reported a reduction in pregnancy rates with prolonged downregulation but again this is retrospective data which may have underestimated the positive effect of the intervention. There is an urgent need to prospectively evaluate prolonged downregulation as an option for couples with adenomyosis undergoing assisted conception both to confirm or refute the validity of this approach.

MODA is designed to offer pragmatic, real-life evaluation of the optimal use of downregulation in affected women. Our modified downregulation protocol is a practical, simple and readily available treatment option that could help women with adenomyosis to improve their chances of conception. The findings of this study will be published in peer- reviewed journals and presented at national and international scientific meetings and congresses. No later than 3 years after the collection of the 6 weeks post pregnancy outcome data, we will deliver a completely deidentified data set to an appropriate data archive for sharing purposes. Ethical approval was granted by the NHS Research Ethics Committees (UK IRAS integrated research application system; reference 19/LO/1567). MODA is registered online with clinicaltrials.gov (NCT03946722).

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Author Statement

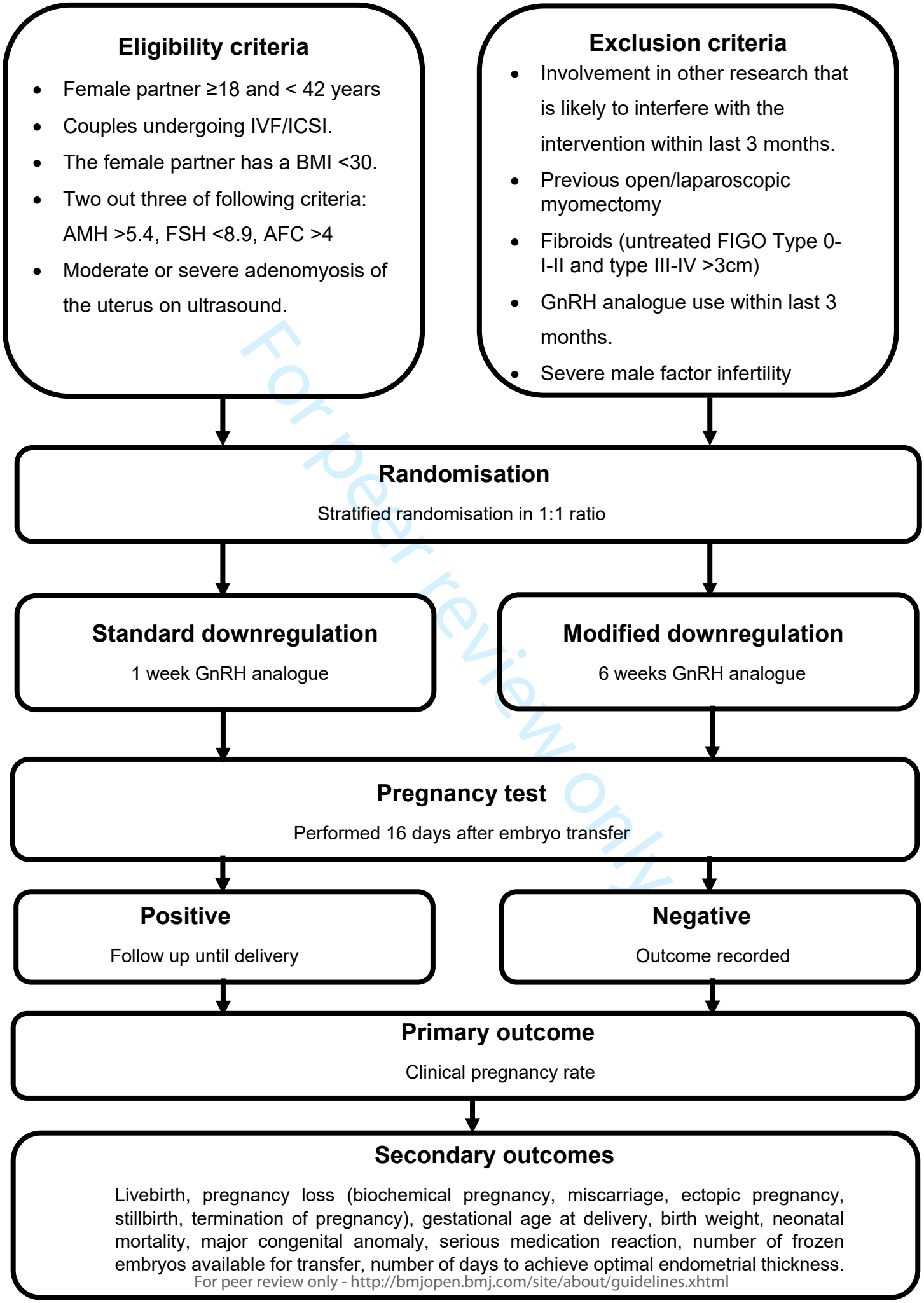
DM conceived of the study. DM and SL initiated and revised study design, drafted and revised the manuscript. All authors contributed to refinement of the study protocol and approved the final manuscript.

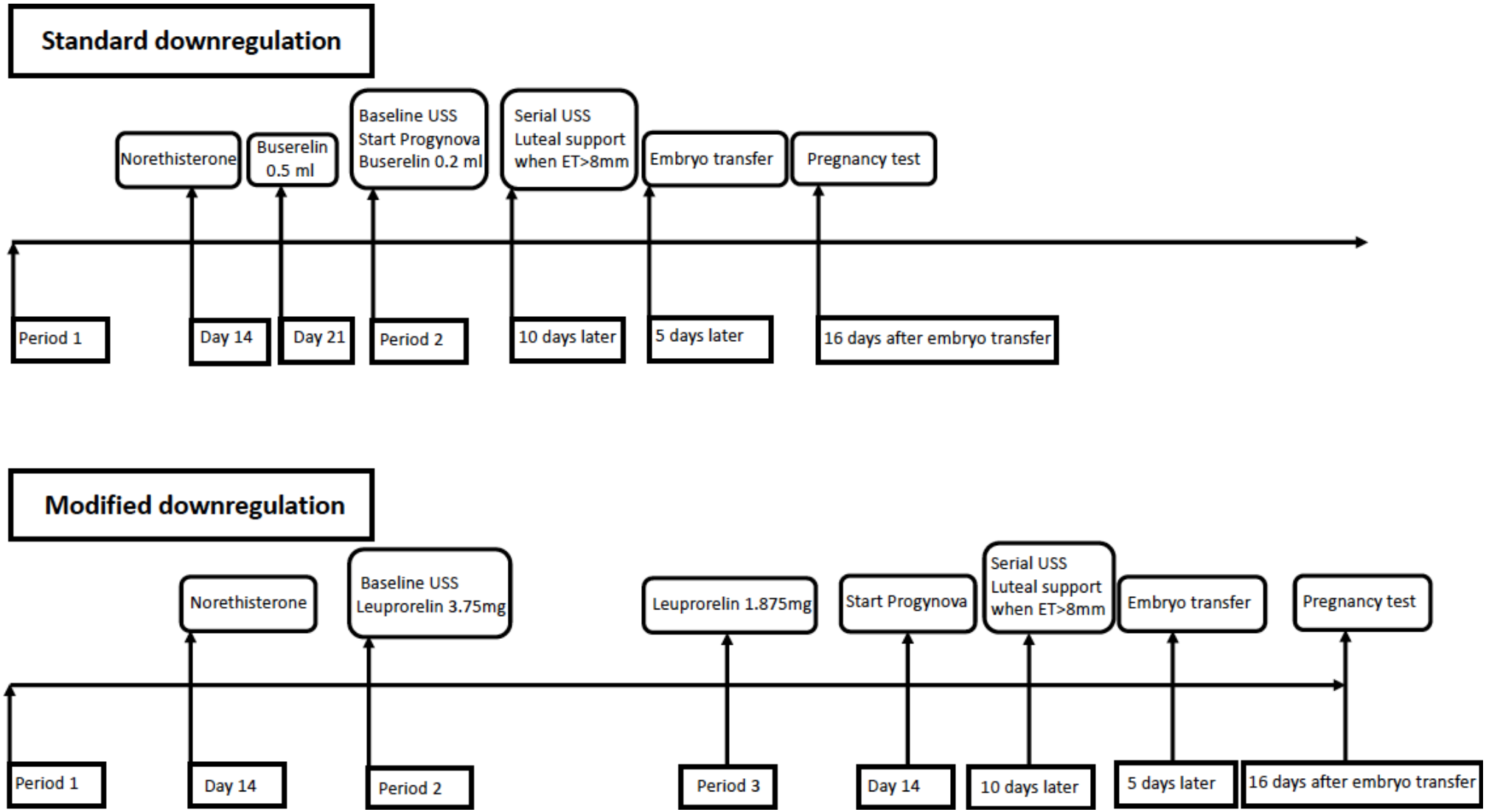
Conflict of Interests

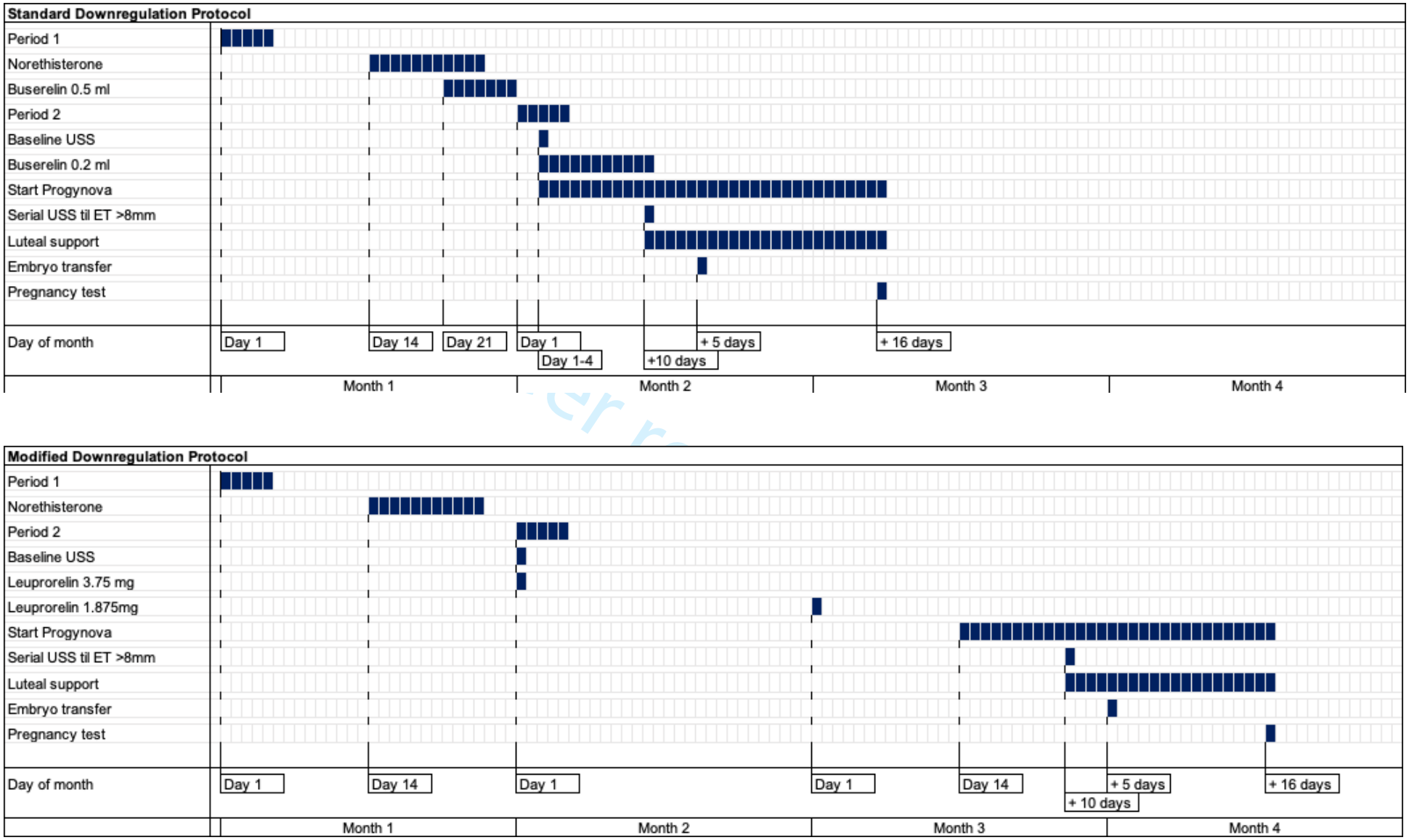
The authors have no conflicts of interest to declare.

Word Count 3349

MODA Trial




Standard downregulation
Norethisterone
Buserelin 0.5 ml
Baseline USS Start Progynova Buserelin 0.2 ml
Serial USS Luteal support when ET>8mm
Embryo transfer
Pregnancy test
Period 1
Day 14
Day 21
Period 2
10 days later
5 days later
16 days after embryo transfer
Modified downregulation
Norethisterone
Baseline USS Leuprorelin 3.75mg
Leuprorelin 1.875mg
Start Progynova
Serial USS Luteal support when ET>8mm
Embryo transfer
Pregnancy test
Period 1
Day 14
Period 2
Period 3
Day 14
10 days later
5 days later
16 days after embryo transfer


Standard Downregulation Protocol
Period 1
Norethisterone
Buserelin 0.5 ml
Period 2
Baseline USS
Buserelin 0.2 ml
Start Progynova
Serial USS til ET >8mm
Luteal support
Embryo transfer
Pregnancy test
Day of month
Day 1
Day 14
Day 21
Day 1
Day 1-4
+10 days
+ 5 days
+ 16 days
Month 1
Month 2
Month 3
Month 4
Modified Downregulation Protocol
Period 1
Norethisterone
Period 2
Baseline USS
Leuprorelin 3.75 mg
Leuprorelin 1.875mg
Start Progynova
Serial USS til ET >8mm
Luteal support
Embryo transfer
Pregnancy test
Day of month
Day 1
Day 14
Day 1
Day 1
Day 14
+ 10 days
+ 5 days
+ 16 days
Month 1
Month 2
Month 3
Month 4

Reporting checklist for protocol of a clinical trial.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 22

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13, 14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	10

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.

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The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.

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Keywords: Infertility, in vitro fertilisation, adenomyosis, downregulation, randomised-controlled trial

WHO trial registration data

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03946722
Date of registration in primary registry	13th May 2019
Source of monetary or material support	Dimitrios Mavrelos (CI)
Primary sponsor	University College London
Contact for public queries	DM, SL (dimitrios.mavrelos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Contact for scientific queries	DM, SL (dimitrios.mavrelos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Scientific title	Modified downregulation for women with moderate/severe adenomyosis of the uterus prior to frozen-thawed embryo transfer.
Descriptive title	The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.
Public title	MODA
Countries of recruitment	UK
Health condition or problem studied	Adenomyosis
Intervention(s)	Active comparator: Prolonged downregulation for 6 weeks.
	Placebo comparator: Standard downregulation for one week.
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years <42 years Sexes eligible for study: female Accepts healthy volunteers: no

Data category	Information
	Inclusion criteria: Women with moderate/severe adenomyosis undergoing IVF treatment, BMI < 30 kg/m^2, two out of three of the following criteria are met: AMH > 5.4 pmol/L, FSH < 8.9 IU/L, antral follicle count > 4.
	Exclusion criteria: Previous open or laparoscopic myomectomy, uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids > 3 cm), untreated endometrial polyps, untreated hydrosalpinges, use of GnRH analogues within previous 3 months, severe male factor infertility (sperm count < 2 x 10^6/ml, use of surgically retrieved spermatozoa)
Study type	Interventional
	Allocation: randomized intervention model. Parallel assignment masking: unblinded.
	Primary purpose: to determine effectiveness of modified downregulation.
	Phase III
Date of first enrolment	October 2020
Target sample size	162
Recruitment status	Recruiting
Primary outcome	Clinical pregnancy rate
Key secondary outcomes	Livebirth, pregnancy loss (biochemical pregnancy, miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication reaction, frequency and severity of medication side effects, ~~number of frozen embryos available for transfer~~, number of days to achieve optimal endometrial thickness.

Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update

1	3/4/2019	N/A	N/A
2	1/1/2020	Novin Fard	Hospital Trust formulary update; Triptorelin changed to Leuprorelin.

Trial personnel

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Abstract

Introduction: Adenomyosis can adversely reduce chances of pregnancy in couples undergoing assisted conception. We aim to evaluate the effect of two different downregulation protocols on the reproductive outcomes in women with moderate and severe adenomyosis undergoing frozen-thawed embryo transfer (FTET).

Methods and analysis: We will conduct a two-armed pragmatic randomised clinical trial comparing modified downregulation with gonadotrophin releasing hormone (GnRH) analogue for six weeks to standard downregulation with GnRH analogue for one week prior to FTET. Our primary outcome is clinical pregnancy, defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation, with other secondary reproductive, neonatal and safety outcomes. We aim to randomise 162 patients over 3 years to achieve 80% power for detecting a 20% difference in the primary outcome at 5% significance.

Ethics and dissemination: To date there is no consensus on the optimal protocol for management of subfertile women with adenomyosis. Modified downregulation could improve the clinical pregnancy rate by reducing the endometrial inflammatory reaction and/ or myometrial contractility and their impact on uterine receptivity in women with moderate and severe adenomyosis of the uterus undergoing frozen thawed embryo transfer. The MODA trial is designed to offer pragmatic, real-life evaluation of the optimal protocol for downregulation for this population during assisted conception treatments. Our findings will be published in peer-reviewed journals and presented at national and international scientific meetings and congresses. Ethical approval was granted by the NHS Research Ethics Committees (19/LO/1567).

Trial registration number: NCT03946722

Article Summary

Strengths and limitations of this study

- The MODA trial offers a pragmatic evaluation of two different downregulation protocols used in current practice to optimise the reproductive outcomes of women with adenomyosis.
- We will report on established core outcomes of interest for stakeholders in assisted conception and will randomise a large number of women to achieve sufficient power to evaluate the treatments of interest across different participant subgroups.
- The intervention is unblinded.

Introduction

Adenomyosis is characterised by the presence of ectopic endometrial glands and stroma located within hypertrophic and hyperplastic myometrium, affecting up to 20.9% of women at reproductive age (1, 2). Recent advances in ultrasound and MRI technology have facilitated the diagnosis of adenomyosis with a reported accuracy of up to 81% using two and three dimensional ultrasound (2).

Two meta-analyses suggested that women with adenomyosis have lower implantation, pregnancy and livebirth rates with higher miscarriage rate, thus its impact on fertility is marked (3,4). This impact is directly linked to the severity of the adenomyosis with rate of clinical pregnancy decreasing from 42.7% (95% CI 37.1-48.3) in women with no adenomyosis on ultrasound to 22.9% (95% CI 13.4-32.6) for those with four features and 13.0% (95% CI 2.2-23.9) for those with all seven features (5). Several theories have been suggested to explain its negative impact on fertility, such as abnormal uterotubal transport due to anatomical distortion of the uterine cavity and disturbed uterine peristalsis (6). Ultrastructural myometrial abnormalities may cause hyperperistalsis and increase the intrauterine pressure due to a disturbance in normal myocyte contractility with subsequent loss of normal rhythmic contraction (7). Several molecular alterations have also been noted in the eutopic endometrium of women with adenomyosis. These include increased levels of inflammatory markers, increased oxidative stress, reduced expression of implantation markers, lack of expression of adhesion molecules and changes in the sex steroid hormone pathway, resulting in impaired implantation (6).

Treatment with gonadotrophin-releasing hormone (GnRH) analogues for prolonged periods could reduce the amount of inflammatory reaction in the eutopic endometrium of women with

adenomyosis (8). It is also possible that prolonged downregulation may improve abnormal uterine peristalsis seen in women with adenomyosis. A study examining the impact of prolonged downregulation in women with adenomyosis undergoing IVF treatment first showed increased clinical pregnancy rates a decade ago (9). More recently, three large retrospective studies suggest a significant benefit in the reproductive outcomes with prolonged downregulation prior to frozen embryo transfer, in contrast to one retrospective analysis that showed an adverse impact of prolonged downregulation on pregnancy rates, and another retrospective study that showed no difference in outcomes (10 - 14). The true benefit of prolonged versus standard downregulation remains imprecise in this population.

Objective: We aim to determine whether modified downregulation prior to frozen thawed embryo transfer (FTET) improves the chance of clinical pregnancy in women with moderate and severe adenomyosis.

Methods

Trial design

The MODA Trial is a pragmatic, multi-site, randomised controlled trial of two parallel arms comparing prolonged downregulation with GnRH analogue for six weeks to standard downregulation with GnRH analogue for one week prior to frozen-thawed embryo transfer, recruiting participants from fertility centres across the UK. Participants will be followed-up until six weeks after the pregnancy outcome is determined. The trial design is summarised in Figure 1.

Inclusion criteria

1. Couples who are undergoing a cycle of IVF/ICSI, where a cycle is defined as egg collection following ovarian stimulation.
2. The female partner is ≥18 and < 42 years of age.
3. The female partner has a BMI <30 kg/m^2.
4. Two out of three of the following criteria are met: AMH >5.4 pmol/L, FSH <8.9 iU, antral follicle count >4 (15).
5. Moderate or severe adenomyosis of the uterus diagnosed on ultrasound scan.
6. Both partners are willing and able to provide written informed consent.

Exclusion criteria

1. Concurrent and/or recent involvement in other research that is likely to interfere with the intervention within the previous 3 months of study enrolment.
2. Previous open or laparoscopic myomectomy
3. Uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids > 3 cm)
4. Untreated endometrial polyps
5. Untreated hydrosalpinges
6. Use of GnRH analogues within previous 3 months.
7. Severe male factor infertility (sperm count < 2 x 10^6/ml, use of surgically retrieved spermatozoa)
8. Couples who in the opinion of the researcher by virtue of language or learning impairment would be unable to give fully informed consent to the study.

Outcomes

The primary outcome of the study is clinical pregnancy, defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation.

Our secondary outcomes will include livebirth, pregnancy loss (biochemical pregnancy, miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication reaction, frequency and severity of medication side effects , ~~number of frozen embryos available for transfer~~, number of days to achieve optimal endometrial thickness.

Enrolment

Enrolment of participants will involve coordinated registration and allocation of participant trial numbers by the trial co-ordinator. All participants will be asked by a member of the research team to complete a written consent at least 24 hours after providing the trial's participant information sheet (PIS) (see model consent form in supplementary files). All consents will be recorded in the medical notes including signature from both partners undergoing the IVF/ICSI procedure. A member of the research team will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. No trial procedures will be conducted prior to the participant giving consent by signing the consent form.

Once consent has been granted a TVS will be performed by a member of the research team. The scan will be performed in a systematic fashion starting from the uterus in longitudinal plane with measurement of the endometrial thickness. The probe is then rotated to the transverse plane and the uterus scanned from the cervix to the fundus with any uterine pathologies noted and measured in 3 orthogonal planes. A 3D ultrasound volume is then obtained and saved starting with the uterus in longitudinal view making sure to include all uterine tissue in the 3D volume sweep. Any congenital or acquired uterine anomalies are diagnosed according to published diagnostic criteria. Adenomyosis is diagnosed according to a standardised diagnostic criteria (2) and graded for severity according to the number of

adenomyosis features present (assign a score of 1 for each of: i) asymmetrical myometrial thickening, ii) parallel shadowing, iii) myometrial cysts, iv) irregular endometrial-myometrial

junction, v) linear striations, vi) hyperechoic islands, vii) adenomyoma). Patients with four or more features of adenomyosis are considered to have moderate or severe adenomyosis (5). Videosonography for a period of 4 minutes will be performed to assess uterine peristalsis. The operator will then sweep to the adnexae, starting from the left to identify and measure the ovaries in three orthogonal planes and document the antral follicle count. Each ovary is examined for the presence of cysts as well as for mobility and tenderness by gentle pressure with the ultrasound probe. Once the ovaries have been assessed the operator examines the pouch of Douglas for the presence of free fluid as well as any evidence of endometriosis such as obliteration, endometriotic nodules and endometriomas, as previously described (16). Once the ultrasound scan is concluded all information is added to the clinical database (RedCap, Vanderbilt University).

After the scan and once eligibility is confirmed participants will be asked to confirm if they want to participate in the trial. Those that confirm their consent will proceed with FTET preceded by the downregulation protocol allocated at randomisation. If an eligible participant undergoes a fresh transfer they will be followed through their cycle to determine pregnancy outcome and will be offered the opportunity to participate in MODA for their subsequent FTET.

Randomisation

Participants will be randomised using an online sequence generation and allocation system (www.sealedenvelope.com) in a ratio of 1:1, using stratified randomisation to adjust for age (age < 37, age ≥ 37), with permuted blocks of random sizes. The block sizes will not be disclosed to ensure concealment. Randomisation will be performed by a member of the UCLH Reproductive Medicine Unit administration team, independent to the research team. Participants will be informed of their assigned treatment group and this will be recorded on the

Trial Subject Enrolment Log. The principal investigator (PI) will hold the randomisation list. It is not feasible to perform blinding in our setting.

Procedures

Standard downregulation protocol: Participants allocated to the standard downregulation protocol will start Norethisterone on day 14 of downregulation cycle and continue for 11 days, followed by Buserelin 0.5ml subcutaneously from day 21. A baseline scan will be performed between days one to four of their bleed, Buserelin reduced to 0.2ml and they will commence Progynova 2mg three times daily orally. Serial scanning will be performed from day ten until an endometrial thickness of greater than 8mm is achieved, followed by luteal support with Cyclogest 400mg twice daily vaginally or rectally and Lubion 25mg twice daily subcutaneously. Blastocyst embryo transfer will be performed with a minimum morphological quality of B-C on the appropriate day for embryo age (Figure 2 and 3).

Modified downregulation protocol: Participants allocated to the modified downregulation protocol will have a baseline scan between days one and four of their bleed and will administer Leuprorelin acetate 3.75 mg subcutaneously, followed by Leuprorelin acetate 1.875 mg subcutaneously 28 days later. They will commence Progynova 2mg three times daily orally 14 days later. Serial scanning will be performed from day ten until an endometrial thickness of greater than 8mm is achieved, followed by luteal support with Cyclogest 400mg twice daily vaginally or rectally and Lubion 25mg twice daily subcutaneously. Blastocyst embryo transfer will be performed with a minimum morphological quality of B-C on the appropriate day for embryo age (Figure 2 and 3).

Discontinuation/withdrawal of participants:

In consenting to participate in the trial, participants are consenting to intervention, assessments, follow-up and data collection.

A participant may be withdrawn from the trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- Intercurrent illness
- Participants withdrawing consent
- Persistent non-compliance to protocol requirements.

The decision to withdraw a participant from treatment will be recorded in the electronic case report form (eCRF) and medical notes.

Patient and public involvement

Patients were involved as research partners in all aspects of the study including identifying the original research question, in revising study design, and in confirming acceptability of study monitoring methods and the intervention to be administered.

Modification of the protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the CI and research team. They will be approved by the Research Ethics Committee prior to implementation.

Data and trial management

Data will be collected on trial specific electronic case report forms (eCRFs). All eCRFs will be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF. The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679). Personal data will be held on the password protected database. We will adopt the NHS Code of Confidentiality and will allocate a unique participant identification number to ensure participant anonymity at data handling and analysis stage. Access to this will be restricted to the PI. Anonymised data will be stored for twenty years after completion of the trial, after which time data will be disposed of using confidential information trust destruction procedures.

MODA will have a Trial Management Group (TMG) that will include the Chief Investigator (CI) and trial staff to oversee the everyday trial's conduct. The TMG will meet regularly four times a year to review recruitment figures, serious adverse events (SAEs) and substantial amendments to the protocol prior to submission to the REC. We will identify an independent Trial Steering Committee, which has overall responsibility for the conduct of the study. The study will be supervised on a day-to-day basis by the TMG, who will report to the Trial Steering Committe (TSC). We will also identify an independent Data Monitoring Committee (DMC) to provide advice on data management and safety aspects of the trial. The DMC will meet six monthly to review interim analyses, or as necessary to address any issues.

Recording and reporting of adverse events

Each adverse event will be assessed for severity, causality, seriousness and expectedness. All adverse events (AEs) will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All serious adverse events (SAEs) will be recorded in the medical records and the eCRF, and the sponsor's AE log. The AE log of SAEs will be reported to the sponsor at least twice per year. SAEs will be reported to the Sponsor within five days of becoming aware of the event.

Sample size

Our previous observational studies suggest a clinical pregnancy rate of 42.7% in women with mild adenomyosis compared to 22.9% with moderate/severe adenomyosis (7). We theorise that the modified protocol will improve the chance of clinical pregnancy to similar levels in those with mild disease. We need to randomise 162 patients over 3 years to achieve 80% power for detecting a 20% difference in the primary outcome across those groups at 5% significance.

Adenomyosis has an estimated prevalence of 20.9% in benign gynaecology patients (2), we estimate higher prevalence among women seeking assisted conception with history of subfertility. Given our yearly 750 cycles of IVF/ICSI, we estimate a recruitment period of 3 years to achieve our target sample size.

Analysis

Participants with missing data and non-compliers, including participants who decide to withdraw from the study or do not follow their assigned protocol, will be excluded from our analysis. We will perform univariate and multivariate analyses to compare the primary outcome of both groups and report using risk ratio (RR) and 95% confidence intervals (CI) for

dichotomous outcomes as well as mean difference with standard deviation (SD) for continuous outcomes.

Discussion

Women with moderate/severe adenomyosis undergoing assisted conception are known to have a reduced clinical pregnancy rate; there is currently no consensus regarding their treatment. Retrospective studies have identified benefit in prolonged downregulation for these patients however these are subject to selection and publication bias and therefore may not offer a realistic assessment of this protocol modification. Others have reported a reduction in pregnancy rates with prolonged downregulation but again this is retrospective data which may have underestimated the positive effect of the intervention. Co-existing undiagnosed endometriosis is a substantial confounding factor, as not all patients with adenomyosis undergo surgical diagnostic procedures. There is also potential for variability in the diagnosis of adenomyosis by ultrasound. In the MODA trial we have only included fertility centres with an expert ultrasound operator and will review ultrasound images to ensure quality of diagnosis. This approach should also reduce the risk of undiagnosed moderate or severe endometriosis as this can be reliably diagnosed on transvaginal ultrasound. Randomization should ensure confounding due to endometriosis coexistence is balanced. We will report the frequency of ultrasound diagnosed endometriosis in the control and treatment arm of the study.

There is an urgent need to prospectively evaluate prolonged downregulation as an option for couples with adenomyosis undergoing assisted conception both to confirm or refute the validity of this approach. MODA is designed to offer pragmatic, real-life evaluation of the optimal use of downregulation in affected women. Our modified downregulation protocol is a practical,

simple and readily available treatment option that could help women with adenomyosis to improve their chances of conception. The findings of this study will be published in peer-reviewed journals and presented at national and international scientific meetings and congresses. No later than 3 years after the collection of the 6 weeks post pregnancy outcome data, we will deliver a completely deidentified data set to an appropriate data archive for sharing purposes. Ethical approval was granted by the NHS Research Ethics Committees (UK IRAS integrated research application system; reference 19/LO/1567). MODA is registered online with clinicaltrials.gov (NCT03946722).

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Author Statement

DM conceived of the study. SL, BW, NB, TL, ES, EY, PS and DM initiated and revised the study design, drafted and revised the manuscript critically and contributed to refinement of the study protocol. SL, BW, NB, TL, ES, EY, PS and DM approved the final manuscript and are in agreement to be accountable for all aspects of the work.

Conflict of Interests

The authors have no conflicts of interest to declare.

Figure Legends

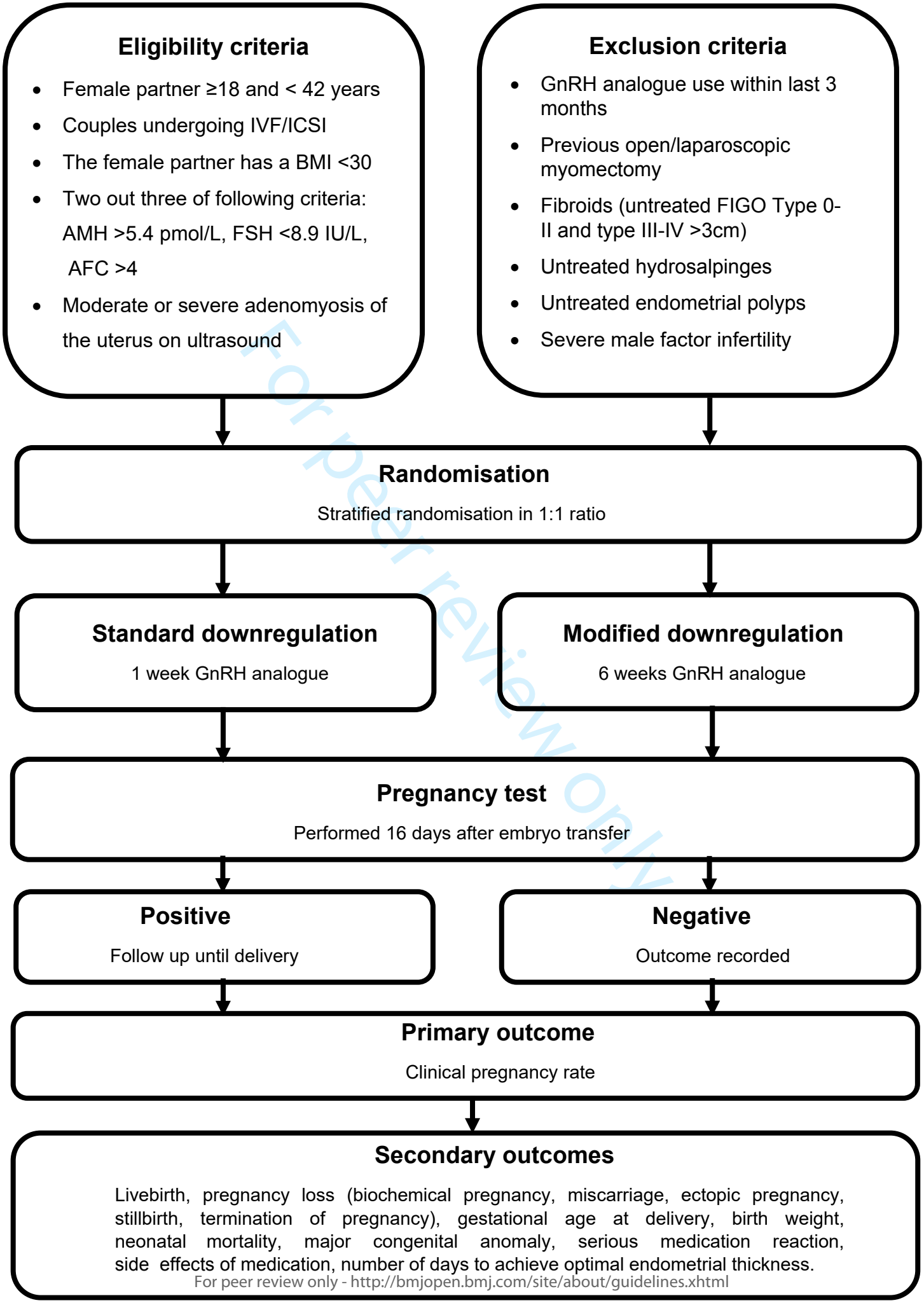
Figure 1. MODA trial study design

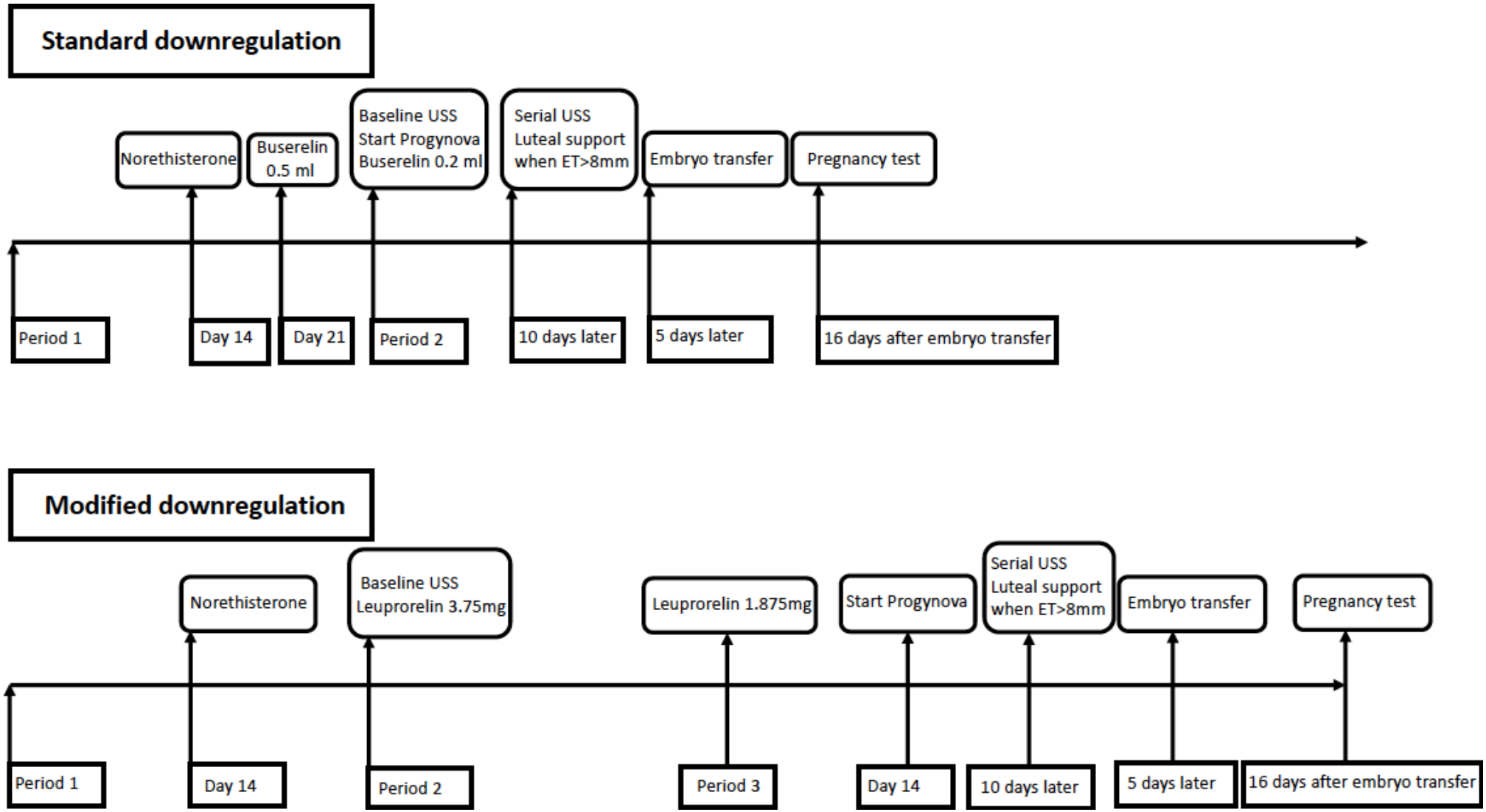
Figure 2. Standard and modified downregulation protocol overview

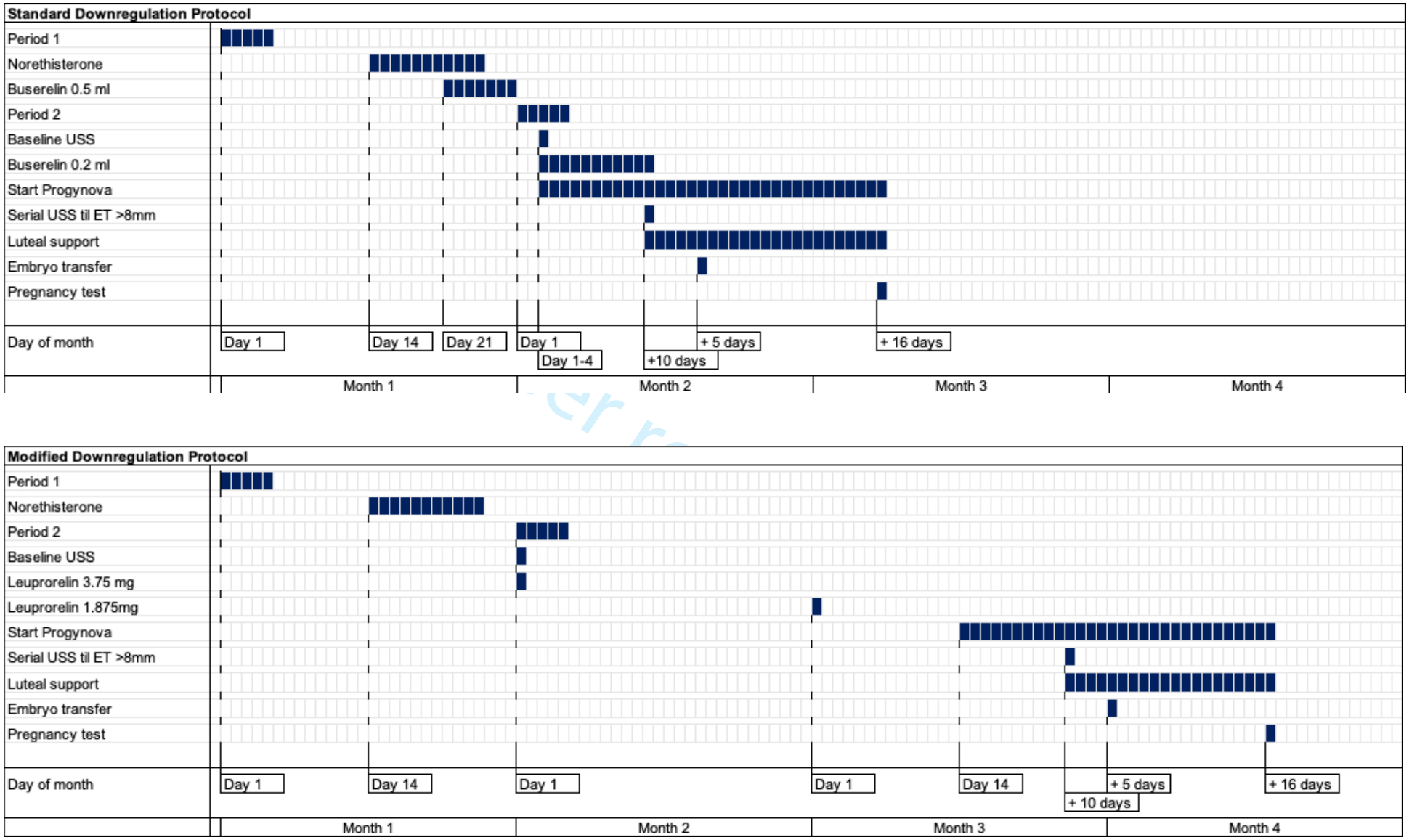
Figure 3. Standard and modified downregulation protocol daily schedule

Word Count 3573

MODA Trial




Standard downregulation
Norethisterone
Buserelin 0.5 ml
Baseline USS Start Progynova Buserelin 0.2 ml
Serial USS Luteal support when ET>8mm
Embryo transfer
Pregnancy test
Period 1
Day 14
Day 21
Period 2
10 days later
5 days later
16 days after embryo transfer
Modified downregulation
Norethisterone
Baseline USS Leuprorelin 3.75mg
Leuprorelin 1.875mg
Start Progynova
Serial USS Luteal support when ET>8mm
Embryo transfer
Pregnancy test
Period 1
Day 14
Period 2
Period 3
Day 14
10 days later
5 days later
16 days after embryo transfer


Standard Downregulation Protocol
Period 1
Norethisterone
Buserelin 0.5 ml
Period 2
Baseline USS
Buserelin 0.2 ml
Start Progynova
Serial USS til ET >8mm
Luteal support
Embryo transfer
Pregnancy test
Day of month
Day 1
Day 14
Day 21
Day 1
Day 1-4
+10 days
+ 5 days
+ 16 days
Month 1
Month 2
Month 3
Month 4
Modified Downregulation Protocol
Period 1
Norethisterone
Period 2
Baseline USS
Leuprorelin 3.75 mg
Leuprorelin 1.875mg
Start Progynova
Serial USS til ET >8mm
Luteal support
Embryo transfer
Pregnancy test
Day of month
Day 1
Day 14
Day 1
Day 1
Day 14
+ 10 days
+ 5 days
+ 16 days
Month 1
Month 2
Month 3
Month 4

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 22

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be	7

		collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13, 14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.

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The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.

Sania Latif[1], Bassel H. Al Wattar[1], Neerujah Balachandren[1], Tomasz Lukaszewski[1], Ertan Saridogan[1], Ephia Yasmin[1], Paul Serhal[2], Dimitrios Mavrelos[1]

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Keywords: Infertility, in vitro fertilisation, adenomyosis, downregulation, randomised-controlled trial

Table 1. WHO Trial Registration Data

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03946722
Date of registration in primary registry	13th May 2019
Source of monetary or material support	Dimitrios Mavrelos (CI)
Primary sponsor	University College London
Contact for public queries	DM, SL (dimitrios.mavrelos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Contact for scientific queries	DM, SL (dimitrios.mavrelos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Scientific title	Modified downregulation for women with moderate/severe adenomyosis of the uterus prior to frozen-thawed embryo transfer.
Descriptive title	The effectiveness of modified downregulation for women with moderate and severe adenomyosis of the uterus prior to frozen thawed embryo transfer (MODA) study protocol: a pragmatic randomised-controlled trial.
Public title	MODA
Countries of recruitment	UK

Data category	Information
Health condition or problem studied	Adenomyosis
Intervention(s)	Active comparator: Prolonged downregulation for 6 weeks.
	Placebo comparator: Standard downregulation for one week.
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years <42 years Sexes eligible for study: female Accepts healthy volunteers: no
	Inclusion criteria: Women with moderate/severe adenomyosis undergoing IVF treatment, BMI < 30 kg/m^2, two out of three of the following criteria are met: AMH > 5.4 pmol/L, FSH < 8.9 IU/L, antral follicle count > 4.
	Exclusion criteria: Previous open or laparoscopic myomectomy, uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids > 3 cm), untreated endometrial polyps, untreated hydrosalpinges, use of GnRH analogues within previous 3 months, severe male factor infertility (sperm count < 2 x 10^6/ml, use of surgically retrieved spermatozoa)
Study type	Interventional
	Allocation: randomized intervention model. Parallel assignment masking: unblinded.
	Primary purpose: to determine effectiveness of modified downregulation.
	Phase III
Date of first enrolment	October 2020
Target sample size	162

Data category	Information
Recruitment status	Recruiting
Primary outcome	Clinical pregnancy rate
Key secondary outcomes	Livebirth, pregnancy loss (biochemical pregnancy, miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication reaction, frequency and severity of medication side effects, number of days to achieve optimal endometrial thickness.

Table 2. Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1	3/4/2019	N/A	N/A
2	1/1/2020	Novin Fard	Hospital Trust formulary update; Triptorelin changed to Leuprorelin.

Table 3. Trial personnel

Chief investigator:	Mr Dimitrios Mavrelos Consultant Obstetrician & Gynaecologist and Subspecialist in Reproductive Medicine Reproductive Medicine Unit University College London Hospital 235 Euston Road London NW1 2BU
Sponsor Representative:	Pushpsen Joshi Joint Research Office UCL Gower Street London WC1E 6BT pushpsen.joshi1@nhs.net
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Statistician: Dr George Ploubidis

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Abstract

Introduction: Adenomyosis can adversely reduce chances of pregnancy in couples undergoing assisted conception. We aim to evaluate the effect of two different downregulation protocols on the reproductive outcomes in women with moderate and severe adenomyosis undergoing frozen-thawed embryo transfer (FTET).

Methods and analysis: We will conduct a two-armed pragmatic randomised clinical trial comparing modified downregulation with gonadotrophin releasing hormone (GnRH) analogue for six weeks to standard downregulation with GnRH analogue for one week prior to FTET. Our primary outcome is clinical pregnancy, defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation, with other secondary reproductive, neonatal and safety outcomes. We aim to randomise 162 patients over 3 years to achieve 80% power for detecting a 20% difference in the primary outcome at 5% significance.

Ethics and dissemination: To date there is no consensus on the optimal protocol for management of subfertile women with adenomyosis. Modified downregulation could

improve the clinical pregnancy rate by reducing the endometrial inflammatory reaction and/ or myometrial contractility and their impact on uterine receptivity in women with moderate and severe adenomyosis of the uterus undergoing frozen thawed embryo transfer. The MODA trial is designed to offer pragmatic, real-life evaluation of the optimal protocol for downregulation for this population during assisted conception treatments. Our findings will be published in peer-reviewed journals and presented at national and international scientific meetings and congresses. Ethical approval was granted by the NHS Research Ethics Committees (19/LO/1567).

Trial registration number: NCT03946722

Article Summary

Strengths and limitations of this study

- The MODA trial offers a pragmatic evaluation of two different downregulation protocols used in current practice to optimise the reproductive outcomes of women with adenomyosis.
- We will report on established core outcomes of interest for stakeholders in assisted conception and will randomise a large number of women to achieve sufficient power to evaluate the treatments of interest across different participant subgroups.
- The intervention is unblinded.

Introduction

Adenomyosis is characterised by the presence of ectopic endometrial glands and stroma located within hypertrophic and hyperplastic myometrium, affecting up to 20.9% of women at reproductive age (1, 2). Recent advances in ultrasound and MRI technology have facilitated the diagnosis of adenomyosis with a reported accuracy of up to 81% using two and three dimensional ultrasound (2).

Two meta-analyses suggested that women with adenomyosis have lower implantation, pregnancy and livebirth rates with higher miscarriage rates, thus its impact on fertility is marked (3,4). This impact is directly linked to the severity of the adenomyosis with rate of clinical pregnancy decreasing from 42.7% (95% CI 37.1-48.3) in women with no adenomyosis on ultrasound to 22.9% (95% CI 13.4-32.6) for those with four features and 13.0% (95% CI 2.2-23.9) for those with all seven features (5). Several theories have been suggested to explain its negative impact on fertility, such as abnormal uterotubal transport due to anatomical distortion of the uterine cavity and disturbed uterine peristalsis (6). Ultrastructural myometrial abnormalities may cause hyperperistalsis and increase the intrauterine pressure due to a disturbance in normal myocyte contractility with subsequent loss of normal rhythmic contraction (7). Several molecular alterations have also been noted in the eutopic endometrium of women with adenomyosis. These include increased levels of inflammatory markers, increased oxidative stress, reduced expression of implantation markers, lack of expression of adhesion molecules and changes in the sex steroid hormone pathway, resulting in impaired implantation (6).

Treatment with gonadotrophin-releasing hormone (GnRH) analogues for prolonged periods could reduce the amount of inflammatory reaction in the eutopic endometrium of women with

adenomyosis (8). It is also possible that prolonged downregulation may improve abnormal uterine peristalsis seen in women with adenomyosis. A study examining the impact of prolonged downregulation in women with adenomyosis undergoing in vitro fertilisation (IVF) treatment first showed increased clinical pregnancy rates a decade ago (9). More recently, three large retrospective studies suggest a significant benefit in the reproductive outcomes of women with adenomyosis following prolonged downregulation prior to frozen embryo transfer, in contrast to one retrospective analysis that showed an adverse impact of prolonged downregulation on pregnancy rates, and another retrospective study that showed no difference in outcomes (10 - 14). The true benefit of prolonged versus standard downregulation in this population remains imprecise.

Objective: We aim to determine whether modified downregulation prior to frozen thawed embryo transfer (FTET) improves the chance of clinical pregnancy in women with moderate and severe adenomyosis.

Methods

Trial design

The MODA Trial is a pragmatic, multi-site, randomised controlled trial of two parallel arms comparing prolonged downregulation with GnRH analogue for six weeks to standard

downregulation with GnRH analogue for one week prior to frozen-thawed embryo transfer, recruiting participants from fertility centres across the UK. Participants will be followed-up until six weeks after the pregnancy outcome is determined. The trial design is summarised in Figure 1.

Inclusion criteria

1. Couples who are undergoing a cycle of IVF/ICSI, where a cycle is defined as egg collection following ovarian stimulation.
2. The female partner is ≥18 and < 42 years of age.
3. The female partner has a BMI <30 kg/m^2.
4. Two out of three of the following criteria are met: AMH >5.4 pmol/L, FSH <8.9 IU/L, antral follicle count >4 (15).
5. Moderate or severe adenomyosis of the uterus diagnosed on ultrasound scan.
6. Both partners are willing and able to provide written informed consent.

Exclusion criteria

1. Concurrent and/or recent involvement in other research that is likely to interfere with the intervention within the previous 3 months of study enrolment.
2. Previous open or laparoscopic myomectomy
3. Uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids > 3 cm)
4. Untreated endometrial polyps
5. Untreated hydrosalpinges
6. Use of GnRH analogues within previous 3 months.
7. Severe male factor infertility (sperm count < 2 x 10^6/ml, use of surgically retrieved spermatozoa)
8. Couples who in the opinion of the researcher by virtue of language or learning impairment would be unable to give fully informed consent to the study.

Outcomes

The primary outcome of the study is clinical pregnancy, defined as a viable intrauterine pregnancy confirmed by ultrasound at greater than 6 weeks gestation.

Our secondary outcomes will include livebirth, pregnancy loss (biochemical pregnancy, miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication

reaction, frequency and severity of medication side effects, number of days to achieve optimal endometrial thickness.

Enrolment

Enrolment of participants will involve coordinated registration and allocation of participant trial numbers by the trial co-ordinator. All participants will be asked by a member of the research team to complete a written consent at least 24 hours after providing the trial's participant information sheet (PIS) (see model consent form in supplementary files). All consents will be recorded in the medical notes including signature from both partners undergoing the IVF/ICSI procedure. A member of the research team will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. No trial procedures will be conducted prior to the participant giving consent by signing the consent form.

Once consent has been granted a TVS will be performed by a member of the research team. The scan will be performed in a systematic fashion starting from the uterus in longitudinal plane with measurement of the endometrial thickness. The probe is then rotated to the transverse plane and the uterus scanned from the cervix to the fundus with any uterine pathologies noted and measured in 3 orthogonal planes. A 3D ultrasound volume is then obtained and saved starting with the uterus in longitudinal view making sure to include all uterine tissue in the 3D volume sweep. Any congenital or acquired uterine anomalies are diagnosed according to published diagnostic criteria. Adenomyosis is diagnosed according to a standardised diagnostic criteria (2) and graded for severity according to the number of

adenomyosis features present (assign a score of 1 for each of: i) asymmetrical myometrial thickening, ii) parallel shadowing, iii) myometrial cysts, iv) irregular endometrial-myometrial

junction, v) linear striations, vi) hyperechoic islands, vii) adenomyoma). Patients with four or more features of adenomyosis are considered to have moderate or severe adenomyosis (5). Videosonography for a period of 4 minutes will be performed to assess uterine peristalsis. The operator will then sweep to the adnexae, starting from the left to identify and measure the ovaries in three orthogonal planes and document the antral follicle count. Each ovary is examined for the presence of cysts as well as for mobility and tenderness by gentle pressure with the ultrasound probe. Once the ovaries have been assessed the operator examines the pouch of Douglas for the presence of free fluid as well as any evidence of endometriosis such as obliteration, endometriotic nodules and endometriomas, as previously described (16). Once the ultrasound scan is concluded all information is added to the clinical database (RedCap, Vanderbilt University).

After the scan and once eligibility is confirmed participants will be asked to confirm if they want to participate in the trial. Those that confirm their consent will proceed with FTET preceded by the downregulation protocol allocated at randomisation. If an eligible participant undergoes a fresh transfer they will be followed through their cycle to determine pregnancy outcome and will be offered the opportunity to participate in MODA for their subsequent FTET.

Randomisation

Participants will be randomised using an online sequence generation and allocation system (www.sealedenvelope.com) in a ratio of 1:1, using stratified randomisation to adjust for age (age < 37, age ≥ 37), with permuted blocks of random sizes. The block sizes will not be disclosed

to ensure concealment. Randomisation will be performed by a member of the UCLH Reproductive Medicine Unit administration team, independent to the research team. Participants will be informed of their assigned treatment group and this will be recorded on the

Trial Subject Enrolment Log. The principal investigator (PI) will hold the randomisation list. It is not feasible to perform blinding in our setting.

Procedures

Standard downregulation protocol: Participants allocated to the standard downregulation protocol will start Norethisterone on day 14 of downregulation cycle and continue for 11 days, followed by Buserelin 0.5 ml subcutaneously from day 21. A baseline scan will be performed between days one to four of their bleed, Buserelin reduced to 0.2 ml and they will commence Progynova 2 mg three times daily orally. Serial scanning will be performed from day ten until an endometrial thickness of greater than 8mm is achieved, followed by luteal support with Cyclogest 400 mg twice daily vaginally or rectally and Lubion 25 mg twice daily subcutaneously. Blastocyst embryo transfer will be performed with a minimum morphological quality of B-C on the appropriate day for embryo age (Figure 2 and 3).

Modified downregulation protocol: Participants allocated to the modified downregulation protocol will have a baseline scan between days one and four of their bleed and will administer Leuprorelin acetate 3.75 mg subcutaneously, followed by Leuprorelin acetate 1.875 mg subcutaneously 28 days later. They will commence Progynova 2 mg three times daily orally 14 days later. Serial scanning will be performed from day ten until an endometrial thickness of greater than 8mm is achieved, followed by luteal support with Cyclogest 400 mg twice daily vaginally or rectally and Lubion 25 mg twice daily subcutaneously. Blastocyst embryo transfer

will be performed with a minimum morphological quality of B-C on the appropriate day for embryo age (Figure 2 and 3).

Discontinuation/withdrawal of participants:

In consenting to participate in the trial, participants are consenting to intervention, assessments, follow-up and data collection.

A participant may be withdrawn from the trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- Intercurrent illness
- Participants withdrawing consent
- Persistent non-compliance to protocol requirements.

The decision to withdraw a participant from treatment will be recorded in the electronic case report form (eCRF) and medical notes.

Patient and public involvement

Patients were involved as research partners in all aspects of the study including identifying the original research question, in revising study design, and in confirming acceptability of study monitoring methods and the intervention to be administered.

Modification of the protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study

design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the CI and research team. They will be approved by the Research Ethics Committee prior to implementation.

Data and trial management

Data will be collected on trial specific electronic case report forms (eCRFs). All eCRFs will be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF. The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679). Personal data will be held on the password protected database. We will adopt the NHS Code of Confidentiality and will allocate a unique participant identification number to ensure participant anonymity at data handling and analysis stage. Access to this will be restricted to the PI. Anonymised data will be stored for twenty years after completion of the trial, after which time data will be disposed of using confidential information trust destruction procedures.

MODA will have a Trial Management Group (TMG) that will include the Chief Investigator (CI) and trial staff to oversee the everyday trial's conduct (Table 3. Trial Personnel). The TMG will meet regularly four times a year to review recruitment figures, serious adverse events (SAEs) and substantial amendments to the protocol prior to submission to the REC. We will identify an independent Trial Steering Committee, which has overall responsibility for the conduct of the study. The study will be supervised on a day-to-day basis by the TMG, who will report to the Trial Steering Committe (TSC). We will also identify an independent Data Monitoring Committee (DMC) to provide advice on data management and safety aspects of the trial. The DMC will meet six monthly to review interim analyses, or as necessary to address any issues.

Recording and reporting of adverse events

Each adverse event will be assessed for severity, causality, seriousness and expectedness. All adverse events (AEs) will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All serious adverse events (SAEs) will be recorded in the medical records and the eCRF, and the sponsor's AE log. The AE log of SAEs will be reported to the sponsor at least twice per year. SAEs will be reported to the Sponsor within five days of becoming aware of the event.

Sample size

Our previous observational studies suggest a clinical pregnancy rate of 42.7% in women with mild adenomyosis compared to 22.9% with moderate/severe adenomyosis (7). We theorise that the modified protocol will improve the chance of clinical pregnancy to similar levels in those with mild disease. We need to randomise 162 patients over 3 years to achieve 80% power for detecting a 20% difference in the primary outcome across those groups at 5% significance.

Adenomyosis has an estimated prevalence of 20.9% in benign gynaecology patients (2), we estimate higher prevalence among women seeking assisted conception with a history of subfertility. Given our yearly 750 cycles of IVF/ICSI, we estimate a recruitment period of 3 years to achieve our target sample size.

Analysis

Participants with missing data and non-compliers, including participants who decide to withdraw from the study or do not follow their assigned protocol, will be excluded from our analysis. We will perform univariate and multivariate analyses to compare the primary outcome of both groups and report using risk ratio (RR) and 95% confidence intervals (CI) for

dichotomous outcomes as well as mean difference with standard deviation (SD) for continuous outcomes.

Ethics and dissemination

The findings of this study will be published in peer- reviewed journals and presented at national and international scientific meetings and congresses. No later than 3 years after the collection of the 6 weeks post pregnancy outcome data, we will deliver a completely deidentified data set to an appropriate data archive for sharing purposes. Ethical approval was granted by the NHS Research Ethics Committees (UK IRAS integrated research application system; reference 19/LO/1567). MODA is registered online with clinicaltrials.gov (NCT03946722). See table 1-3 for WHO trial registration data, protocol version history and trial personnel.

Discussion

Women with moderate/severe adenomyosis undergoing assisted conception are known to have a reduced clinical pregnancy rate; there is currently no consensus regarding their treatment and the existing literature is conflicting. Retrospective studies have identified benefit in prolonged downregulation for these patients however these are subject to selection and publication bias and therefore may not offer a realistic assessment of this protocol modification (10, 11, 12). Others have reported a reduction in pregnancy rates with prolonged downregulation but again this is retrospective data which may have underestimated the positive effect of the intervention (13).

One retrospective study showed increased clinical pregnancy rates in women with adenomyosis following GnRH agonist treatment for 2-3 months prior to frozen embryo

transfer, whereas no benefit was noted in women who had prolonged downregulation prior to fresh embryo transfer (11). The hyperoestrogenic state following controlled ovarian stimulation in a fresh embryo transfer cycle is postulated to diminish the effect of GnRH agonist pre-treatment. A higher dose and longer duration of gonadotrophins were required during controlled ovarian stimulation to overcome the prolonged downregulation effect (11). Another retrospective study in which women with adenomyosis received 3 months downregulation with GnRH analogue prior to fresh embryo transfer found a reduction in clinical pregnancy rates, with a significantly lower endometrial thickness in the pre-treatment group that did not fall pregnant (13). However, prolonged downregulation for a less extended duration of 6 weeks prior to frozen thawed embryo transfer has previously shown improved clinical pregnancy rates, without any negative effects on endometrial preparation (10). We are therefore evaluating a similar protocol in the MODA trial.

Co-existing undiagnosed endometriosis is a substantial confounding factor, as not all patients with adenomyosis undergo surgical diagnostic procedures. There is also potential for variability in the diagnosis of adenomyosis by ultrasound. In the MODA trial we have only included fertility centres with an expert ultrasound operator and will review ultrasound images to ensure quality of diagnosis. This approach should also reduce the risk of undiagnosed moderate or severe endometriosis as this can be reliably diagnosed on transvaginal ultrasound. Randomization should ensure confounding due to endometriosis coexistence is balanced. We will report the frequency of ultrasound diagnosed endometriosis in the control and treatment arm of the study.

There is an urgent need to prospectively evaluate prolonged downregulation as an option for couples with adenomyosis undergoing assisted conception both to confirm or refute the validity of this approach. The MODA trial is designed to offer pragmatic, real-life

evaluation of the optimal use of downregulation in affected women. Our modified downregulation protocol is a practical, simple and readily available treatment option that could help women with adenomyosis to improve their chances of conception.

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Author Statement

DM conceived of the study. SL, BW, NB, TL, ES, EY, PS and DM initiated and revised the study design, drafted and revised the manuscript critically and contributed to refinement of the study protocol. SL, BW, NB, TL, ES, EY, PS and DM approved the final manuscript and are in agreement to be accountable for all aspects of the work.

Conflict of Interests

The authors have no conflicts of interest to declare.

Figure and table legends

Figure 1. MODA trial study design

Figure 2. Standard and modified downregulation protocol overview

Figure 3. Standard and modified downregulation protocol daily schedule

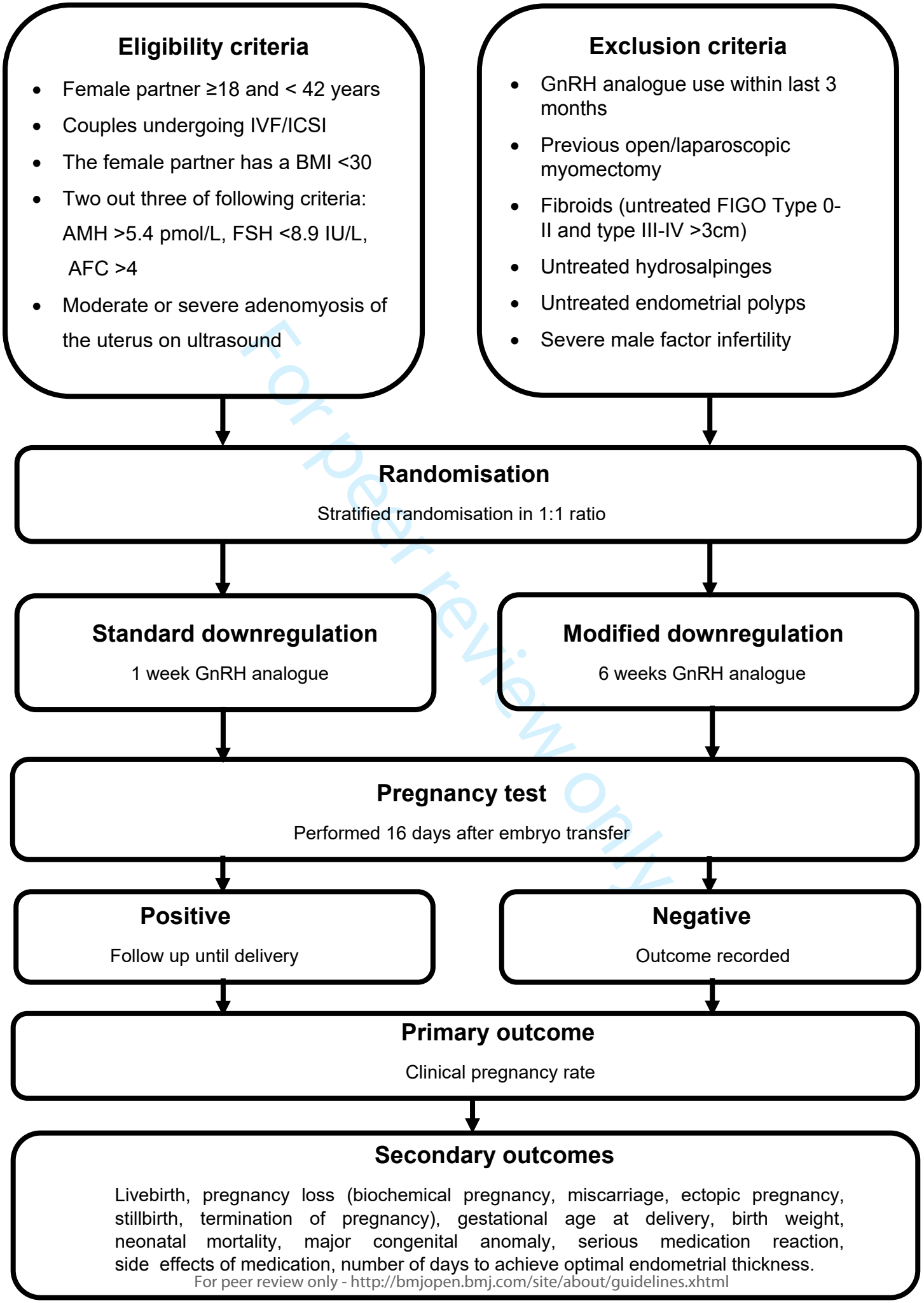
Table 1. WHO Trial Registration Data

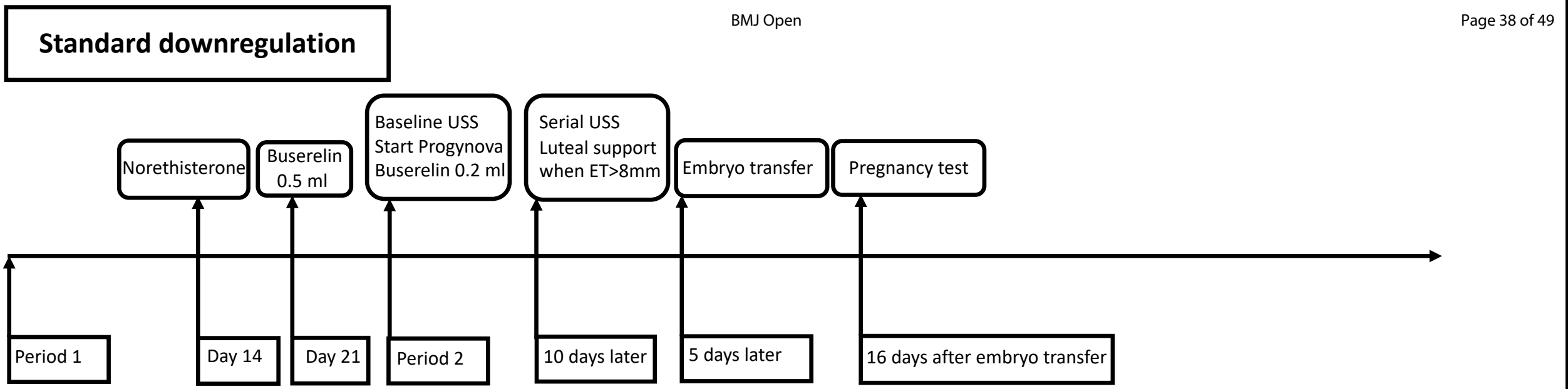
Table 2. Protocol Version History

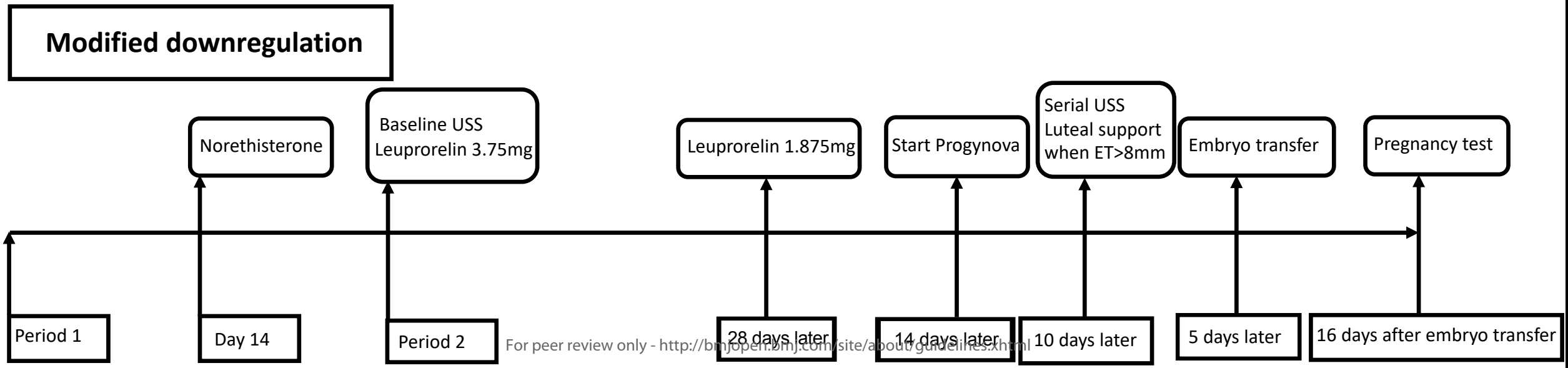
Table 3. Trial Personnel

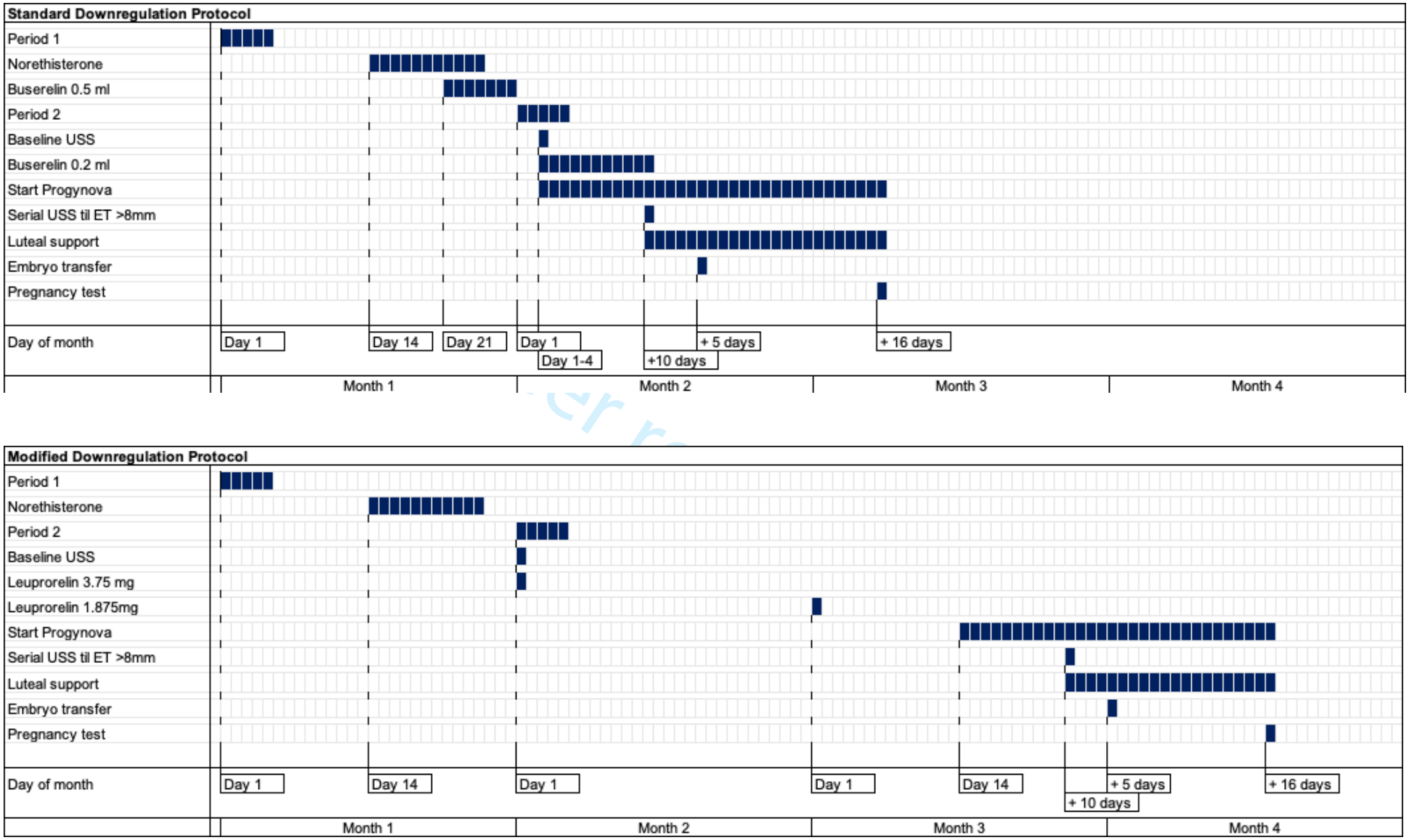
Word Count 3723

MODA Trial








Standard Downregulation Protocol
Period 1
Norethisterone
Buserelin 0.5 ml
Period 2
Baseline USS
Buserelin 0.2 ml
Start Progynova
Serial USS til ET >8mm
Luteal support
Embryo transfer
Pregnancy test
Day of month
Day 1
Day 14
Day 21
Day 1
Day 1-4
+10 days
+ 5 days
+ 16 days
Month 1
Month 2
Month 3
Month 4
Modified Downregulation Protocol
Period 1
Norethisterone
Period 2
Baseline USS
Leuprorelin 3.75 mg
Leuprorelin 1.875mg
Start Progynova
Serial USS til ET >8mm
Luteal support
Embryo transfer
Pregnancy test
Day of month
Day 1
Day 14
Day 1
Day 1
Day 14
+ 10 days
+ 5 days
+ 16 days
Month 1
Month 2
Month 3
Month 4

University College London Hospitals NHS
NHS Foundation Trust

CONSENT FORM

Centre number: ……101……

Study number: …….245873……...

Patient trial ID number: ….……

Title of project: Modified downregulation before embryo transfer for women with moderate or severe adenomyosis.

Please tick box.

1. I confirm that I have read and understand the information sheet dated for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily. ☐

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

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from University College Hospital NHS Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

6. I agree to my GP being informed that I am taking part in this study. ☐

7. I agree to my medical records being accessed by the research team to obtain information relevant to this research study. ☐

Name of Patient	Date	Signature
Name of Partner	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 22

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be	7

		collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13, 14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A