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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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**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	13 <sup>th</sup> 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: $\geq 18$ 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 <sup>6</sup> /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.

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For peer review only

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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

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2  
3 adenomyosis (8). It is also possible that prolonged downregulation may improve abnormal  
4 uterine peristalsis seen in women with adenomyosis. Two retrospective studies suggested a  
5 significant benefit in the reproductive outcomes with prolonged downregulation prior to  
6 frozen embryo transfer, in contrast to one retrospective analysis that showed an  
7 adverse impact of prolonged downregulation on pregnancy rates (9, 10, 11).  
8 Therefore, the true benefit of prolonged versus standard downregulation remains  
9 imprecise in this population.  
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23 **Objective:** We aim to determine whether modified downregulation prior to frozen thawed  
24 embryo transfer (FTET) improves the chance of clinical pregnancy in women with moderate  
25 and severe adenomyosis.  
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## 33 **Methods**

### 34 *Trial design*

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

- 55 1. Couples who are undergoing a cycle of IVF/ICSI, where a cycle is defined as egg collection  
56 following ovarian stimulation.  
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- 3 2. The female partner is  $\geq 18$  and  $< 42$  years of age.
- 4
- 5 3. The female partner has a BMI  $< 30$ .
- 6 4. Two out of three of the following criteria are met: AMH  $> 5.4$ , FSH  $< 8.9$ , antral follicle count
- 7  $> 4$ .
- 8
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- 10
- 11 5. Moderate or severe adenomyosis of the uterus diagnosed on ultrasound scan.
- 12
- 13 6. Both partners are willing and able to provide written informed consent.
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#### *Exclusion criteria*

- 17
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- 21 1. Concurrent and/or recent involvement in other research that is likely to interfere with the
- 22 intervention within the previous 3 months of study enrolment.
- 23
- 24
- 25 2. Previous open or laparoscopic myomectomy
- 26
- 27 3. Uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids  $> 3$  cm)
- 28
- 29 4. Use of GnRH analogues within previous 3 months.
- 30
- 31 5. Severe male factor infertility (sperm count  $< 2 \times 10^6$ /ml, use of surgically retrieved
- 32 spermatozoa)
- 33
- 34 6. Couples who in the opinion of the researcher by virtue of language or learning impairment
- 35 would be unable to give fully informed consent to the study.
- 36
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#### *Outcomes*

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44  
45 The primary outcome of the study is clinical pregnancy, defined as a viable intrauterine  
46 pregnancy confirmed by ultrasound at greater than 6 weeks gestation.  
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53 Our secondary outcomes will include livebirth, pregnancy loss (biochemical pregnancy,  
54 miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at  
55 delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication  
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3 reaction, number of frozen embryos available for transfer, number of days to achieve optimal  
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5 endometrial thickness.  
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### 8 *Enrolment* 9

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12 Enrolment of participants will involve coordinated registration and allocation of participant  
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14 trial numbers by the trial co-ordinator. All participants will be asked by a member of the  
15  
16 research team to complete a written consent at least 24 hours after providing the trial's  
17  
18 participant information sheet (PIS). All consents will be recorded in the medical notes  
19  
20 including signature from both partners undergoing the IVF/ICSI procedure. A member of the  
21  
22 research team will explain that participants are under no obligation to enter the trial and that  
23  
24 they can withdraw at any time during the trial, without having to give a reason. No trial  
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26 procedures will be conducted prior to the participant giving consent by signing the consent  
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28 form.  
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34 Once consent has been granted a TVS will be performed by a member of the research team.  
35  
36 The scan will be performed in a systematic fashion starting from the uterus in longitudinal  
37  
38 plane with measurement of the endometrial thickness. The probe is then rotated to  
39  
40 the transverse plane and the uterus scanned from the cervix to the fundus with any  
41  
42 uterine pathologies noted and measured in 3 orthogonal planes. A 3D ultrasound volume  
43  
44 is then obtained and saved starting with the uterus in longitudinal view making sure to  
45  
46 include all uterine tissue in the 3D volume sweep. Any congenital or acquired uterine  
47  
48 anomalies are diagnosed according to published diagnostic criteria. Adenomyosis is  
49  
50 diagnosed according to a standardised diagnostic criteria (2) and graded for severity  
51  
52 according to the number of adenomyosis features present (assign a score of 1 for each  
53  
54 of: i) asymmetrical myometrial thickening, ii) parallel shadowing, iii) myometrial cysts, iv)  
55  
56 irregular endometrial-myometrial  
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3 junction, v) linear striations, vi) hyperechoic islands, vii) adenomyoma). Patients with four or  
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5 more features of adenomyosis are considered to have moderate or severe adenomyosis (5).  
6  
7 Videosonography for a period of 5 minutes will be performed to assess uterine peristalsis. The  
8  
9 operator will then sweep to the adnexae, starting from the left to identify and measure the  
10  
11 ovaries in three orthogonal planes and document the antral follicle count. Each ovary is  
12  
13 examined for the presence of cysts as well as for mobility and tenderness by gentle pressure  
14  
15 with the ultrasound probe. Once the ovaries have been assessed the operator examines the  
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17 pouch of Douglas for the presence of free fluid as well as any evidence of endometriosis such  
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19 as obliteration, endometriotic nodules and endometriomas, as previously described (12).  
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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](http://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

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3 Trial Subject Enrolment Log. The principal investigator (PI) will hold the randomisation list.  
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5 It is not feasible to perform blinding in our setting.  
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### 10 11 *Procedures*

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14 *Standard downregulation protocol:* Participants allocated to the standard downregulation  
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16 protocol will start Norethisterone on day 14 of downregulation cycle and continue for 11 days,  
17  
18 followed by Buserelin 0.5ml subcutaneously from day 21. A baseline scan will be performed  
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20 between days one to four of their bleed, Buserelin reduced to 0.2ml and they will commence  
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22 Progynova 2mg three times daily orally. Serial scanning will be performed from day ten until  
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24 an endometrial thickness of greater than 8mm is achieved, followed by luteal support with  
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26 Cyclogest 400mg twice daily vaginally or rectally and Lubion 25mg twice daily  
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28 subcutaneously. Embryo transfer will be performed on the appropriate day for embryo age  
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30 (Figure 2 and 3).  
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37 *Modified downregulation protocol:* Participants allocated to the modified downregulation  
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39 protocol will have a baseline scan between days one and four of their bleed and will  
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41 administer Leuprorelin acetate 3.75 mg subcutaneously, followed by Leuprorelin acetate  
42  
43 1.875 mg subcutaneously 28 days later. They will commence Progynova 2mg three times  
44  
45 daily orally 14 days later. Serial scanning will be performed from day ten until an  
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47 endometrial thickness of greater than 8mm is achieved, followed by luteal support with  
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49 Cyclogest 400mg twice daily vaginally or rectally and Lubion 25mg twice daily  
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51 subcutaneously. Embryo transfer will be performed on the appropriate day for embryo age  
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53 (Figure 2 and 3).  
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3 *Discontinuation/withdrawal of participants:*

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5 In consenting to participate in the trial, participants are consenting to intervention,  
6 assessments, follow-up and data collection.  
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11 A participant may be withdrawn from the trial whenever continued participation is no longer  
12 in the participant's best interests, but the reasons for doing so must be recorded. Reasons for  
13 discontinuing the trial may include:  
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18 • Intercurrent illness  
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20 • Participants withdrawing consent  
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22 • Persistent non-compliance to protocol requirements.  
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25 The decision to withdraw a participant from treatment will be recorded in the electronic case  
26 report form (eCRF) and medical notes.  
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32 *Patient and public involvement*

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

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

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

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23 Our previous observational studies suggest a clinical pregnancy rate of 22.9% in women with  
24 mild adenomyosis compared to 42.7% with moderate/severe adenomyosis (7). We theorise that  
25 the modified protocol will improve the chance of clinical pregnancy to similar levels in those  
26 with mild disease. We need to randomise 162 patients over 3 years to achieve 80% power for  
27 detecting a 20% difference in the primary outcome across those groups at 5% significance.  
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37 Adenomyosis has an estimated prevalence of 20.9% in benign gynaecology patients (2), we  
38 estimate higher prevalence among women seeking assisted conception with history of  
39 subfertility. Given our yearly 750 cycles of IVF/ICSI, we estimate a recruitment period of 3  
40 years to achieve our target sample size.  
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### 49 *Analysis*

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51 Participants with missing data and non-compliers, including participants who decide to  
52 withdraw from the study or do not follow their assigned protocol, will be excluded from our  
53 analysis. We will perform univariate and multivariate analyses to compare the primary outcome  
54 of both groups and report using risk ratio (RR) and 95% confidence intervals (CI) for  
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3 dichotomous outcomes as well as mean difference with standard deviation (SD) for continuous  
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5 outcomes.  
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## 10 **Discussion**

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14 Women with moderate/severe adenomyosis undergoing assisted conception are known to have  
15  
16 a reduced clinical pregnancy rate; there is currently no consensus regarding their treatment.  
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18 Retrospective studies have identified benefit in prolonged downregulation for these patients  
19  
20 however these are subject to selection and publication bias and therefore may not offer a  
21  
22 realistic assessment of this protocol modification. Others have reported a reduction in  
23  
24 pregnancy rates with prolonged downregulation but again this is retrospective data which  
25  
26 may have underestimated the positive effect of the intervention. There is an urgent  
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28 need to prospectively evaluate prolonged downregulation as an option for couples with  
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30 adenomyosis undergoing assisted conception both to confirm or refute the validity of this  
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32 approach.  
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38 MODA is designed to offer pragmatic, real-life evaluation of the optimal use of downregulation  
39  
40 in affected women. Our modified downregulation protocol is a practical, simple and readily  
41  
42 available treatment option that could help women with adenomyosis to improve their chances of  
43  
44 conception. The findings of this study will be published in peer- reviewed journals and  
45  
46 presented at national and international scientific meetings and congresses. No later than 3 years  
47  
48 after the collection of the 6 weeks post pregnancy outcome data, we will deliver a completely  
49  
50 deidentified data set to an appropriate data archive for sharing purposes. Ethical approval was  
51  
52 granted by the NHS Research Ethics Committees (UK IRAS integrated research application  
53  
54 system; reference 19/LO/1567). MODA is registered online with clinicaltrials.gov  
55  
56 (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**

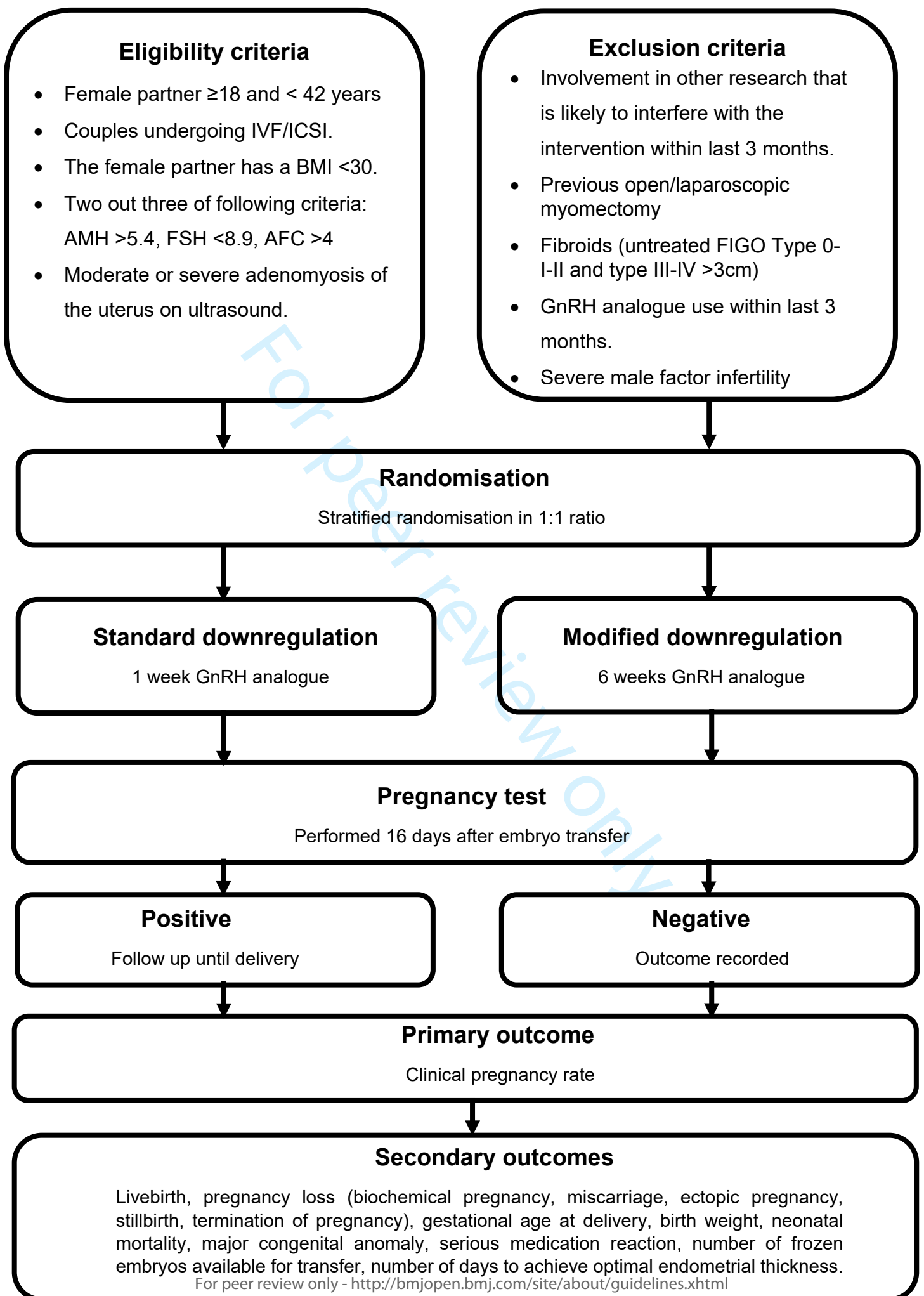
The authors have no conflicts of interest to declare.

**Word Count** 3349

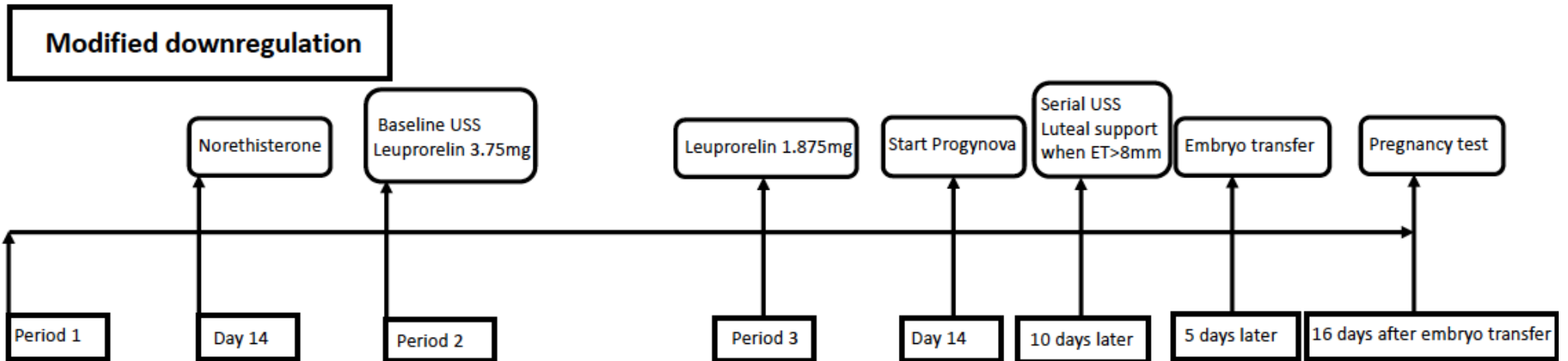
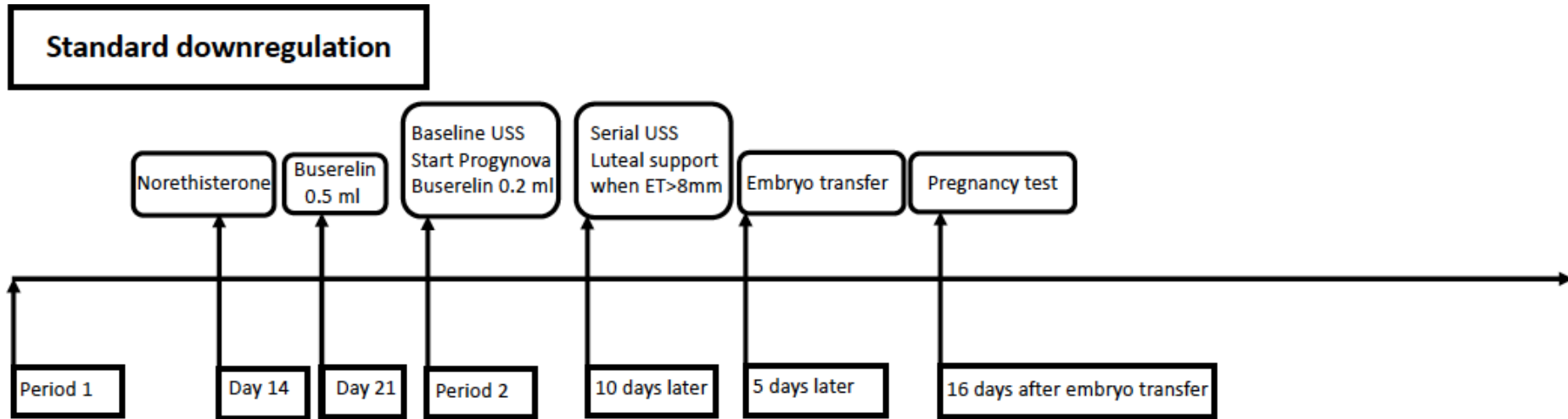
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For peer review only

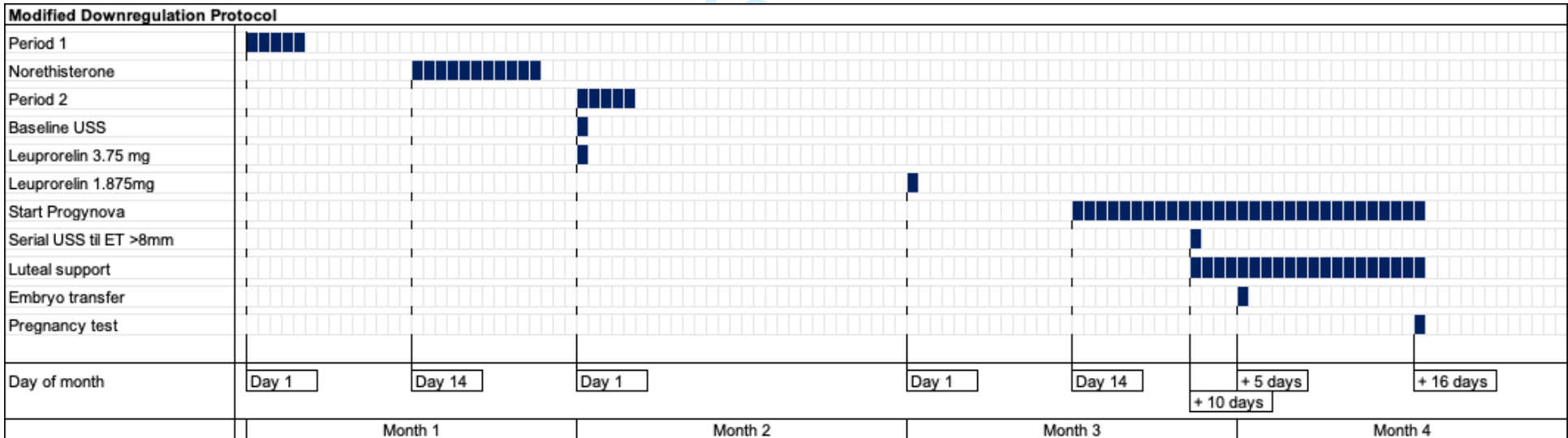
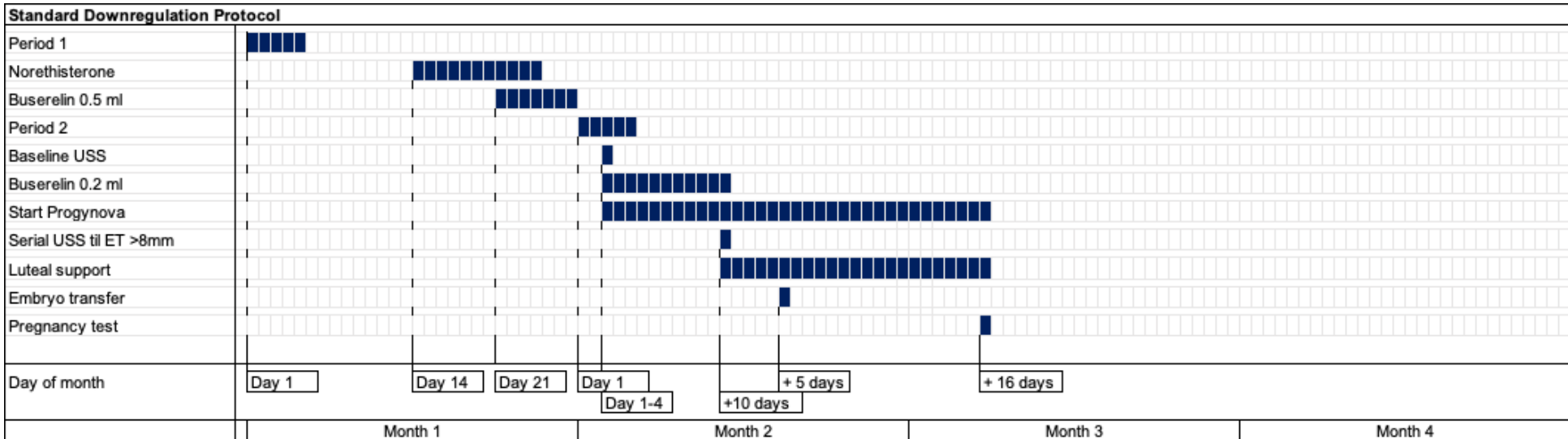




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# Reporting checklist for protocol of a clinical trial.

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

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	3
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	22
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	17
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	6-7
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	7
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
38				
39				
40	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	7
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46	<b>Methods:</b>			
47	<b>Participants,</b>			
48	<b>interventions, and</b>			
49	<b>outcomes</b>			
50				
51				
52				
53	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	7
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
56				
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1	Eligibility criteria	<a href="#">#10</a>	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
2				
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5				
6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11
7	description			
8				
9				
10	Interventions:	<a href="#">#11b</a>	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
11	modifications			
12				
13				
14				
15	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
16	adherence			
17				
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20	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
21	concomitant care			
22				
23				
24	Outcomes	<a href="#">#12</a>	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
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34	Participant timeline	<a href="#">#13</a>	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
35				
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40	Sample size	<a href="#">#14</a>	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
41				
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44				
45	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
46				
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48				
49	<b>Methods: Assignment</b>			
50	<b>of interventions (for</b>			
51	<b>controlled trials)</b>			
52				
53				
54	Allocation: sequence	<a href="#">#16a</a>	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
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
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10			
11	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol
12	implementation		participants, and who will assign participants to interventions
13			
14	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial
15			participants, care providers, outcome assessors, data analysts),
16			and how
17			
18			
19			
20	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible,
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	<b>Methods: Data</b>		
26	<b>collection,</b>		
27	<b>management, and</b>		
28	<b>analysis</b>		
29			
30			
31			
32	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
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43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any
49			related processes to promote data quality (eg, double data entry;
50			range checks for data values). Reference to where details of data
51			management procedures can be found, if not in the protocol
52			
53			
54			
55	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
58			
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1	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	16
2	analyses		analyses)	
3				
4	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	16
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
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9				
10	<b>Methods: Monitoring</b>			
11				
12	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of	15
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
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22	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	15
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
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27	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	15
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
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33	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	15
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
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38	<b>Ethics and</b>			
39	<b>dissemination</b>			
40				
41				
42	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	17
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	17
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
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53	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	9
54			participants or authorised surrogates, and how (see Item 32)	
55				
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
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6	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	15
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators	21
12			for the overall trial and each study site	
13				
14				
15	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and	15
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results	18
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
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32				
33	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	N/A
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	18
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	<b>Appendices</b>			
42				
43	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given to	N/A
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
50				
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# 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.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050248.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Jul-2021
Complete List of Authors:	Latif, Sania; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Wattar, Bassel H.AI; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Balachandren, Neerujah; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Lukaszewski, Tomasz; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Saridogan, Ertan; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Yasmin, Ephia; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Serhal, Paul; Centre for Reproductive and Genetic Health Mavrelou, Dimitrios; University College London, Institute of Women's Health
<b>Primary Subject Heading</b>:	Reproductive medicine
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Reproductive medicine < GYNAECOLOGY, Subfertility < GYNAECOLOGY, REPRODUCTIVE MEDICINE

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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<sup>1</sup>, Bassel H. Al Wattar<sup>1</sup>, Neerujah Balachandren<sup>1</sup>, Tomasz Lukaszewski<sup>1</sup>, Ertan Saridogan<sup>1</sup>, Ephraim Yasmin<sup>1</sup>, Paul Serhal<sup>2</sup>, Dimitrios Mavrelou<sup>1</sup>

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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	13 <sup>th</sup> May 2019
Source of monetary or material support	Dimitrios Mavrellos (CI)
Primary sponsor	University College London
Contact for public queries	DM, SL (dimitrios.mavrellos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Contact for scientific queries	DM, SL (dimitrios.mavrellos@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: $\geq 18$ years <42 years Sexes eligible for study: female Accepts healthy volunteers: no

Data category	Information
	<p>Inclusion criteria: Women with moderate/severe adenomyosis undergoing IVF treatment, BMI &lt; 30 kg/m<sup>2</sup>, two out of three of the following criteria are met: AMH &gt; 5.4 pmol/L, FSH &lt; 8.9 IU/L, antral follicle count &gt; 4.</p> <p>Exclusion criteria: Previous open or laparoscopic myomectomy, uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids &gt; 3 cm), untreated endometrial polyps, untreated hydrosalpinges, use of GnRH analogues within previous 3 months, severe male factor infertility (sperm count &lt; 2 x 10<sup>6</sup>/ml, use of surgically retrieved spermatozoa)</p>
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	<p>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, <del>number of frozen embryos available for transfer</del>, number of days to achieve optimal endometrial thickness.</p>

### 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.

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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

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3 adenomyosis (8). It is also possible that prolonged downregulation may improve abnormal  
4 uterine peristalsis seen in women with adenomyosis. A study examining the impact of  
5 prolonged downregulation in women with adenomyosis undergoing IVF treatment first showed  
6 increased clinical pregnancy rates a decade ago (9). More recently, three large retrospective  
7 studies suggest a significant benefit in the reproductive outcomes with prolonged  
8 downregulation prior to frozen embryo transfer, in contrast to one retrospective analysis  
9 that showed an adverse impact of prolonged downregulation on pregnancy rates, and  
10 another retrospective study that showed no difference in outcomes (10 - 14). The true benefit  
11 of prolonged versus standard downregulation remains imprecise in this population.  
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27 **Objective:** We aim to determine whether modified downregulation prior to frozen thawed  
28 embryo transfer (FTET) improves the chance of clinical pregnancy in women with moderate  
29 and severe adenomyosis.  
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## 37 **Methods**

### 38 *Trial design*

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

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- 3 1. Couples who are undergoing a cycle of IVF/ICSI, where a cycle is defined as egg collection
- 4 following ovarian stimulation.
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- 7 2. The female partner is  $\geq 18$  and  $< 42$  years of age.
- 8
- 9 3. The female partner has a BMI  $< 30$  kg/m<sup>2</sup>.
- 10
- 11 4. Two out of three of the following criteria are met: AMH  $> 5.4$  pmol/L, FSH  $< 8.9$  iU, antral
- 12 follicle count  $> 4$  (15).
- 13
- 14 5. Moderate or severe adenomyosis of the uterus diagnosed on ultrasound scan.
- 15
- 16 6. Both partners are willing and able to provide written informed consent.
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#### 20 *Exclusion criteria*

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

51  
52 The primary outcome of the study is clinical pregnancy, defined as a viable intrauterine  
53 pregnancy confirmed by ultrasound at greater than 6 weeks gestation.  
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3 Our secondary outcomes will include livebirth, pregnancy loss (biochemical pregnancy,  
4 miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at  
5 delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication  
6 reaction, frequency and severity of medication side effects , ~~number of frozen embryos~~  
7 available for transfer, number of days to achieve optimal endometrial thickness.  
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### 15 *Enrolment*

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19 Enrolment of participants will involve coordinated registration and allocation of participant  
20 trial numbers by the trial co-ordinator. All participants will be asked by a member of the  
21 research team to complete a written consent at least 24 hours after providing the trial's  
22 participant information sheet (PIS) (see model consent form in supplementary files). All  
23 consents will be recorded in the medical notes including signature from both partners  
24 undergoing the IVF/ICSI procedure. A member of the research team will explain that  
25 participants are under no obligation to enter the trial and that they can withdraw at any time  
26 during the trial, without having to give a reason. No trial procedures will be conducted prior to  
27 the participant giving consent by signing the consent form.  
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41 Once consent has been granted a TVS will be performed by a member of the research team.  
42 The scan will be performed in a systematic fashion starting from the uterus in longitudinal  
43 plane with measurement of the endometrial thickness. The probe is then rotated to the  
44 transverse plane and the uterus scanned from the cervix to the fundus with any uterine  
45 pathologies noted and measured in 3 orthogonal planes. A 3D ultrasound volume is then  
46 obtained and saved starting with the uterus in longitudinal view making sure to include all  
47 uterine tissue in the 3D volume sweep. Any congenital or acquired uterine anomalies are  
48 diagnosed according to published diagnostic criteria. Adenomyosis is diagnosed according to  
49 a standardised diagnostic criteria (2) and graded for severity according to the number of  
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3 adenomyosis features present (assign a score of 1 for each of: i) asymmetrical myometrial  
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5 thickening, ii) parallel shadowing, iii) myometrial cysts, iv) irregular endometrial-myometrial  
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3 junction, v) linear striations, vi) hyperechoic islands, vii) adenomyoma). Patients with four or  
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5 more features of adenomyosis are considered to have moderate or severe adenomyosis (5).  
6  
7 Videosonography for a period of 4 minutes will be performed to assess uterine peristalsis. The  
8  
9 operator will then sweep to the adnexae, starting from the left to identify and measure the  
10  
11 ovaries in three orthogonal planes and document the antral follicle count. Each ovary is  
12  
13 examined for the presence of cysts as well as for mobility and tenderness by gentle pressure  
14  
15 with the ultrasound probe. Once the ovaries have been assessed the operator examines the pouch  
16  
17 of Douglas for the presence of free fluid as well as any evidence of endometriosis such as  
18  
19 obliteration, endometriotic nodules and endometriomas, as previously described (16). Once the  
20  
21 ultrasound scan is concluded all information is added to the clinical database (RedCap,  
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26 Vanderbilt University).

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29 After the scan and once eligibility is confirmed participants will be asked to confirm if  
30  
31 they want to participate in the trial. Those that confirm their consent will proceed with  
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33 FTET preceded by the downregulation protocol allocated at randomisation. If an  
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35 eligible participant undergoes a fresh transfer they will be followed through their cycle to  
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37 determine pregnancy outcome and will be offered the opportunity to participate in MODA for  
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39 their subsequent FTET.  
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#### 47 *Randomisation*

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49 Participants will be randomised using an online sequence generation and allocation system  
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51 (www.sealedenvelope.com) in a ratio of 1:1, using stratified randomisation to adjust for age  
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53 (age < 37, age ≥ 37), with permuted blocks of random sizes. The block sizes will not be disclosed  
54  
55 to ensure concealment. Randomisation will be performed by a member of the UCLH  
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57 Reproductive Medicine Unit administration team, independent to the research team. Participants  
58  
59 will be informed of their assigned treatment group and this will be recorded on the  
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3 Trial Subject Enrolment Log. The principal investigator (PI) will hold the randomisation list.  
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5 It is not feasible to perform blinding in our setting.  
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### 10 11 *Procedures*

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14 *Standard downregulation protocol:* Participants allocated to the standard downregulation  
15 protocol will start Norethisterone on day 14 of downregulation cycle and continue for 11 days,  
16 followed by Buserelin 0.5ml subcutaneously from day 21. A baseline scan will be performed  
17 between days one to four of their bleed, Buserelin reduced to 0.2ml and they will commence  
18 Progynova 2mg three times daily orally. Serial scanning will be performed from day ten until  
19 an endometrial thickness of greater than 8mm is achieved, followed by luteal support with  
20 Cyclogest 400mg twice daily vaginally or rectally and Lubion 25mg twice daily  
21 subcutaneously. Blastocyst embryo transfer will be performed with a minimum morphological  
22 quality of B-C on the appropriate day for embryo age (Figure 2 and 3).  
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36 *Modified downregulation protocol:* Participants allocated to the modified downregulation  
37 protocol will have a baseline scan between days one and four of their bleed and will administer  
38 Leuprorelin acetate 3.75 mg subcutaneously, followed by Leuprorelin acetate 1.875 mg  
39 subcutaneously 28 days later. They will commence Progynova 2mg three times daily orally 14  
40 days later. Serial scanning will be performed from day ten until an endometrial thickness of  
41 greater than 8mm is achieved, followed by luteal support with Cyclogest 400mg twice daily  
42 vaginally or rectally and Lubion 25mg twice daily subcutaneously. Blastocyst embryo transfer  
43 will be performed with a minimum morphological quality of B-C on the appropriate day for  
44 embryo age (Figure 2 and 3).  
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3 *Discontinuation/withdrawal of participants:*  
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5 In consenting to participate in the trial, participants are consenting to intervention,  
6 assessments, follow-up and data collection.  
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11 A participant may be withdrawn from the trial whenever continued participation is no longer  
12 in the participant's best interests, but the reasons for doing so must be recorded. Reasons for  
13 discontinuing the trial may include:  
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18 • Intercurrent illness  
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20 • Participants withdrawing consent  
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23 • Persistent non-compliance to protocol requirements.  
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25 The decision to withdraw a participant from treatment will be recorded in the electronic case  
26 report form (eCRF) and medical notes.  
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32 *Patient and public involvement*  
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36 Patients were involved as research partners in all aspects of the study including identifying  
37 the original research question, in revising study design, and in confirming acceptability of  
38 study monitoring methods and the intervention to be administered.  
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46 *Modification of the protocol*  
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49 Any modifications to the protocol which may impact on the conduct of the study, potential  
50 benefit of the patient or may affect patient safety, including changes of study objectives, study  
51 design, patient population, sample sizes, study procedures, or significant administrative aspects  
52 will require a formal amendment to the protocol. Such amendment will be agreed upon by the  
53 CI and research team. They will be approved by the Research Ethics Committee prior to  
54 implementation.  
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### *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 Committee (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*

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3 Each adverse event will be assessed for severity, causality, seriousness and expectedness. All  
4  
5 adverse events (AEs) will be recorded with clinical symptoms and accompanied with a simple,  
6  
7 brief description of the event, including dates as appropriate. All serious adverse events (SAEs)  
8  
9 will be recorded in the medical records and the eCRF, and the sponsor's AE log. The AE log  
10  
11 of SAEs will be reported to the sponsor at least twice per year. SAEs will be reported to the  
12  
13 Sponsor within five days of becoming aware of the event.  
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### 20 *Sample size*

21  
22 Our previous observational studies suggest a clinical pregnancy rate of 42.7% in women with  
23  
24 mild adenomyosis compared to 22.9% with moderate/severe adenomyosis (7). We theorise that  
25  
26 the modified protocol will improve the chance of clinical pregnancy to similar levels in those  
27  
28 with mild disease. We need to randomise 162 patients over 3 years to achieve 80% power for  
29  
30 detecting a 20% difference in the primary outcome across those groups at 5% significance.  
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36 Adenomyosis has an estimated prevalence of 20.9% in benign gynaecology patients (2), we  
37  
38 estimate higher prevalence among women seeking assisted conception with history of  
39  
40 subfertility. Given our yearly 750 cycles of IVF/ICSI, we estimate a recruitment period of 3  
41  
42 years to achieve our target sample size.  
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### 49 *Analysis*

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51 Participants with missing data and non-compliers, including participants who decide to  
52  
53 withdraw from the study or do not follow their assigned protocol, will be excluded from our  
54  
55 analysis. We will perform univariate and multivariate analyses to compare the primary outcome  
56  
57 of both groups and report using risk ratio (RR) and 95% confidence intervals (CI) for  
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3 dichotomous outcomes as well as mean difference with standard deviation (SD) for continuous  
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5 outcomes.  
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## 10 **Discussion**

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14 Women with moderate/severe adenomyosis undergoing assisted conception are known to have  
15 a reduced clinical pregnancy rate; there is currently no consensus regarding their treatment.  
16 Retrospective studies have identified benefit in prolonged downregulation for these patients  
17 however these are subject to selection and publication bias and therefore may not offer a  
18 realistic assessment of this protocol modification. Others have reported a reduction in  
19 pregnancy rates with prolonged downregulation but again this is retrospective data which may  
20 have underestimated the positive effect of the intervention. Co-existing undiagnosed  
21 endometriosis is a substantial confounding factor, as not all patients with adenomyosis undergo  
22 surgical diagnostic procedures. There is also potential for variability in the diagnosis of  
23 adenomyosis by ultrasound. In the MODA trial we have only included fertility centres with an  
24 expert ultrasound operator and will review ultrasound images to ensure quality of diagnosis.  
25 This approach should also reduce the risk of undiagnosed moderate or severe endometriosis as  
26 this can be reliably diagnosed on transvaginal ultrasound. Randomization should ensure  
27 confounding due to endometriosis coexistence is balanced. We will report the frequency of  
28 ultrasound diagnosed endometriosis in the control and treatment arm of the study.  
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52 There is an urgent need to prospectively evaluate prolonged downregulation as an option for  
53 couples with adenomyosis undergoing assisted conception both to confirm or refute the validity  
54 of this approach. MODA is designed to offer pragmatic, real-life evaluation of the optimal use  
55 of downregulation in affected women. Our modified downregulation protocol is a practical,  
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3 simple and readily available treatment option that could help women with adenomyosis to  
4  
5 improve their chances of conception. The findings of this study will be published in peer-  
6  
7 reviewed journals and presented at national and international scientific meetings and  
8  
9 congresses. No later than 3 years after the collection of the 6 weeks post pregnancy outcome  
10  
11 data, we will deliver a completely deidentified data set to an appropriate data archive for  
12  
13 sharing purposes. Ethical approval was granted by the NHS Research Ethics Committees (UK  
14  
15 IRAS integrated research application system; reference 19/LO/1567). MODA is registered  
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17 online with [clinicaltrials.gov](http://clinicaltrials.gov) (NCT03946722).  
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5 accuracy? A multicentre diagnostic accuracy study. *BMC Womens Health*. 2013;13-43.  
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## 10 **Funding**

11  
12  
13 This research received no specific grant from any funding agency in the public, commercial or  
14 not-for-profit sectors.  
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## 18 **Author Statement**

19  
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21 DM conceived of the study. SL, BW, NB, TL, ES, EY, PS and DM initiated and revised the  
22 study design, drafted and revised the manuscript critically and contributed to refinement of the  
23 study protocol. SL, BW, NB, TL, ES, EY, PS and DM approved the final manuscript and are  
24 in agreement to be accountable for all aspects of the work.  
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## 35 **Conflict of Interests**

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37 The authors have no conflicts of interest to declare.  
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## 42 **Figure Legends**

43  
44 Figure 1. MODA trial study design

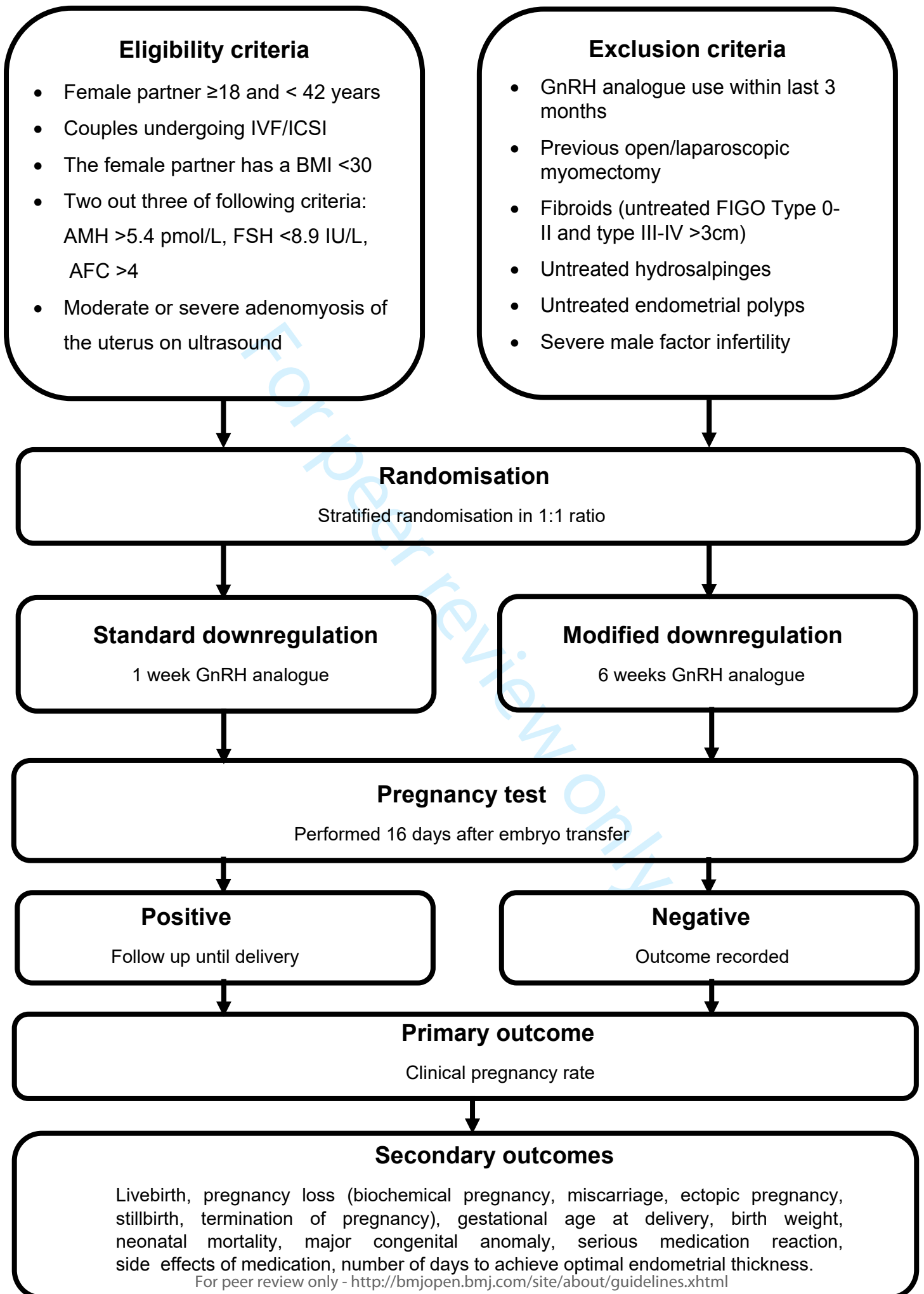
45  
46 Figure 2. Standard and modified downregulation protocol overview

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48 Figure 3. Standard and modified downregulation protocol daily schedule  
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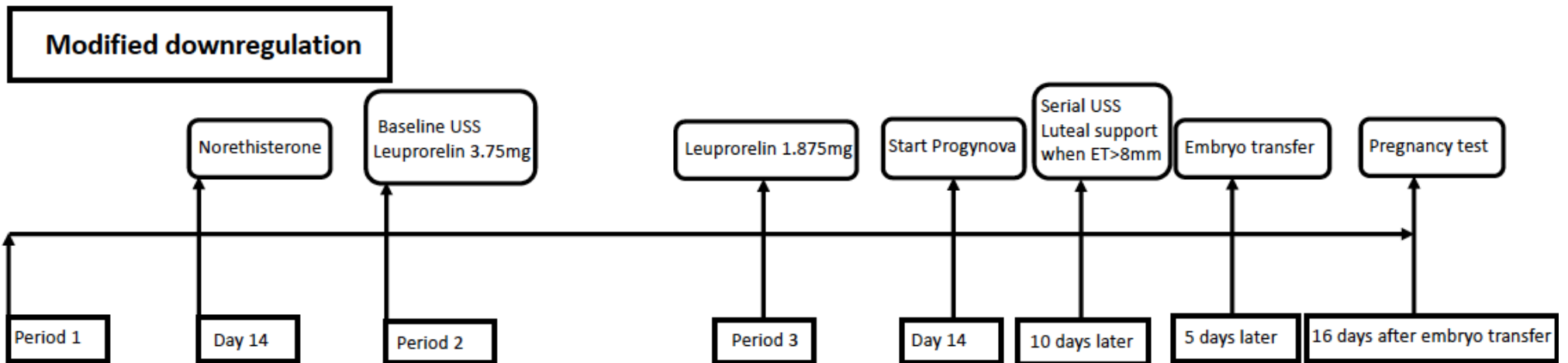
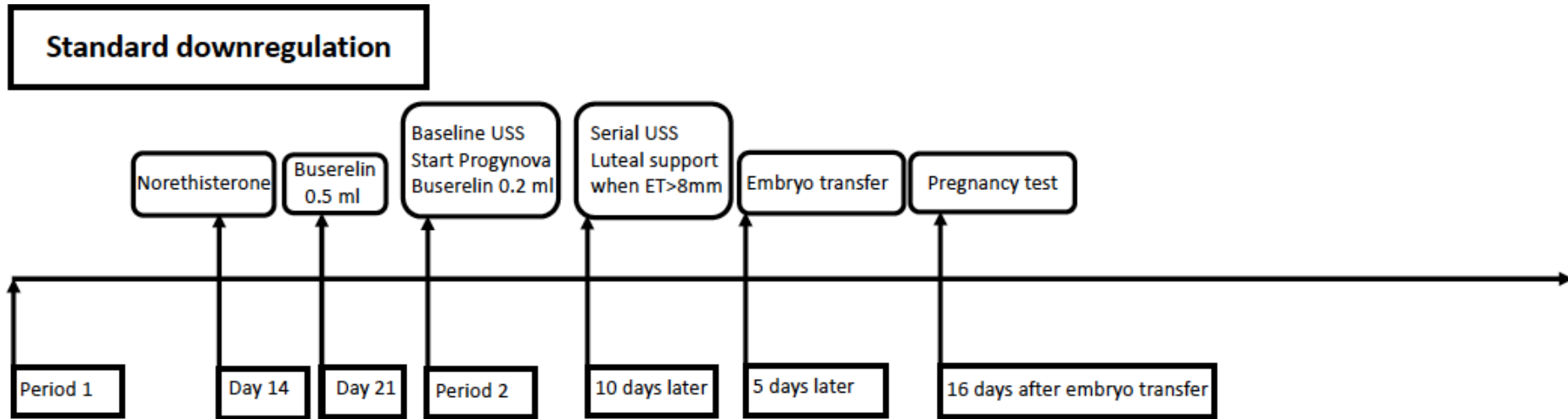
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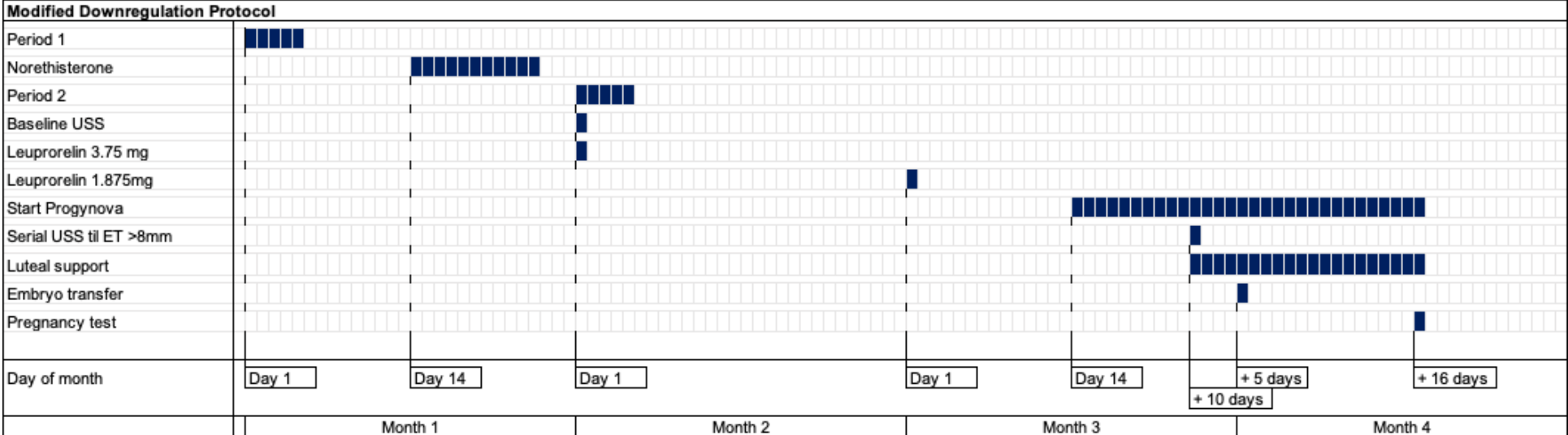
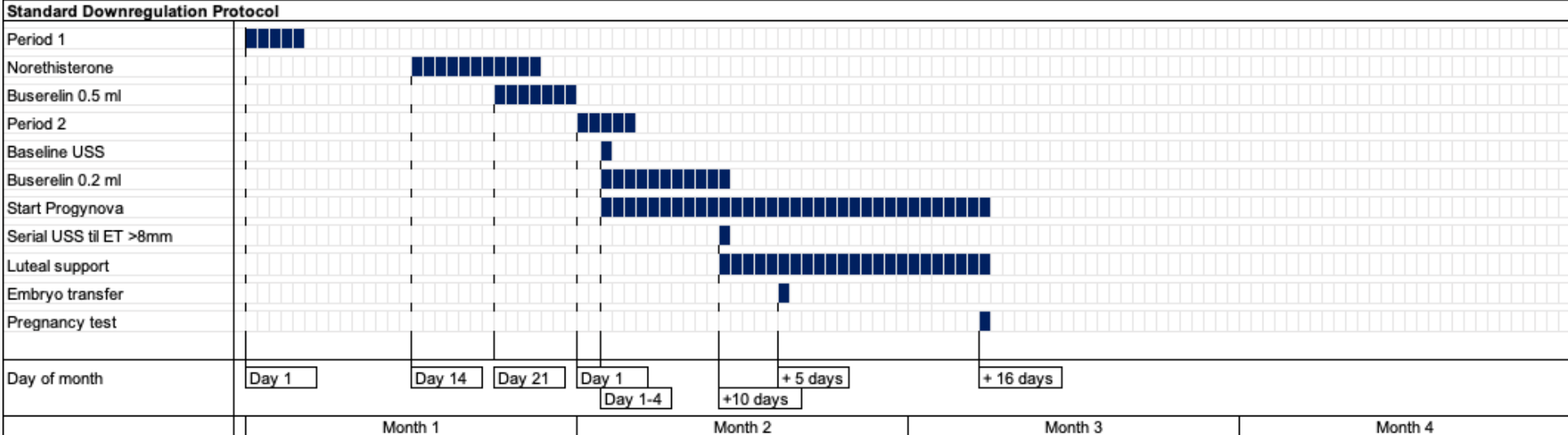
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# Reporting checklist for protocol of a clinical trial.

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

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	3
2	responsibilities:			
3	sponsor contact			
4	information			
5				
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8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	22
9	responsibilities:		collection, management, analysis, and interpretation of	
10	sponsor and funder		data; writing of the report; and the decision to submit the	
11			report for publication, including whether they will have	
12			ultimate authority over any of these activities	
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	17
17	responsibilities:		centre, steering committee, endpoint adjudication	
18	committees		committee, data management team, and other individuals	
19			or groups overseeing the trial, if applicable (see Item 21a	
20			for data monitoring committee)	
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23				
24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for	6-7
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
31				
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34	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	7
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
40				
41	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg,	7
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
45				
46				
47				
48	<b>Methods:</b>			
49	<b>Participants,</b>			
50	<b>interventions, and</b>			
51	<b>outcomes</b>			
52				
53				
54				
55	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	7
56			academic hospital) and list of countries where data will be	
57				
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1		collected. Reference to where list of study sites can be	
2		obtained	
3			
4	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If	7-8
5		applicable, eligibility criteria for study centres and	
6		individuals who will perform the interventions (eg,	
7		surgeons, psychotherapists)	
8			
9			
10			
11	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	11
12	description	replication, including how and when they will be	
13		administered	
14			
15			
16	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated	12
17	modifications	interventions for a given trial participant (eg, drug dose	
18		change in response to harms, participant request, or	
19		improving / worsening disease)	
20			
21			
22			
23	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols,	N/A
24	adherence	and any procedures for monitoring adherence (eg, drug	
25		tablet return; laboratory tests)	
26			
27			
28	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are	N/A
29	concomitant care	permitted or prohibited during the trial	
30			
31			
32	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the	8
33		specific measurement variable (eg, systolic blood	
34		pressure), analysis metric (eg, change from baseline, final	
35		value, time to event), method of aggregation (eg, median,	
36		proportion), and time point for each outcome. Explanation	
37		of the clinical relevance of chosen efficacy and harm	
38		outcomes is strongly recommended	
39			
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42			
43	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any	13, 14
44		run-ins and washouts), assessments, and visits for	
45		participants. A schematic diagram is highly recommended	
46		(see Figure)	
47			
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49			
50	Sample size	<a href="#">#14</a> Estimated number of participants needed to achieve study	16
51		objectives and how it was determined, including clinical	
52		and statistical assumptions supporting any sample size	
53		calculations	
54			
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57	Recruitment	<a href="#">#15</a> Strategies for achieving adequate participant enrolment to	N/A
58		reach target sample size	
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**Methods:****Assignment of interventions (for controlled trials)**

Allocation: sequence generation	<a href="#">#16a</a>	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	<a href="#">#16b</a>	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	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	<a href="#">#17b</a>	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	<a href="#">#18a</a>	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
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1	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete	15
2	retention		follow-up, including list of any outcome data to be	
3			collected for participants who discontinue or deviate from	
4			intervention protocols	
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8	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	15
9			including any related processes to promote data quality	
10			(eg, double data entry; range checks for data values).	
11			Reference to where details of data management procedures	
12			can be found, if not in the protocol	
13				
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16	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	16
17			outcomes. Reference to where other details of the	
18			statistical analysis plan can be found, if not in the protocol	
19				
20				
21	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and	16
22	analyses		adjusted analyses)	
23				
24				
25	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	16
26	population and		adherence (eg, as randomised analysis), and any statistical	
27	missing data		methods to handle missing data (eg, multiple imputation)	
28				
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30				
31	<b>Methods:</b>			
32	<b>Monitoring</b>			
33				
34	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);	15
35	formal committee		summary of its role and reporting structure; statement of	
36			whether it is independent from the sponsor and competing	
37			interests; and reference to where further details about its	
38			charter can be found, if not in the protocol. Alternatively,	
39			an explanation of why a DMC is not needed	
40				
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44	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping	15
45	interim analysis		guidelines, including who will have access to these interim	
46			results and make the final decision to terminate the trial	
47				
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49	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	15
50			solicited and spontaneously reported adverse events and	
51			other unintended effects of trial interventions or trial	
52			conduct	
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1	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
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6	<b>Ethics and</b>			
7	<b>dissemination</b>			
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10	Research ethics approval	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
11				
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14	Protocol amendments	<a href="#">#25</a>	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
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21	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
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26	Consent or assent: ancillary studies	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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31	Confidentiality	<a href="#">#27</a>	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
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38	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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42	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
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47	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
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53	Dissemination policy: trial results	<a href="#">#31a</a>	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
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1	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	N/A
2	authorship		professional writers	
3				
4	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	18
5	reproducible research		participant-level dataset, and statistical code	
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## 8 Appendices

10	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given	Supplementary
11	materials		to participants and authorised surrogates	material
12				
13	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
14			biological specimens for genetic or molecular analysis in	
15			the current trial and for future use in ancillary studies, if	
16			applicable	
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 23 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050248.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2021
Complete List of Authors:	Latif, Sania; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Wattar, Bassel H.Al; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Balachandren, Neerujah; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Lukaszewski, Tomasz; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Saridogan, Ertan; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Yasmin, Ephia; University College London Hospitals NHS Foundation Trust, Institute of Women's Health Serhal, Paul; Centre for Reproductive and Genetic Health Mavrellos, Dimitrios; University College London, Institute of Women's Health
<b>Primary Subject Heading</b>:	Reproductive medicine
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Reproductive medicine < GYNAECOLOGY, Subfertility < GYNAECOLOGY, REPRODUCTIVE MEDICINE

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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<sup>1</sup>, Bassel H. Al Wattar<sup>1</sup>, Neerujah Balachandren<sup>1</sup>, Tomasz Lukaszewski<sup>1</sup>, Ertan Saridogan<sup>1</sup>, Ephraim Yasmin<sup>1</sup>, Paul Serhal<sup>2</sup>, Dimitrios Mavrelou<sup>1</sup>

<sup>1</sup>Reproductive Medicine Unit, University College London Hospital, UK

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**Corresponding author:** Dimitrios Mavrelou, Reproductive Medicine Unit, University College London Hospital, UK. Email: [d.mavrelou@ucl.ac.uk](mailto:d.mavrelou@ucl.ac.uk)

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

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**Table 1. WHO Trial Registration Data**

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03946722
Date of registration in primary registry	13 <sup>th</sup> May 2019
Source of monetary or material support	Dimitrios Mavrellos (CI)
Primary sponsor	University College London
Contact for public queries	DM, SL (dimitrios.mavrellos@nhs.net, sanialatif@nhs.net) University College London Hospital, UK
Contact for scientific queries	DM, SL (dimitrios.mavrellos@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	<p>Ages eligible for study: <math>\geq 18</math> years <math>&lt; 42</math> years</p> <p>Sexes eligible for study: female</p> <p>Accepts healthy volunteers: no</p>
	<p>Inclusion criteria: Women with moderate/severe adenomyosis undergoing IVF treatment, BMI <math>&lt; 30</math> kg/m<sup>2</sup>, two out of three of the following criteria are met: AMH <math>&gt; 5.4</math> pmol/L, FSH <math>&lt; 8.9</math> IU/L, antral follicle count <math>&gt; 4</math>.</p>
	<p>Exclusion criteria: Previous open or laparoscopic myomectomy, uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids <math>&gt; 3</math> cm), untreated endometrial polyps, untreated hydrosalpinges, use of GnRH analogues within previous 3 months, severe male factor infertility (sperm count <math>&lt; 2 \times 10^6</math>/ml, use of surgically retrieved spermatozoa)</p>
Study type	Interventional
	Allocation: randomized intervention model.
	Parallel assignment masking: unblinded.
	Primary purpose: to determine effectiveness of modified downregulation.
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:**

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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

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2  
3 improve the clinical pregnancy rate by reducing the endometrial inflammatory reaction and/  
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5 or myometrial contractility and their impact on uterine receptivity in women with moderate  
6  
7 and severe adenomyosis of the uterus undergoing frozen thawed embryo transfer. The  
8  
9 MODA trial is designed to offer pragmatic, real-life evaluation of the  
10  
11 optimal protocol for downregulation for this population during assisted conception  
12  
13 treatments. Our findings will be published in peer-reviewed journals and presented at  
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15 national and international scientific meetings and congresses. Ethical approval was granted by  
16  
17 the NHS Research Ethics Committees (19/LO/1567).  
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22 **Trial registration number:** NCT03946722  
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## 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).



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3 Treatment with gonadotrophin-releasing hormone (GnRH) analogues for prolonged periods  
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5 could reduce the amount of inflammatory reaction in the eutopic endometrium of women with  
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3 adenomyosis (8). It is also possible that prolonged downregulation may improve abnormal uterine  
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5 peristalsis seen in women with adenomyosis. A study examining the impact of prolonged  
6  
7 downregulation in women with adenomyosis undergoing in vitro fertilisation (IVF) treatment first  
8  
9 showed increased clinical pregnancy rates a decade ago (9). More recently, three large retrospective  
10  
11 studies suggest a significant benefit in the reproductive outcomes of women with adenomyosis  
12  
13 following prolonged downregulation prior to frozen embryo transfer, in contrast to one  
14  
15 retrospective analysis that showed an adverse impact of prolonged downregulation on  
16  
17 pregnancy rates, and another retrospective study that showed no difference in outcomes (10 - 14).  
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19 The true benefit of prolonged versus standard downregulation in this population remains  
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21 imprecise.  
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33 **Objective:** We aim to determine whether modified downregulation prior to frozen thawed  
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35 embryo transfer (FTET) improves the chance of clinical pregnancy in women with moderate  
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37 and severe adenomyosis.  
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## 47 **Methods**

### 54 *Trial design*

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

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2  
3 downregulation with GnRH analogue for one week prior to frozen-thawed embryo transfer,  
4 recruiting participants from fertility centres across the UK. Participants will be followed-up  
5 until six weeks after the pregnancy outcome is determined. The trial design is summarised  
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10 in Figure 1.

### 11 12 13 14 15 *Inclusion criteria*

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21 1. Couples who are undergoing a cycle of IVF/ICSI, where a cycle is defined as egg collection  
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25 following ovarian stimulation.  
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- 30 2. The female partner is  $\geq 18$  and  $< 42$  years of age.  
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- 34 3. The female partner has a BMI  $< 30$  kg/m<sup>2</sup>.  
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- 37 4. Two out of three of the following criteria are met: AMH  $> 5.4$  pmol/L, FSH  $< 8.9$  IU/L, antral  
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39 follicle count  $> 4$  (15).  
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- 44 5. Moderate or severe adenomyosis of the uterus diagnosed on ultrasound scan.  
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- 48 6. Both partners are willing and able to provide written informed consent.  
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### 55 56 *Exclusion criteria*

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- 3 1. Concurrent and/or recent involvement in other research that is likely to interfere with the
- 4 intervention within the previous 3 months of study enrolment.
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- 7 2. Previous open or laparoscopic myomectomy
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- 12 3. Uterine fibroids (untreated FIGO Type 0-I-II and type III-IV fibroids > 3 cm)
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- 17 4. Untreated endometrial polyps
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- 21 5. Untreated hydrosalpinges
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- 25 6. Use of GnRH analogues within previous 3 months.
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- 27
- 28 7. Severe male factor infertility (sperm count < 2 x 10<sup>6</sup>/ml, use of surgically retrieved
- 29 spermatozoa)
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- 31
- 32 8. Couples who in the opinion of the researcher by virtue of language or learning impairment
- 33 would be unable to give fully informed consent to the study.
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### 39 *Outcomes*

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44 The primary outcome of the study is clinical pregnancy, defined as a viable intrauterine  
45 pregnancy confirmed by ultrasound at greater than 6 weeks gestation.  
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53 Our secondary outcomes will include livebirth, pregnancy loss (biochemical pregnancy,  
54 miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy), gestational age at  
55 delivery, birth weight, neonatal mortality, major congenital anomaly, serious medication  
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3 reaction, frequency and severity of medication side effects, number of days to achieve optimal  
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5 endometrial thickness.  
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10 *Enrolment*  
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18 Enrolment of participants will involve coordinated registration and allocation of participant  
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20 trial numbers by the trial co-ordinator. All participants will be asked by a member of the  
21  
22 research team to complete a written consent at least 24 hours after providing the trial's  
23  
24 participant information sheet (PIS) (see model consent form in supplementary files). All  
25  
26 consents will be recorded in the medical notes including signature from both partners  
27  
28 undergoing the IVF/ICSI procedure. A member of the research team will explain that  
29  
30 participants are under no obligation to enter the trial and that they can withdraw at any time  
31  
32 during the trial, without having to give a reason. No trial procedures will be conducted prior to  
33  
34 the participant giving consent by signing the consent form.  
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41 Once consent has been granted a TVS will be performed by a member of the research team.  
42  
43 The scan will be performed in a systematic fashion starting from the uterus in longitudinal  
44  
45 plane with measurement of the endometrial thickness. The probe is then rotated to the  
46  
47 transverse plane and the uterus scanned from the cervix to the fundus with any uterine  
48  
49 pathologies noted and measured in 3 orthogonal planes. A 3D ultrasound volume is then  
50  
51 obtained and saved starting with the uterus in longitudinal view making sure to include all  
52  
53 uterine tissue in the 3D volume sweep. Any congenital or acquired uterine anomalies are  
54  
55 diagnosed according to published diagnostic criteria. Adenomyosis is diagnosed according to  
56  
57 a standardised diagnostic criteria (2) and graded for severity according to the number of  
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3 adenomyosis features present (assign a score of 1 for each of: i) asymmetrical myometrial  
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5 thickening, ii) parallel shadowing, iii) myometrial cysts, iv) irregular endometrial-myometrial  
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3 junction, v) linear striations, vi) hyperechoic islands, vii) adenomyoma). Patients with four or  
4  
5 more features of adenomyosis are considered to have moderate or severe adenomyosis (5).  
6  
7 Videosonography for a period of 4 minutes will be performed to assess uterine peristalsis. The  
8  
9 operator will then sweep to the adnexae, starting from the left to identify and measure the  
10  
11 ovaries in three orthogonal planes and document the antral follicle count. Each ovary is  
12  
13 examined for the presence of cysts as well as for mobility and tenderness by gentle pressure  
14  
15 with the ultrasound probe. Once the ovaries have been assessed the operator examines the pouch  
16  
17 of Douglas for the presence of free fluid as well as any evidence of endometriosis such as  
18  
19 obliteration, endometriotic nodules and endometriomas, as previously described (16). Once the  
20  
21 ultrasound scan is concluded all information is added to the clinical database (RedCap,  
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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](http://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

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2  
3 to ensure concealment. Randomisation will be performed by a member of the UCLH  
4  
5 Reproductive Medicine Unit administration team, independent to the research team. Participants  
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7 will be informed of their assigned treatment group and this will be recorded on the  
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3 Trial Subject Enrolment Log. The principal investigator (PI) will hold the randomisation list.  
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5 It is not feasible to perform blinding in our setting.  
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#### 14 *Procedures*

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20 *Standard downregulation protocol:* Participants allocated to the standard downregulation  
21 protocol will start Norethisterone on day 14 of downregulation cycle and continue for 11 days,  
22 followed by Buserelin 0.5 ml subcutaneously from day 21. A baseline scan will be performed  
23 between days one to four of their bleed, Buserelin reduced to 0.2 ml and they will commence  
24 Progynova 2 mg three times daily orally. Serial scanning will be performed from day ten until  
25 an endometrial thickness of greater than 8mm is achieved, followed by luteal support with  
26 Cyclogest 400 mg twice daily vaginally or rectally and Lubion 25 mg twice daily  
27 subcutaneously. Blastocyst embryo transfer will be performed with a minimum morphological  
28 quality of B-C on the appropriate day for embryo age (Figure 2 and 3).  
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43 *Modified downregulation protocol:* Participants allocated to the modified downregulation  
44 protocol will have a baseline scan between days one and four of their bleed and will administer  
45 Leuprorelin acetate 3.75 mg subcutaneously, followed by Leuprorelin acetate 1.875 mg  
46 subcutaneously 28 days later. They will commence Progynova 2 mg three times daily orally 14  
47 days later. Serial scanning will be performed from day ten until an endometrial thickness of  
48 greater than 8mm is achieved, followed by luteal support with Cyclogest 400 mg twice daily  
49 vaginally or rectally and Lubion 25 mg twice daily subcutaneously. Blastocyst embryo transfer  
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3 will be performed with a minimum morphological quality of B-C on the appropriate day for  
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5 embryo age (Figure 2 and 3).  
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3 *Discontinuation/withdrawal of participants:*  
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5 In consenting to participate in the trial, participants are consenting to intervention,  
6 assessments, follow-up and data collection.  
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12 A participant may be withdrawn from the trial whenever continued participation is no longer  
13 in the participant's best interests, but the reasons for doing so must be recorded. Reasons for  
14 discontinuing the trial may include:  
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- 17  
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19 • Intercurrent illness  
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23  
24 • Participants withdrawing consent  
25  
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29 • Persistent non-compliance to protocol requirements.  
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33 The decision to withdraw a participant from treatment will be recorded in the electronic case  
34 report form (eCRF) and medical notes.  
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40 *Patient and public involvement*  
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45 Patients were involved as research partners in all aspects of the study including identifying  
46 the original research question, in revising study design, and in confirming acceptability of  
47 study monitoring methods and the intervention to be administered.  
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54 *Modification of the protocol*  
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56  
57 Any modifications to the protocol which may impact on the conduct of the study, potential  
58 benefit of the patient or may affect patient safety, including changes of study objectives, study  
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1  
2 design, patient population, sample sizes, study procedures, or significant administrative aspects  
3  
4 will require a formal amendment to the protocol. Such amendment will be agreed upon by the  
5  
6 CI and research team. They will be approved by the Research Ethics Committee prior to  
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8 implementation.  
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### *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 Committee (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.

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*Recording and reporting of adverse events*

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3 Each adverse event will be assessed for severity, causality, seriousness and expectedness. All  
4  
5 adverse events (AEs) will be recorded with clinical symptoms and accompanied with a simple,  
6  
7 brief description of the event, including dates as appropriate. All serious adverse events (SAEs)  
8  
9 will be recorded in the medical records and the eCRF, and the sponsor's AE log. The AE log  
10  
11 of SAEs will be reported to the sponsor at least twice per year. SAEs will be reported to the  
12  
13 Sponsor within five days of becoming aware of the event.  
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### 24 *Sample size*

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28 Our previous observational studies suggest a clinical pregnancy rate of 42.7% in women with  
29  
30 mild adenomyosis compared to 22.9% with moderate/severe adenomyosis (7). We theorise that  
31  
32 the modified protocol will improve the chance of clinical pregnancy to similar levels in those  
33  
34 with mild disease. We need to randomise 162 patients over 3 years to achieve 80% power for  
35  
36 detecting a 20% difference in the primary outcome across those groups at 5% significance.  
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45 Adenomyosis has an estimated prevalence of 20.9% in benign gynaecology patients (2), we  
46  
47 estimate higher prevalence among women seeking assisted conception with a history of  
48  
49 subfertility. Given our yearly 750 cycles of IVF/ICSI, we estimate a recruitment period of 3  
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51 years to achieve our target sample size.  
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### 59 *Analysis*

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5 Participants with missing data and non-compliers, including participants who decide to  
6 withdraw from the study or do not follow their assigned protocol, will be excluded from our  
7 analysis. We will perform univariate and multivariate analyses to compare the primary outcome  
8 of both groups and report using risk ratio (RR) and 95% confidence intervals (CI) for  
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3 dichotomous outcomes as well as mean difference with standard deviation (SD) for continuous  
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5 outcomes.  
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### 10 **Ethics and dissemination**

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13 The findings of this study will be published in peer- reviewed journals and presented at national  
14 and international scientific meetings and congresses. No later than 3 years after the collection  
15 of the 6 weeks post pregnancy outcome data, we will deliver a completely deidentified data set  
16 to an appropriate data archive for sharing purposes. Ethical approval was granted by the NHS  
17 Research Ethics Committees (UK IRAS integrated research application system; reference  
18 19/LO/1567). MODA is registered online with clinicaltrials.gov (NCT03946722). See table  
19 1-3 for WHO trial registration data, protocol version history and trial personnel.  
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### 39 **Discussion**

40 Women with moderate/severe adenomyosis undergoing assisted conception are known to have a  
41 reduced clinical pregnancy rate; there is currently no consensus regarding their treatment and  
42 the existing literature is conflicting. Retrospective studies have identified benefit in prolonged  
43 downregulation for these patients however these are subject to selection and publication bias  
44 and therefore may not offer a realistic assessment of this protocol modification (10, 11, 12).  
45 Others have reported a reduction in pregnancy rates with prolonged downregulation but again  
46 this is retrospective data which may have underestimated the positive effect of the intervention  
47 (13).  
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57 One retrospective study showed increased clinical pregnancy rates in women with  
58 adenomyosis following GnRH agonist treatment for 2-3 months prior to frozen embryo  
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3 transfer, whereas no benefit was noted in women who had prolonged downregulation prior to  
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5 fresh embryo transfer (11). The hyperoestrogenic state following controlled ovarian stimulation  
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7 in a fresh embryo transfer cycle is postulated to diminish the effect of GnRH agonist pre-  
8  
9 treatment. A higher dose and longer duration of gonadotrophins were required during controlled  
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11 ovarian stimulation to overcome the prolonged downregulation effect (11). Another  
12  
13 retrospective study in which women with adenomyosis received 3 months downregulation with  
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15 GnRH analogue prior to fresh embryo transfer found a reduction in clinical pregnancy rates,  
16  
17 with a significantly lower endometrial thickness in the pre-treatment group that did not fall  
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19 pregnant (13). However, prolonged downregulation for a less extended duration of 6 weeks  
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21 prior to frozen thawed embryo transfer has previously shown improved clinical pregnancy rates,  
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23 without any negative effects on endometrial preparation (10). We are therefore evaluating a  
24  
25 similar protocol in the MODA trial.  
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31 Co-existing undiagnosed endometriosis is a substantial confounding factor, as not all  
32  
33 patients with adenomyosis undergo surgical diagnostic procedures. There is also potential for  
34  
35 variability in the diagnosis of adenomyosis by ultrasound. In the MODA trial we have only  
36  
37 included fertility centres with an expert ultrasound operator and will review ultrasound images  
38  
39 to ensure quality of diagnosis. This approach should also reduce the risk of undiagnosed  
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41 moderate or severe endometriosis as this can be reliably diagnosed on transvaginal ultrasound.  
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43 Randomization should ensure confounding due to endometriosis coexistence is balanced. We  
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45 will report the frequency of ultrasound diagnosed endometriosis in the control and treatment  
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47 arm of the study.  
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56 There is an urgent need to prospectively evaluate prolonged downregulation as an  
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58 option for couples with adenomyosis undergoing assisted conception both to confirm or refute  
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60 the validity of this approach. The MODA trial is designed to offer pragmatic, real-life

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3 evaluation of the optimal use of downregulation in affected women. Our modified  
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5 downregulation protocol is a practical, simple and readily available treatment option that could  
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7 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

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Table 2. Protocol Version History

Table 3. Trial Personnel

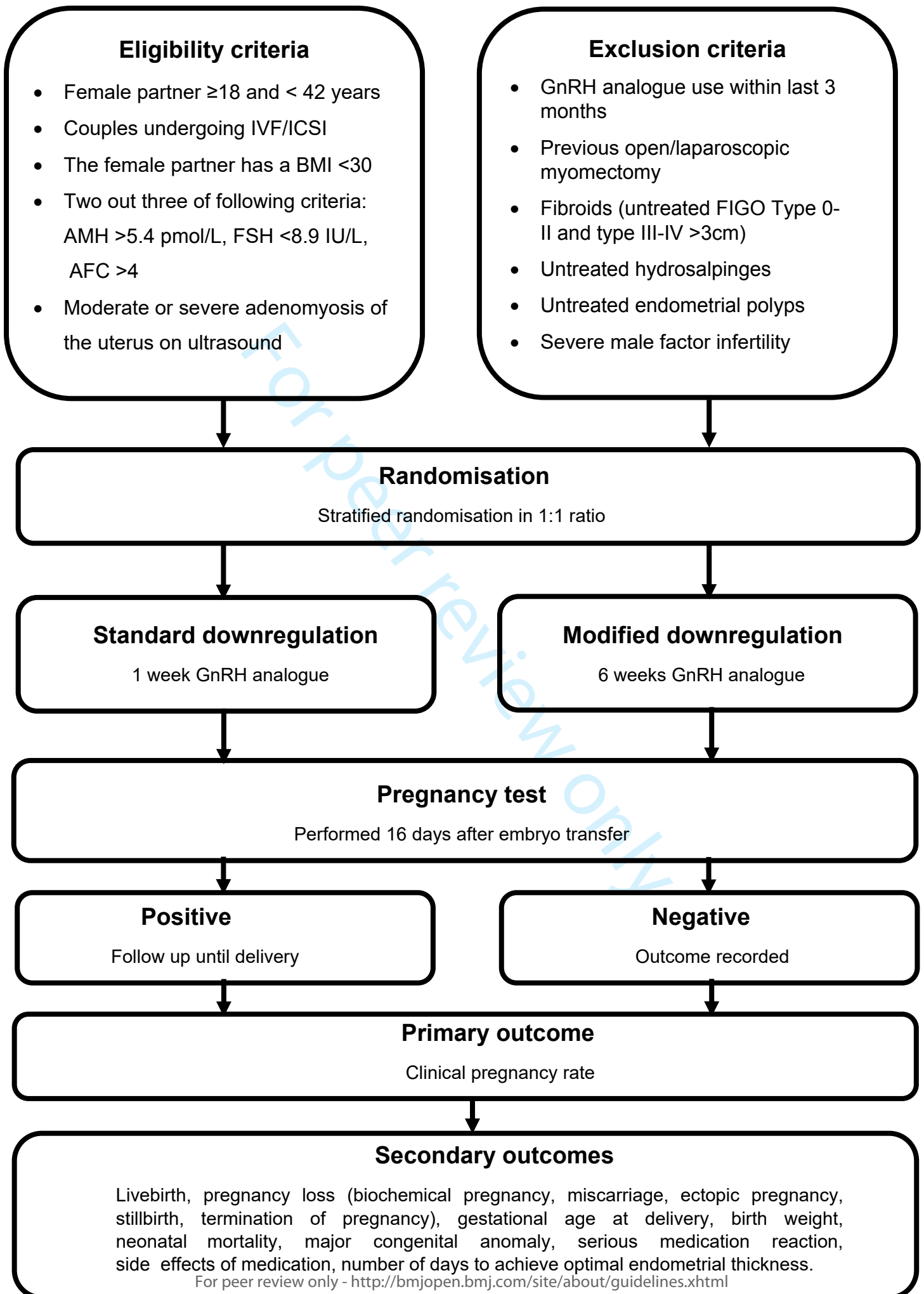
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### Standard downregulation



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

28 days later

14 days later

10 days later

5 days later

16 days after embryo transfer

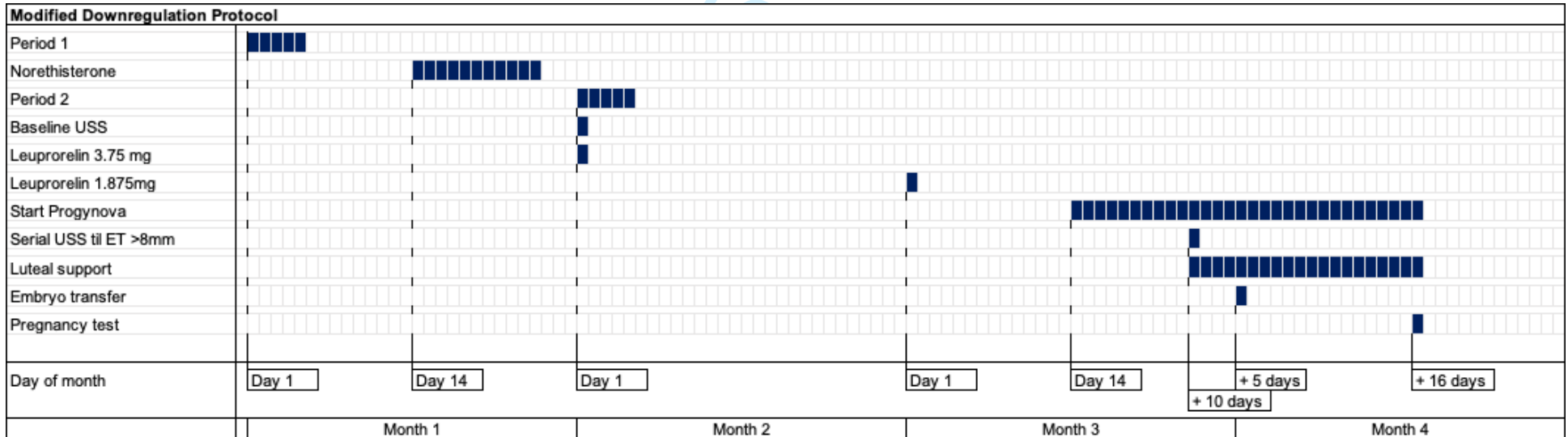
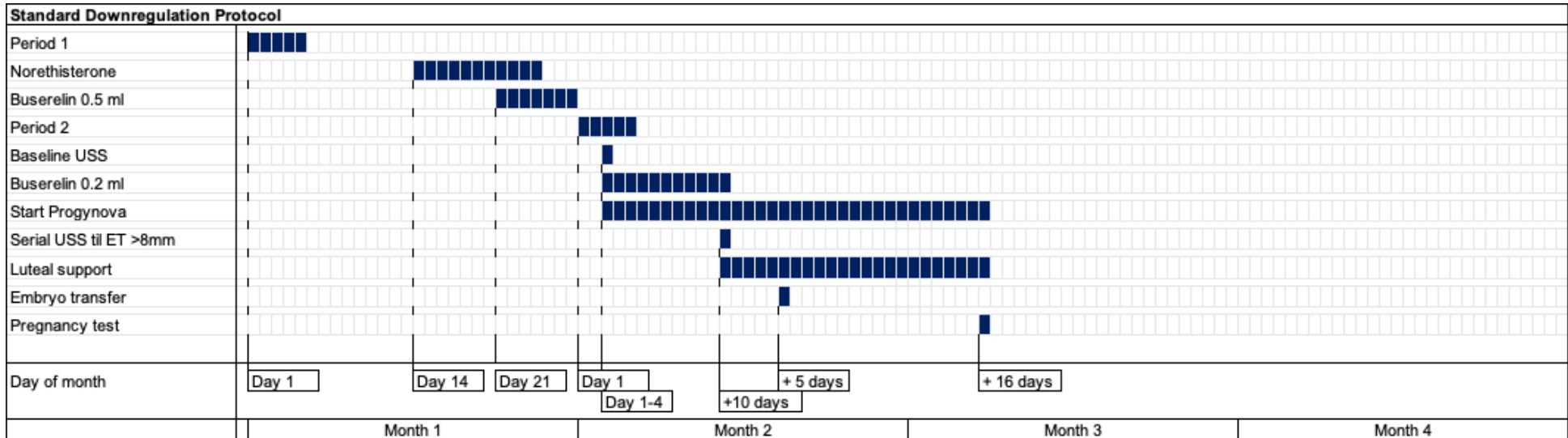
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University College London Hospitals   
NHS Foundation Trust

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.

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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.

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

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	3
2	responsibilities:			
3	sponsor contact			
4	information			
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8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	22
9	responsibilities:		collection, management, analysis, and interpretation of	
10	sponsor and funder		data; writing of the report; and the decision to submit the	
11			report for publication, including whether they will have	
12			ultimate authority over any of these activities	
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	17
17	responsibilities:		centre, steering committee, endpoint adjudication	
18	committees		committee, data management team, and other individuals	
19			or groups overseeing the trial, if applicable (see Item 21a	
20			for data monitoring committee)	
21				
22				
23				
24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for	6-7
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
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34	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	7
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
40				
41	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg,	7
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
45				
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47				
48	<b>Methods:</b>			
49	<b>Participants,</b>			
50	<b>interventions, and</b>			
51	<b>outcomes</b>			
52				
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54				
55	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	7
56			academic hospital) and list of countries where data will be	
57				
58				
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60				

1		collected. Reference to where list of study sites can be	
2		obtained	
3			
4	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If	7-8
5		applicable, eligibility criteria for study centres and	
6		individuals who will perform the interventions (eg,	
7		surgeons, psychotherapists)	
8			
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10			
11	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	11
12	description	replication, including how and when they will be	
13		administered	
14			
15			
16	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated	12
17	modifications	interventions for a given trial participant (eg, drug dose	
18		change in response to harms, participant request, or	
19		improving / worsening disease)	
20			
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22			
23	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols,	N/A
24	adherence	and any procedures for monitoring adherence (eg, drug	
25		tablet return; laboratory tests)	
26			
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28	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are	N/A
29	concomitant care	permitted or prohibited during the trial	
30			
31			
32	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the	8
33		specific measurement variable (eg, systolic blood	
34		pressure), analysis metric (eg, change from baseline, final	
35		value, time to event), method of aggregation (eg, median,	
36		proportion), and time point for each outcome. Explanation	
37		of the clinical relevance of chosen efficacy and harm	
38		outcomes is strongly recommended	
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42			
43	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any	13, 14
44		run-ins and washouts), assessments, and visits for	
45		participants. A schematic diagram is highly recommended	
46		(see Figure)	
47			
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49			
50	Sample size	<a href="#">#14</a> Estimated number of participants needed to achieve study	16
51		objectives and how it was determined, including clinical	
52		and statistical assumptions supporting any sample size	
53		calculations	
54			
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57	Recruitment	<a href="#">#15</a> Strategies for achieving adequate participant enrolment to	N/A
58		reach target sample size	
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1 **Methods:**

2 **Assignment of**  
3 **interventions (for**  
4 **controlled trials)**  
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7			
8	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,
9	generation		computer-generated random numbers), and list of any
10			factors for stratification. To reduce predictability of a
11			random sequence, details of any planned restriction (eg,
12			blocking) should be provided in a separate document that
13			is unavailable to those who enrol participants or assign
14			interventions
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19	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg,
20	concealment		central telephone; sequentially numbered, opaque, sealed
21	mechanism		envelopes), describing any steps to conceal the sequence
22			until interventions are assigned
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26	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol
27	implementation		participants, and who will assign participants to
28			interventions
29			
30			
31	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,
32			trial participants, care providers, outcome assessors, data
33			analysts), and how
34			
35			
36	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is
37	emergency unblinding		permissible, and procedure for revealing a participant's
38			allocated intervention during the trial
39			
40			

41 **Methods: Data**  
42 **collection,**  
43 **management, and**  
44 **analysis**  
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48			
49	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,
50			and other trial data, including any related processes to
51			promote data quality (eg, duplicate measurements, training
52			of assessors) and a description of study instruments (eg,
53			questionnaires, laboratory tests) along with their reliability
54			and validity, if known. Reference to where data collection
55			forms can be found, if not in the protocol
56			
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1	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete	15
2	retention		follow-up, including list of any outcome data to be	
3			collected for participants who discontinue or deviate from	
4			intervention protocols	
5				
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8	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	15
9			including any related processes to promote data quality	
10			(eg, double data entry; range checks for data values).	
11			Reference to where details of data management procedures	
12			can be found, if not in the protocol	
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16	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	16
17			outcomes. Reference to where other details of the	
18			statistical analysis plan can be found, if not in the protocol	
19				
20				
21	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and	16
22	analyses		adjusted analyses)	
23				
24				
25	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	16
26	population and		adherence (eg, as randomised analysis), and any statistical	
27	missing data		methods to handle missing data (eg, multiple imputation)	
28				
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30				
31	<b>Methods:</b>			
32	<b>Monitoring</b>			
33				
34	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);	15
35	formal committee		summary of its role and reporting structure; statement of	
36			whether it is independent from the sponsor and competing	
37			interests; and reference to where further details about its	
38			charter can be found, if not in the protocol. Alternatively,	
39			an explanation of why a DMC is not needed	
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44	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping	15
45	interim analysis		guidelines, including who will have access to these interim	
46			results and make the final decision to terminate the trial	
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49	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	15
50			solicited and spontaneously reported adverse events and	
51			other unintended effects of trial interventions or trial	
52			conduct	
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1	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
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6	<b>Ethics and</b>			
7	<b>dissemination</b>			
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10	Research ethics approval	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
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14	Protocol amendments	<a href="#">#25</a>	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
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21	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
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26	Consent or assent: ancillary studies	<a href="#">#26b</a>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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31	Confidentiality	<a href="#">#27</a>	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
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38	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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42	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
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47	Ancillary and post trial care	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
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53	Dissemination policy: trial results	<a href="#">#31a</a>	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
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1	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	N/A
2	authorship		professional writers	
3				
4	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	18
5	reproducible research		participant-level dataset, and statistical code	
6				
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## 8 Appendices

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11	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given	Supplementary
12	materials		to participants and authorised surrogates	material
13				
14				
15	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
16			biological specimens for genetic or molecular analysis in	
17			the current trial and for future use in ancillary studies, if	
18			applicable	
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 23 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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