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Fibroids and unexplained infertility treatment with epigallocatechin gallate: a natural compound in green tea (FRIEND) – protocol for a randomised placebo-controlled US multicentre clinical trial of EGCG to improve fertility in women with uterine fibroids

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ABSTRACT

Introduction Uterine fibroids affect 30%–77% of reproductive-age women and are a significant cause of infertility. Surgical myomectomies can restore fertility, but they often have limited and temporary benefits, with postoperative complications such as adhesions negatively impacting fertility. Existing medical therapies, such as oral contraceptives, gonadotropin hormone-releasing hormone (GnRH) analogues and GnRH antagonists, can manage fibroid symptoms but are not fertility friendly. This study addresses the pressing need for non-hormonal, non-surgical treatment options for women with fibroids desiring pregnancy. Previous preclinical and clinical studies have shown that epigallocatechin gallate (EGCG) effectively reduces uterine fibroid size. We hypothesise that EGCG from green tea extract will shrink fibroids, enhance endometrial quality and increase pregnancy likelihood. To investigate this hypothesis, we initiated a National Institute of Child Health and Human Development Confirm-funded trial to assess EGCG's efficacy in treating women with fibroids and unexplained infertility.

Methods and analysis This multicentre, prospective, interventional, randomised, double-blinded clinical trial aims to enrol 200 participants with fibroids and unexplained infertility undergoing intrauterine insemination (IUI). Participants will be randomly assigned in a 3:1 ratio to two groups: green tea extract (1650 mg daily) or a matched placebo, combined with clomiphene citrate-induced ovarian stimulation and timed IUI for up to four cycles. EGCG constitutes approximately 45% of the green tea extract. The primary outcome is the cumulative live birth rate, with secondary outcomes including conception rate, time to conception, miscarriage rate, change in fibroid volume and symptom severity scores and health-related quality of life questionnaire scores.

Ethics and dissemination The FRIEND trial received approval from the Food and Drug adminstration (FDA) (investigational new drug number 150951), the central Institutional Review Board (IRB) at Johns Hopkins University and FRIEND-collaborative site local IRBs. The data will be disseminated at major conferences, published in peer-reviewed journals and support a large-scale clinical trial.

Trial registration number NCT05364008.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, prospective, randomised, double-blind, placebo-controlled study.
⇒ The eligibility criteria require documentation of fibroid diagnosis along with classification based on FIGO criteria thereby documenting standardised sonographic evidence prior to study drug exposure.
⇒ Participants receive standard-of-care intrauterine insemination treatments as per the local study site, improving the generality of the results.
⇒ The small sample size may offer insights into the effect of epigallocatechin gallate on live birth rate but is not powered to detect statistical differences in other outcomes of interest.

INTRODUCTION

Uterine fibroids (UFs) are the most common benign neoplasm of the female reproductive tract in women of reproductive age.[1] Their prevalence is age-dependent and can be detected in up to 80% of women by 50 years of age.[2] In particular, UFs affect 30%–77% of reproductive age women.[3] Unfortunately, the actual prevalence may be much higher.[4] The live birth rate among women with fibroids is influenced by location; submucosal fibroids are associated with a 70% reduction in

delivery rate compared with women without fibroids, while intramural fibroids reduce the delivery rate by approximately 30%.[5] At present, a woman with symptomatic fibroids who wants to preserve her fertility has no non-surgical, safe method of treatment that will manage her fibroid-related symptoms without risking subsequent chances of achieving a healthy, safe pregnancy. Furthermore, if myomectomy is performed, the rate of recurrence is high, up to 38%, at 3 years after surgery and any surgery includes the risk of additional complications.[6 7] Currently, women are delaying childbearing, which significantly affects fertility because the prevalence of fibroids increases with age.[8]

A study by Bulletti *et al* evaluated spontaneous conception in infertile women with or without fibroids and reported a significant difference in pregnancy rate between the two groups (11% with fibroids vs 25% without fibroids).[8] In the USA, the fertility of reproductive age women with fibroids is of concern, including the risk of undergoing hysterectomy, lack of effective medical treatment and hindrance of future fertility by the currently available fibroid medications.[2] Unquestionably, the prevalence of UFs is higher in patients with infertility.[9 10] Nevertheless, with the lack of well-designed controlled clinical studies, the evidence base in relation to fibroids and infertility is still complex even with the abundance of observational studies. Donnez and Jadoul conducted a review of 106 articles of myomas and myomectomy and their impact on fertility and pregnancy outcome in infertile women.[11] The authors reported that regardless of these tumours' characteristics, UFs are found to be the only abnormality in approximately 2.4% of infertile women.[11] Others reported that fibroids have a detrimental effect on fertility in up to 10% of cases.[12] It is established that submucosal fibroids affect fertility as evidenced by decreased rates of clinical pregnancy, implantation and ongoing pregnancy/live birth, as well as an increased rate of spontaneous miscarriage[10]; however, fibroids in other locations and sizes also reduce fertility and increase miscarriage.[13] Consistent with an effect on fertility, fibroids reduce the likelihood of pregnancy and increase miscarriage in patients pursuing the assisted reproductive technologies (ART).[5 13] Submucosal fibroids adversely affect ART outcomes, resulting in reduced pregnancy and live birth rates with an OR of 0.3.[14 15] Hart *et al* studied the effect of intramural fibroids on the outcome of in vitro fertilisation (IVF) or intracytoplasmic sperm injection treatment prospectively; they concluded that an intramural fibroid halves the chances of an ongoing pregnancy following assisted conception.[12] Bajekal and Li reported that submucosal fibroids have the most detrimental effects on pregnancy rate with IVF, followed by intramural fibroids, and subserosal fibroids have the least effect.[13] Sunkara *et al* studied the effects of intramural fibroids without cavity distortion on IVF outcomes.[16] These authors conducted a meta-analysis of 19 observational studies with a total 6087 IVF cycles that revealed a significant decrease in live birth (21%) following IVF in women with non-cavity-distorting intramural fibroids compared with those without fibroids.[16]

Several mechanisms have been proposed to explain the antifertility effects of fibroids including the simple physical impedance by impairing and/or obstructing the transport of gametes or embryo,[17] hindering implantation by (1) alteration of normal pattern of myometrial contractions[18 19]; (2) inducing a chronic inflammatory reaction and fibrosis[20 21]; (3) impairing endometrial decidualisation in the mid-luteal window of implantation by alterations in the endomyometrial junctional (EMJ) zone by significantly reducing the concentrations of both macrophages and uterine natural killer cells in this zone[22]; physical disruptions of the EMJ and alteration of the steroid receptors[22 23]; acceleration of myometrial peristalsis in the mid-luteal period[24 25] and/or increasing the milieu prolactin and aromatase levels. However, the most compelling evidence is likely related to the negative impact of the fibroid secretome on endometrial receptivity.[26 27]

Green tea leaves contain polyphenols such as catechins or flavin-3-ols that include epicatechin, epicatechin gallate, epigallocatechin gallate (EGCG) and alkaloids. Catechins are the major components of tea phenols and constitute about 30%–42% of the dry weight of green tea.[28] EGCG catechin is the most abundant and active compound responsible for most of green tea's role in promoting health and likely accounts for the favourable research result cited in the medical literature with the use of green tea extracts. EGCG is a highly polyphenolic compound which makes it the major antioxidant agent in green tea. A study conducted by the US Department of Agriculture reported that green tea has potent antineoplastic effects against a wide range of human tumour cells.[29] The EGCG polyphenol has been shown to inhibit key pathways of tumour growth. EGCG appears to block each stage of tumourigenesis by modulating signalling pathways involved in apoptosis, oxidative stress, inflammation, transformation, cell proliferation and invasion.[29] Studies by Zhang *et al* demonstrated increasing levels of catechol-O-methyl transferase (COMT) in uterine leiomyoma compared with adjacent myometrium and described its important role in fibroid pathogenesis.[30] In addition to various useful antioxidant and anti-inflammatory effects, EGCG exerts a potent COMT inhibitor effect which also contributes to its antifibroid action.[30 31] Furthermore, EGCG is capable of inhibiting fibroid tumour formation in vivo as demonstrated in a nude mouse model.[32]

In this study, the primary outcome to be determined is whether a novel treatment (EGCG) and will promote live birth in infertile women with fibroids. The ability of EGCG to decrease fibroid size and dramatically decreasing transforming growth factor-β3 production by its secretome suggests that EGCG plays a role in modifying the endometrium to favour implantation and successful placentation. Bone morphogenetic protein 2 (BMP-2) is a growth factor that belongs to the transforming growth

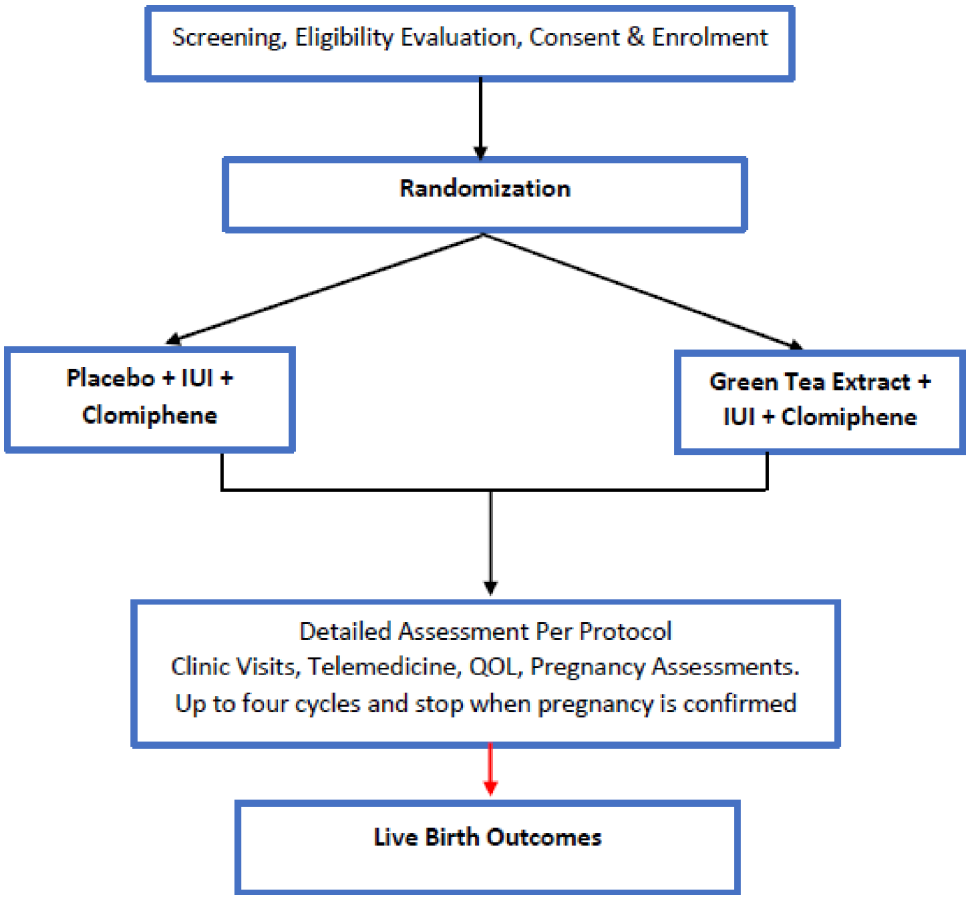

Figure 1 Study design. IUI, intrauterine insemination; QOL, quality of life.

factor-β family and plays a critical role in the process of embryo implantation.[33–36] Conditional ablation of BMP-2 in murine endometrium causes infertility. Sinclair *et al* demonstrated impaired BMP action in endometrial cells of women with fibroid uteri.[37] Al-Hendy's research team reported that EGCG inhibits human fibroid cell proliferation at the gene level and induces apoptosis.[38] This study also showed a 14-fold increase in BMP-2 gene expression in EGCG-treated human fibroid cells compared with untreated controls as a plausible reason for the ability of the endometrium to overcome fibroid-induced BMP resistance. This phenomenon may improve endometrial decidualisation with subsequent enhancement of implantation, as well as fertility and pregnancy outcomes.

EGCG may promote spontaneous pregnancy or it may facilitate an improved response to traditional therapies used to treat unexplained infertility such as the use of clomiphene citrate (CC) combined with intrauterine insemination (IUI) timed by human chorionic gonadotropin (hCG) administration. Study design elaborated in figure 1.

METHODS AND ANALYSIS

This is a multicentre, prospective, randomised, double-blind, placebo-controlled trial to study the efficacy of EGCG pretreatment for women with fibroids who are undergoing fertility treatment (IUI). The study is planned to take place between 2022 and 2025. Informed consent form for the study is attached in (item1).

Participants

Participants will be recruited based on the following inclusion criteria:

1. Intramural fibroids and/or subserosal fibroids that meet the criteria for International Federation of Gynecology and Obstetrics (FIGO) types 2–6; at least one fibroid with an average diameter of at least 1 cm in three dimensions. Participants with multiple fibroids including FIGO type 0 and type 1 will be allowed only in combination with additional fibroids type 2–6.
2. Women ≥18 to ≤40 years of age with a history of infertility who desire conception and ovulate regularly (defined as nine or more menses per year) at initiation of participation. Infertility is defined as the failure to conceive despite active attempts for 12 months in women <35 years of age, or 6 months in women ≥35 years of age.
3. Baseline Anti-Mullerian Hormone (AMH)≥0.7 ng/mL.
4. At least one open fallopian tube confirmed by hysterosalpingography, sonohysterosalpingography or laparoscopy within 3 years from entering the study.

An uncomplicated intrauterine non-IVF pregnancy and uncomplicated delivery and postpartum course resulting in live birth within the last 3 years before study entry will also serve as sufficient evidence of having at least one patent fallopian tube and a normal uterine cavity provided the participant did not acquire during or after the pregnancy any risk factors for developing an intrauterine abnormality or tubal occlusion.

5. Evidence of adequate ovarian function/reserve as assessed by day 3 (±2 days) follicle stimulating hormone (FSH)≤12 IU/L within 1 year prior to study initiation.
6. Good health as assessed by the principal investigator (PI) and use of no medications which could interfere with the study.
7. Ability to undergo inseminations following hCG administration.
8. If applicable, the study participant will inform their partner of trial participation.
9. Male partner with a total motile sperm concentration of at least 5 million sperm/mL in the ejaculate within 1 year of study initiation.
10. Participant agreement to abstain from use of green tea products in any form during course of study participation in the trial.

Participants will be recruited based on the following exclusion criteria:

1. The presence of intracavity UFs (FIGO type 0 or type 1) that are not in combination with other types of fibroids (FIGO types 2–6).
2. Currently pregnant.
3. Clinical intrauterine miscarriage within 3 months of initiating participation. No exclusion for biochemical pregnancies.
4. Use of green tea/EGCG within 2 weeks prior to study enrolment. Matcha (Japanese green tea), maca powder, green tea beverages and all other forms of green tea require a 2-week wash-out. Patients with a detectable EGCG level at the screening visit will be excluded.
5. Undiagnosed abnormal uterine bleeding.
6. Suspicious ovarian mass.
7. Use of oral contraceptives, depoprogestins or hormonal implants (including Implanon) within 2 months of study participation. Longer wash-outs may be necessary for certain depot contraceptive forms or implants, especially when the implants are still in place. A 1-month wash-out will be required for participants taking oral cyclic progestins.
8. Known 21-hydroxylase deficiency or other enzyme defects causing congenital adrenal hyperplasia.
9. Uncontrolled diabetes with Glycated Haemoglobin (HbA1c)>8%.
10. Known significant anaemia (haemoglobin <8 g/dL).
11. History of deep venous thrombosis, pulmonary embolus or cerebrovascular event.
12. Known heart disease (New York Heart Association class II or higher).
13. Known liver disease (Asparatate aminotransferase (AST) or alanine transaminase (ALT)>2 times normal or total bilirubin >2.5 mg/dL).
14. Known renal disease (Blood urea nitrogen (BUN)>30 mg/dL or serum creatinine >1.4 mg/dL).
15. History of, or suspected cervical carcinoma, endometrial carcinoma or breast carcinoma.
16. History of alcohol abuse (>14 drinks/week) or binge drinking (≥6 drinks at one time).
17. Known Cushing's disease.
18. Known or suspected adrenal or ovarian androgen-secreting tumours.
19. Allergy or contraindication to the treatment medications: EGCG, CC or hCG.
20. Couples with reversal of a previous sterilisation procedures (eg, vasectomy, tubal ligation).
21. Untreated poorly controlled hypertension is defined as a systolic blood pressure ≥160 mm Hg or a diastolic ≥100 mm Hg based on two measures obtained at least 60 min apart.
22. Previous bariatric surgery procedure within 12 months of study participation, and are in a period of acute weight loss or have been advised against pregnancy by their bariatric surgeon.
23. Stages 3 and 4 endometriosis and the presence of endometriomas >3 cm as per PI discretion.
24. Known polycystic ovary syndrome as evidenced by oligoanovulation, the presence of androgen excess skin manifestations (eg, hirsutism, acne, temporal balding), hyperandrogenaemia and polycystic ovarian morphology on ultrasound examination.
25. Medical conditions that are contraindications to pregnancy.

Intervention

EGCG/placebo treatment

Participants will be randomised into one of the two treatment groups: 1650 mg of low caffeine green tea extract contained in a powdered form or matched (smell, taste, colour, texture) placebo, taken orally on a daily basis for up to 6 months. Treatment assignments will be randomised within each site, and further randomised within the age groups by a varying-block-size design. Randomisation will be followed by up to four cycles of CC-IUI therapy.

IUI treatment

CC will be administered orally for 5 days starting on day 3 (±2 days) of the menstrual cycle. The initial CC dose will be 100 mg. However, the CC dose can be adjusted between 50 and 150 mg per physician discretion on a case-by-case basis in subsequent treatment cycles. The IUI will be performed 24–48 hours after hCG administration when the lead follicle measures >20 mm in mean diameter during mid-cycle ultrasound monitoring.

Women may undergo a total of up to four cycles of CC-IUI therapy. Participants may begin subsequent cycles immediately following failed cycles, as long as they meet baseline criteria of a negative serum pregnancy test within

4 days of starting CC, a day 3 (±2 days) serum oestradiol <95 pg/mL and a day 3 (±2 days) vaginal ultrasound showing no ovarian cyst >3 cm. However, a 30-day break between treatment cycles will be allowed to accommodate a participant's personal needs.

Randomisation

Eligible women will be randomised in a 3:1 fashion to one of the two treatments:

1. Low caffeine green tea extract (1650 mg in six capsules) taken orally on a daily basis for up to 6 months that includes 1 month for every CC-IUI cycle for up to four cycles if no pregnancy is achieved.
2. Matched placebo capsules based on smell, taste, colour and texture taken orally on a daily basis for up to 6 months that includes 1 month for every CC-IUI cycle for up to four cycles if no pregnancy is achieved).

The randomisation scheme will be coordinated through the data coordination centre. The randomisation will be stratified by each study site and within each site for age groups 18–34 and 35–40 using a varying-block-size design.

Outcome measures

The primary outcome measure will be the cumulative live birth rate, defined as live birth at >24 weeks of gestation.

For the secondary outcomes, conception rate, miscarriage rate, time to pregnancy, the change of fibroid volume, symptom severity score and UF symptom health-related quality-of-life score, from baseline to completion of treatment and endometrial receptivity biomarkers will be compared between the two study arms. Adverse events will be monitored and assessed between the two study arms.

Statistical analysis

Sample size and power calculations

This will be a pilot study of 200 study subjects. The sample size was determined by practical considerations based on a similar pilot study and available funding.[30] This pilot study is not powered to determine a difference between control and treated groups. Rather, the results will be used to estimate the SD and effect size, which can then be used to inform a larger trial. To enhance recruitment and increase the likelihood of determining a possible effect of EGCG, a randomisation scheme of 3:1 will be used. The National Institutes of Health and the Data and Safety Monitoring Board (DSMB) have reviewed and approved the study design and planned sample size. Based on the results from a similar pilot study,[30] the total sample size of 200, when taking into account a drop rate of 15% and a 3:1 green tea extract versus placebo randomisation, will have a power of 0.23 for the live birth outcome, with a live birth rate of 0.2 for placebo and 0.3 for green tea extract at an alpha of 0.05.

Analysis of outcome measures

For the primary efficacy parameter, we will use the intention-to-treat (ITT) paradigm where all randomised participants are considered according to their randomised treatment assignments, regardless of actual treatment received, protocol violations, etc. The primary outcome, that is, the live birth rates, will be compared among the two intervention arms by ITT using the Pearson χ^2 test of independence. In addition, we will also conduct sensitivity analyses by considering the actual treatments and excluding dropouts in order to assess the impact of these deviations on the conclusion of the primary hypothesis. Those sensitivity analyses will be performed using regression techniques such as logistic regression or other models as appropriate and needed. Prior to the primary analysis above, we will assess the balance of baseline characteristics between the two randomisation assignments. If the imbalance is of concern such as the unadjusted p value is less than 0.05, we will examine the pertinent baseline characteristics in their potential impact on the primary outcomes. In short, although the primary analysis will be based on a straightforward statistical test, extensive subsequent analyses will be performed to ensure that our final conclusion is thoroughly scrutinised and appropriately reported.

For secondary efficacy parameters, depending on the characteristics of the outcome and exposure(s) of interest, Student's t-test or Wilcoxon rank-sum test will be used to test the difference between the two treatment arms. In addition, multivariable regression models will also be performed to compare the treatment effect on the outcomes, while adjusting some other potential variables.

Based on prior experience, we expect a data completion rate of at least 99.5% and we do not expect missing data to significantly affect trial analysis or results. In the unlikely event of unexpectedly high rates of missing data, we will examine the potential mechanisms for missing data (eg, missing completely at random, missing at random or missing not at random). We will compare the available characteristics of those with missing data to those with complete data. If necessary, imputation techniques may be used.

Safety and adverse events monitoring

A pharmacokinetic safety study was performed in which EGCG was used with current ovulation induction drugs such as CC and found concurrent use of EGCG and CC to be safe with no significant adverse events. All adverse events are collected regardless of their grade of severity and reported based on established criteria. The DSMB will receive unblinded data and provide advice on any potential safety issues. The choice of continuing therapy or trial participation based on adverse events is at the discretion of the investigator and DSMB determinations. Reporting of all adverse events will be provided to the Johns Hopkins University School of Medicine Institutional Review Board (JHM IRB) at annual continuing review of the study. Any serious adverse event that requires prompt reporting to the IRB will be done according to the established IRB guidelines.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics and dissemination

The FRIEND trial was approved by the JHM IRB on 26 April 2022, application # IRB00215624, with reliance agreements at all participating sites.

All protocol modifications will be reviewed by the JHM IRB and reported to the funder. If protocol changes lead to generation of new informed consent forms, participating investigators. Providers and study staff will be retrained and kept update date using email. Significant protocol modifications will also be noted on ClinicalTrials.gov website.

The results of this trial may reveal a new medical modality for the treatment of UFs in conjunction with concurrent infertility treatments.

The trial will be conducted in accordance with relevant regulations and standard operating procedures, including data protection. Each subject is assigned a unique code for deidentification. Data will be collected electronically and abstracted from the electronic medical record in a deidentified manner. Any medical information that is obtained in connection with this programme that could identify a subject will remain confidential and will be disclosed only as required by law. All persons responsible for the quality control of the data take all necessary precautions to ensure the confidentiality of information regarding trial participants and in particular the identity of the participants and the results obtained. The final trial dataset will be available to study investigators and research ethic boards at all participating sites. Results of the trial will be published in peer-reviewed journals. We will submit data and samples collected by the trial to the Eunice Kennedy Shriver National Institute of Child Health and Human Development Data and Specimen Hub. The informed consent will include permission to bank these samples. The processes included initial data and documentation preparation (eg, codebooks, protocols, informed consent for data sharing), data quality control and submission.

Trial status and registration

The study was conceived and designed in 2019. Recruitment is expected to begin in August 2022. The study is registered on ClinicalTrials.gov Identifier: NCT05364008. The manuscript describes the latest version, last updated March 2023.

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Contributors AA-H, JHS, HST, FG, HS, MZ, HA, BS, VAF, GMC, JJJ, HH and HZ each made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures. AA-H is the chief investigator for the study. AA-H, JHS, FG and HST are principal investigators and the study sites. HZ is the lead trial biostatistician and leads the study's data consortium centre. All authors read and revised the protocol critically for important intellectual content and approved the final version to be published. All authors approved the final version to be published.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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