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IVF and IUI in couples with unexplained infertility (FIIX study): study protocol of a non-inferiority randomized controlled trial

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STUDY QUESTIONS: In couples with unexplained infertility and a poor prognosis of natural conception, are four cycles of IUI with ovarian stimulation (IUI-OS) non-inferior to one completed cycle of IVF for the outcome of cumulative live birth?
Are four cycles of IUI-OS associated with a lower cost per live birth compared to one completed cycle of IVF?
Will four cycles of IUI-OS followed by one complete cycle of IVF result in as many live births at lower cost per live birth, than two complete cycles of IVF?
Will four cycles of IUI-OS followed by two complete cycles of IVF result in more live births at lower cost per live birth, than two complete cycles of IVF alone?

WHAT IS KNOWN ALREADY: IUI is widely used in the USA, the UK and Europe as a low cost, less invasive alternative to IVF for couples with unexplained infertility. Although three to six cycles of IUI were comparable to IVF in the three major studies carried out to date, gonadotrophin ovarian stimulation was used in the majority of cases, and this also resulted in a high multiple pregnancy rate in some studies. Ovarian stimulation with clomiphene citrate is known to have lower multiple pregnancy rates.

STUDY DESIGN, SIZE, DURATION: The FIIX study is a multicentre, open label, parallel, pragmatic non-inferiority randomized controlled trial of 580 couples with unexplained infertility comparing four cycles of IUI-OS with clomiphene citrate and one completed cycle of IVF. Variable block randomization stratified by age and clinic with electronic allocation will be used.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Couples with poor prognosis for natural conception and who are eligible for publicly funded fertility treatment in six fertility clinics in New Zealand.

STUDY FUNDING/COMPETING INTEREST(S): Auckland Medical Research Fund (3718892/1119003), A+ Trust, Auckland District Health Board (A + 8479), Maurice and Phyllis Paykel Trust (3718514). No competing interests.

TRIAL REGISTRATION NUMBER: ACTRN12619001003167.

TRIAL REGISTRATION DATE: 15 July 2019

DATE OF FIRST PATIENT'S ENROLMENT: 02/08/2019

Key words: unexplained infertility / IVF / IUI / health economics / randomized controlled trial

WHAT DOES THIS MEAN FOR PATIENTS?

Infertility is usually defined as not getting pregnant after a year of trying. Unexplained infertility is diagnosed when there is no obvious reason for not being able to get pregnant, after all the normal tests have been done. People with unexplained infertility may be offered fertility treatments such as IUI or IVF. IUI is a less invasive and cheaper treatment option per cycle compared to IVF, however, people may need to undergo more IUI cycles to achieve the same chance of getting pregnant. Here, we describe the protocol for an ongoing randomized controlled trial (the FIIX study) in 580 couples with unexplained infertility to compare the two approaches to treatment. Multiple pregnancy rates are expected to be similar in both treatment groups.

Introduction

Couples with unexplained infertility, according to the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) definition, have ‘apparently normal ovarian function, normal fallopian tubes, uterus, cervix and pelvis, adequate coital frequency, apparently normal testicular function, genitourinary anatomy and a normal ejaculate’ (Zegers-Hochschild et al., 2017). In New Zealand (NZ) clinics, approximately 30% of infertile couples have unexplained infertility, however, the public funding system requires these couples to have experienced cumulatively 5 years of infertility before being eligible for publicly funded fertility treatment (Northern Regional Fertility Service, 2018). This delay leads to a further age-related reduction in fertility and has been the topic of debate in NZ (Farquhar et al., 2011). Eligible couples are able to access up to two packages of care, each package consisting of either: four stimulated IUI cycles or one complete cycle of IVF, two complete cycles of IVF or eight cycles of IUI. Most couples select two packages of IVF.

IUI is widely used in the USA, the UK and Europe as a low cost, less invasive alternative to IVF for couples with unexplained infertility (The Practice Committee of the American Society for Reproductive Medicine, 2006; Kim et al., 2015). However, in 2013, the UK National Institute for Health and Care Excellence (NICE) recommended ‘that IUI with or without ovarian stimulation should not be routinely offered for couples with unexplained infertility’ and that IVF be considered after 2 years of expectant management (National Institute of Health and Clinical Excellence, 2013). Despite this, a survey of fertility clinics reported that many continue to offer IUI to couples with unexplained infertility.

Recently, our team published a randomized controlled trial (RCT) comparing three cycles of IUI with ovarian stimulation (IUI-OS) with 3 months of expectant management for couples with unexplained infertility and reported a 3-fold increase in live births in women treated with IUI-OS (31% compared to 9% natural conception live birth rate $P < 0.001$) (Farquhar et al., 2018). These findings suggest that IUI-OS is a successful and cost-effective fertility treatment for this population, in which IVF usually offers a live birth rate of a similar magnitude (30%) (De Neubourg et al., 2016).

Three RCTs have compared IUI and IVF (Custers et al., 2011; Bendsdorp et al., 2015; Nandi et al., 2017). Each of these studies used gonadotrophins for ovarian stimulation for IUI, which is associated with higher rates of multiple pregnancies than oral medications. All three studies reported similar live birth outcomes for three to six IUI-OS cycles as one to two IVF cycles. The multiple pregnancy rate in the studies varied from 6% to 14% for IVF with single embryo transfer and 7–25% for IUI using gonadotrophin stimulation and strict cancellation policies (Custers et al., 2011; Bendsdorp et al., 2015; Nandi et al.,

2017). A systematic review suggests that IUI regimens with adherence to strict cancellation criteria led to an acceptable multiple pregnancy rate and that low-dose gonadotrophins were associated with improved live birth/ongoing pregnancy rates compared to clomiphene citrate (Wang et al., 2019). However, this does not take into account the increased cost of gonadotrophins or the cost-effectiveness of different approaches.

The FIIX study will compare four cycles of IUI with one complete cycle of IVF, which will directly assess the two publicly funded treatment package options available in NZ. Additionally, the FIIX study differs from previous RCTs in a number of important ways. Firstly, women to be included in the FIIX study are more infertile at inception (due to public funding criteria resulting in a longer average duration of infertility). Secondly, the medication used for ovarian stimulation in IUI is less expensive and usually has lower multiple pregnancy rates (~NZ\$15 oral agent vs NZ\$1500 for gonadotrophin) than IVF. Thirdly, IVF cycles will be undertaken with single embryo transfer as per NZ policy and practice. Lastly, this study will have a larger sample size and will include a cost-effectiveness analysis (CEA) of treatments under a public funding model.

Outcomes

The primary outcome is cumulative live birth rate (CLBR), defined as any live birth conceived within 185 days of randomization. This will include all live births conceived in this window, including those resulting from randomized treatment cycles, natural conception pregnancies and pregnancies resulting from off protocol treatment cycles. Live birth is defined as birth after 20 completed weeks of gestation, or with a birthweight of at least 400 g if gestation is unknown, of a baby which breathes or shows any other evidence of life, such as heart beat, umbilical cord pulsation or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. Live births are counted as events, for example, a twin live birth is counted as one birth event. Secondary outcomes, including FertiQoL (Boivin et al., 2011), are listed in Table I.

Materials and methods

Study design

A multicentre, open label, parallel, pragmatic RCT of couples with unexplained infertility who are eligible for publicly funded fertility treatment in NZ. Couples will be recruited from six clinics across NZ.

The inclusion and exclusion criteria are listed in Table II.

Table 1 Secondary outcomes for non-inferiority randomized controlled trial of IVF and IUI in couples with unexplained infertility.

Clinical	<p>CLBR at the completion of four IUI-OS cycles or one complete IVF cycle, but conceived no longer than 12 months (365 days) post-randomization.</p> <p>CLBR measured at 550 days (18 months) from randomization regardless of whether all potential treatment cycles are completed.</p> <p>CLBR at the completion of all treatment cycles, but no longer than 24 months (730 days) post-randomization.</p> <p>Time to pregnancy leading to live birth: defined as the time taken to conceive a pregnancy which results in a live birth, measured as calendar time from randomization to pregnancy.</p> <p>Viable pregnancy: defined as an intrauterine pregnancy diagnosed by ultrasonography of at least one foetus with a discernible heartbeat.</p> <p>Ongoing pregnancy: defined as the presence of a heartbeat as seen by ultrasonography 12 weeks gestation (including singleton, twin pregnancy and higher multiples).</p> <p>Multiple pregnancy: defined as two or more gestational sacs seen by ultrasonography.</p> <p>Multiple birth: defined as the complete expulsion or extraction from a woman of more than one foetus, after 20 completed weeks of gestational age or at least 400 g, irrespective of whether it is a live birth or stillbirth. Births refer to the individual newborn; for example, a twin delivery represents two births.</p> <p>Biochemical pregnancy: a pregnancy diagnosed only by the detection of beta hCG in serum or urine, which fails to progress to the point of ultrasound confirmation.</p> <p>Early pregnancy loss: the spontaneous loss of an intrauterine pregnancy, where there is no foetal heartbeat detected at the time of ultrasound at 6–8 weeks.</p> <p>Ectopic pregnancy: defined as a pregnancy outside the uterine cavity, diagnosed by ultrasound, surgical visualization or histopathology.</p> <p>Miscarriage: the spontaneous loss of an intrauterine pregnancy with foetal heartbeat prior to 20 completed weeks of gestational age.</p> <p>Stillbirth: defined as the death of a foetus prior to the complete expulsion or extraction from its mother after 20 completed weeks of gestational age or a birth weight of 400 g or more. The death is determined by the fact that, after such separation, the foetus does not breathe or show any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles. Note: this includes deaths occurring during labour.</p> <p>Termination of pregnancy/induced abortion: intentional loss of an intrauterine pregnancy, through intervention by medical, surgical or unspecified means.</p> <p>Number of embryos remaining at completion of each IVF cycle.</p>
Quality of life	FertiQoL (Boivin <i>et al.</i> , 2011) (treatment related) survey taken at 6 months (185 days) and 18 months (550 days) post-randomization.
Economic measures	<p>Incremental cost per live birth.</p> <p>Incremental cost per couple.</p>
Serious adverse events	<p>Hospital admission for ovarian hyperstimulation syndrome that required drainage of ascites or pleural effusions.</p> <p>Hospital admission from other treatment-related causes such as OHSS, haemorrhage, or pelvic infection requiring active treatment.</p> <p>Serious drug reaction.</p> <p>Death of patient.</p>

CLBR, cumulative live birth rate; IUI-OS, IUI with ovarian stimulation; OHSS: ovarian hyperstimulation syndrome.

Recruitment

Eligible couples will be identified from the IVF public funding waitlist (usually 12 months, there is no waiting list for IUI) and invited to participate in the study. Couples will be approached at approximately 3–6 months from being placed on the waiting list. Couples who meet the eligibility criteria after screening will be invited to participate in the study by written explanation and invitation from a member of the clinic or research staff. Women who agree to participate will sign a written informed consent. The informed consent will be taken by a trained member of the study team. Some women that consent to the study will not be randomized—for example, if a natural conception pregnancy were to occur between consent and randomization. Treatment will aim to be commenced within 6 weeks of randomization.

Randomization and allocation concealment

Couples will be randomly assigned to either the IUI followed by IVF arm or the IVF arm with a 1:1 allocation using a variable block design via

REDCap, a web-based data system (Harris *et al.*, 2019). The block sizes will not be disclosed, to ensure concealment. The randomization will be stratified by centre and by age (<36, ≥36 years). Allocation concealment will be ensured, as the data system will not release the randomization code until the couple has been recruited into the trial, which takes place after baseline measurements have been entered in the system.

The randomization sequence will not be accessible to the recruiters. The study is not blinded because of the nature of the intervention. The clinicians and researchers who measure and collect data for pregnancy outcomes will be aware of the assigned intervention.

The study flow is summarized in Fig. 1.

IUI followed by IVF strategy.

Up to four cycles of IUI-OS, followed by up to two completed cycles of IVF (including any/all frozen embryo transfers) until pregnancy leading to live birth is achieved. Randomization will occur with an aim to commence the first IUI cycle on Day 1 of the woman's next cycle. IUI-OS will be given according to local protocols with 5 days of either

Table II The inclusion and exclusion criteria for the study.

Inclusion criteria	<p>(1) Criteria for public funding for fertility treatment in NZ which includes the following criteria: Age—female <39 years 4 months and male <54 years 4 months at the time of randomization. BMI—female ≤ 32 kg/m². Both partners are non-smokers for at least 3 months. Both partners with no history of illicit drug use or alcohol abuse within the preceding 12 months. Day 2 FSH <15 IU for the female partner measured in the last 12 months. Both partners must be a NZ citizen or resident, hold a NZ work visa or student visa which allows them to stay in NZ continuously for 2 years or more, or be an Australian citizen or resident who can prove intention to stay in NZ for 2 years or more. Couples must have no previous children from NZ publicly funded fertility treatment, no more than one child (including adopted children) of any age to the same relationship and no more than one child from a previous relationship living at home (at least half of the time).</p> <p>(2) Criteria for unexplained infertility Female partner has a regular ovulatory cycle (21–35 days). Female partner has evidence of patent fallopian tube(s) on hysterosalpingogram or at laparoscopy or recent intrauterine miscarriage (within 24 months) (tubal spasm is not considered tubal blockage). Male partner has a total motile sperm count >10 million, on last semen analysis or within two of the past three semen analyses.</p>
Exclusion criteria	<p>Women with a history of stage 3 or 4 endometriosis. Women with submucosal fibroids or any fibroid >8cm or fibroids between 5 and 8 cm if endometrial cavity is distorted or cavity length is >10 cm. Couples who require egg or sperm donation. Women with a past history of ectopic pregnancy or bilateral blocked tubes or tubal surgery for adhesions/hydrosalpinges.</p>

NZ, New Zealand.

oral clomiphene citrate or letrozole. Monitoring for follicular development will be according to local protocols. The IVF cycles will only commence after the four cycles of IUI-OS are completed, and not before 185 days has elapsed from randomization. IVF will be carried out in the same manner as the IVF arm of the study.

IVF strategy.

Up to two completed cycles of IVF will be offered until pregnancy leading to live birth is achieved. The first completed cycle, including using any frozen embryos available, will be completed before commencing the second cycle. The latter will not commence before 185 days has elapsed from randomization. Randomization will occur with an aim to commence the IVF cycle on Day 1 of the woman's next cycle (anticipating that the majority of cycles will be antagonist protocols). The IVF cycle will be carried out as per the fertility clinic's normal practice, with the IVF cycle type, medication used, and monitoring schedule determined by the individual clinics. Single embryo transfers will be standard practice. If there are any frozen embryos these will be replaced in subsequent frozen embryo transfer cycles, according to individual clinic protocols. If the first complete IVF cycle does not result in a pregnancy leading to live birth and there are no remaining frozen embryos, the couple will proceed into a second IVF cycle, but not before 185 days.

The package of four IUI-OS cycles or one complete IVF cycle will be completed before a second package of care commences, even if 185 days have elapsed from randomization. For example, if a couple has only completed three IUI-OS cycles at the 6-month mark, they will continue onto the fourth IUI-OS cycle before commencing an IVF cycle. Once a live birth has been achieved in either strategy no further public funding for fertility treatment is possible.

Statistical analysis plan

The analysis of the primary outcome will be by logistic regression, adjusting for the stratification variables of age (modelled as a continuous

variable) and clinic. We will perform a sensitivity analysis excluding couples who were ineligible (e.g. unrecognized pregnancy at study entry) and will estimate the effect of treatment in participants who comply with the protocol. If any participant has missing data for the primary outcome, we will perform both complete case analysis under a missing at random assumption and subject this to sensitivity analyses based on the CLBR in these participants (see registration website for detailed analysis plan).

Secondary outcomes will be analysed using logistic or linear regression according to the outcome distribution, adjusting for the covariates listed for the primary analysis. An exception is time to pregnancy leading to live birth; we will plot the cumulative incidence for this outcome and will use Cox regression, adjusting for the same covariates as described above. We will conduct additional sensitivity analyses around the censoring assumptions.

Exploratory subgroup analyses will be performed, but the trial is not powered to this end. These will involve tests of interaction between treatment and age (as a continuous variable) and between treatment and number of previous treatment attempts. These analyses will be considered hypothesis generating.

Type I error of the primary analysis will be controlled at 5%, by comparing the lower limit of a 90% two-sided CI for a risk difference, obtained from the logistic model, to the inferiority margin. A significance threshold of 1% will be used for secondary outcomes, which will be analysed using 99% CI.

No adjustment for multiplicity will be made for sensitivity analyses.

Sample size

Sample size calculation was based on the primary outcome, CLBR at 6 months from randomization, and using the following estimates from the literature:

- Estimated CLBR of 30% after four cycles of IUI-OS at 185 days (6 months) (Farquhar et al., 2018).

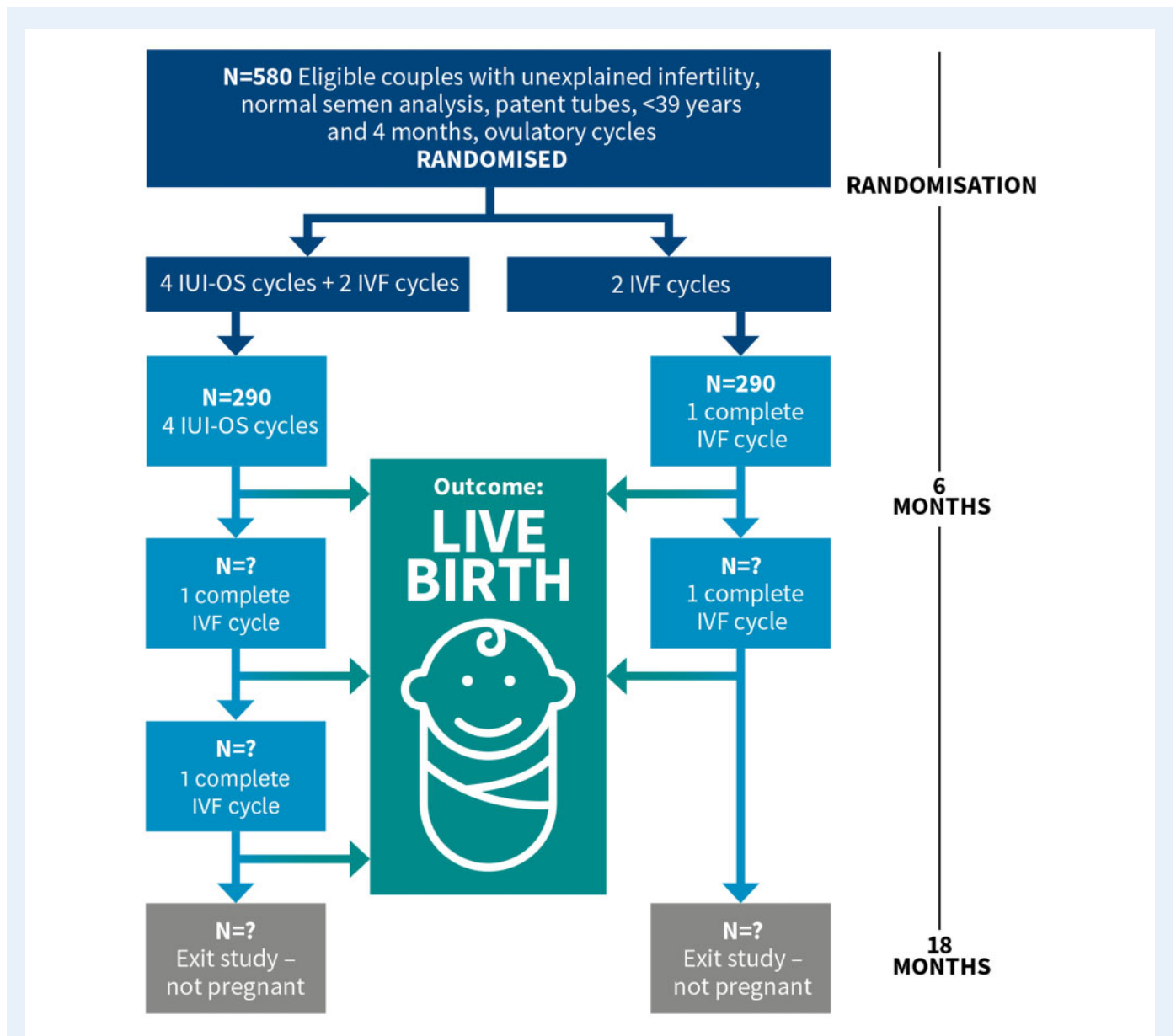


Figure 1. The study flow chart. IUI-OS, IUI with ovarian stimulation.

- Estimate CLBR of 30% for a single completed IVF cycle at 185 days (6 months) (De Neubourg et al., 2016).
- Sample size calculated based on the hypothesis of non-inferiority for CLBR at 6 months. Estimated CLBR is 30% in each group, and requires 580 patients (290 in each arm) for 80% power to reject the null hypothesis that the groups differ by more than 10 percentage points at the 5% level, allowing for 10% withdrawals.

Economic analysis plan

The economic evaluation will take a health systems perspective, accounting for the direct costs of treatments to the NZ health-care system. A CEA will use the patient-level resource use and effectiveness data collected from the trial case report forms in the

data management system. Costs will be expressed in 2020 NZ dollars. Despite this being a non-inferiority study, it is best practice to undertake a full CEA because of the importance of estimating the joint distribution of costs and effects. True equivalence is seldom shown in trials and performing a cost-minimization analysis based on the equivalence in effect is likely to result in biased estimation of uncertainty surrounding the results (Dakin and Wordsworth, 2013; Drummond et al., 2015).

Unit costs will include medication cost of the drugs, using unit costs from the only public clinic (Fertility Plus); intervention services (IUI and IVF) using 2020 unit costs as paid to the Northern Region clinics; pregnancy and delivery costs for singleton and multiple pregnancy sourced from the medical literature (Custers et al., 2011; Bendsdorp et al., 2015; Nandi et al., 2017) or current birth costs in NZ.

Baseline characteristics of the patients in the two trial groups will be summarized. Differences in resource use and costs between the arms will be tested using two-sample Student's *t*-tests (or non-parametric equivalents) and χ^2 tests for continuous and categorical variables, respectively. The mean costs of resource use in each arm and the differences in costs between the arms will be calculated with 95% CIs. Regression analyses will be conducted to examine how the total cost and health outcomes may vary by the patient characteristics, intervention type and clinics and hospitals.

The type of model will be advised by the study statistician and will account for within fertility clinic clustering.

The CEA will align with good practice guidelines (Ramsey et al., 2015), with the CEA presented as incremental costs per live birth at 6 and 18 months. Subgroup analyses will be undertaken to address any issues of underlying heterogeneity including female age at time of randomization (<36, 36–37, \geq 38 years). The results of the cost-effectiveness, including the subgroup and sensitivity analyses, will be presented as point estimates and on cost-effectiveness planes, cost-effectiveness acceptability curves (CEACs) including cost-effectiveness frontiers. The curves will plot the probability of IUI being cost-effective compared with IVF for a range of monetary values of a live birth.

Bootstrapping on the patient-level costs and effects across 50 000 replicates will be used to assess the uncertainty for costs, effects and cost-effectiveness, and 95% CIs will be calculated for the net monetary benefit and CEACs using these replicates. A series of sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of generalizability of the study results. We will also undertake a budget impact analysis, to determine the likely impact on the NZ Health Budget of implementing the most cost-effective intervention.

Accountability for any skewness of the data will be included in the analysis. Imputation will be used to treat missing information if it exists, and multiple imputation methods will be used if needed to assess the uncertainty that occurs when the missing data are replaced in the imputation process.

Data collection

All data collection is summarized in Table III.

Protocol violations

Protocol violations are defined as instances where the treatment received varies from the treatment assigned by randomization (e.g. women in the IUI arm who undergo private IVF treatment) and which is undertaken prior to the end of the assigned treatment. Any fertility treatment accessed by participants after completion of trial treatments is not considered a protocol violation but will be captured in the study database.

Withdrawals

Participants can leave the study at any time for any reason if they wish to do so, without any consequences. If they do not provide consent to collect data they are considered a withdrawal and missing outcome data for this couple will be handled as described under Statistical analysis plan above.

Data protection and management

The data will be held within the Maternal Perinatal Central Coordinating Research Hub electronic data storage tool (REDCap) (Harris et al., 2019). REDCap is password protected and on a University of Auckland server. The consent forms are electronically collected and recorded for the majority of participants. If a paper consent form is obtained this will be scanned into REDCap and the originals will be kept in locked cabinets at the individual trial centres. Data stored on REDCap is identifiable. Only the study investigators can access this information. Within REDCap, individual sites and study coordinators at that site will have restricted access to only their study participants' information. The data provided to the statistician will be de-identified. The data will be stored for a minimum of 10 years.

Adverse event reporting

Serious adverse events (SAEs) are defined as those which led to significant additional treatment, is life-threatening or has led to an unexpected death or major loss of function occurring to a participant during the study, related to any of the treatment arms. The most common SAE is likely to be hospital admission for ovarian hyperstimulation syndrome and this should be reported within 72 h to the Principal Investigator. REDCap has an electronic SAE form, which will be filled out to record any SAE. This is automatically sent to the Trial Management Group (TMG) and Data Monitoring Committee (DMC).

An independent DMC of three members has been formed to monitor the recruitment, data collection, multiple pregnancy rate, all SAE and adherence to the study protocol and the timelines. No interim analyses of the study outcomes by allocated treatment group are planned. The DMC will meet 6 monthly.

Ethics approval

Ethics approval was granted on the 15 April 2019 by the Central Health and Disability Ethics Committee (Reference code 19/CEN/40). An amendment to the consent form, logo and protocol was approved on the 29 July 2019. Reference code 19/CEN/40/AM01. A further amendment for website, survey questions and study letter were approved on 12 May 2020. Reference code 19/CEN/40/AM02.

Trial registration with the Australian New Zealand Clinical Trials Registry (ANZCTR) is completed. Protocol changes will be recorded, dated and agreed to by the TMG. Major changes will be discussed with the ethics approval and funding bodies. Changes will also be recorded with the ANZCTR (ACTRN12619001003167).

Discussion

Although the NZ funding model offers eligible couples with unexplained infertility a choice between IUI and IVF, couples overwhelmingly select IVF even though it has a 1 year waiting list and there is no waiting list for IUI. We speculate that couples and clinicians have a preference for IVF because they consider that IVF is superior in terms of live birth rate, time to pregnancy and the possibility of surplus embryos that can be transferred after the subsequent birth.

The primary objective of the FIIX study is to evaluate the current NZ packages of care for IUI-OS and IVF. If the non-inferiority of IUI-

Table III Data collection.

Baseline characteristics	Duration of infertility, gravidity, parity, outcome for any previous pregnancy, previous IVF and IUI treatments, ovarian reserve testing (AMH), ethnicity and a prediction score (Hunault <i>et al.</i> , 2004), as well as inclusion and exclusion criteria characteristics.
Cycle data relating to IUI and IVF cycles	IUI—ovulation stimulation medication and dose, if a cycle was cancelled prior to IUI and reason, luteal phase support, number of blood tests and ultrasound scans required, if sedation or general anaesthetic was required for IUI, time to complete four cycles, number of IUI cycles completed at 185 days, total number of IUI cycles performed. IVF—IVF cycle type as chosen by the clinic (includes long agonist cycle, short antagonist cycle and flare protocol), IVF cycle duration, cancelled cycle when and why, total amount of gonadotrophin used, other medications used, egg collection under local or general anaesthesia, number of embryos frozen, luteal phase support, number of ultrasound scans and blood tests, number of frozen embryos replaced, embryo replacement cycle type and medication used (manufactured or natural), number of frozen embryos remaining at completion of treatment. Abbreviated information on off-protocol treatments will also be captured.
Clinical outcome data	As listed above under outcomes section.
Additional delivery outcome data	Gestational age at delivery, mode of delivery, neonatal intensive care unit admission, congenital abnormality, birthweight.
Questionnaire	Women will also be asked to complete a FertiQoL survey consisting of four questions related to treatment tolerability (Boivin <i>et al.</i> , 2011). This will be completed at 6 and 18 months from randomization and will be sent via email.

AMH, anti-Müllerian hormone.

OS in this group is proven, it will provide couples with unexplained infertility evidence comparing IVF with IUI. This could have far reaching benefits to the NZ fertility funding model as it would allow couples faster access to fertility treatment because of the reduced waiting time to access IUI. It is possible that the eligibility criteria for this study, imposed by the public funding approach in NZ, may limit the generalizability to other settings. Women in this study are anticipated to have experienced 5 years of infertility on average. With the exception of the duration of infertility, it is likely that other features, such as age and BMI, are likely to be generalizable to women seeking treatment in many European countries. We are also reporting the prediction scores for the women in the study, which are likely to be similar to other studies that use prediction scores <30% as an inclusion criteria (Hunault *et al.*, 2004; Custers *et al.*, 2011; Bendsdorp *et al.*, 2015).

An additional question is whether four cycles of IUI-OS followed by one or two completed IVF cycles will have a higher CLBR with a lower cost per live birth, than two completed IVF cycles alone. While this may appear counter-intuitive, our modelling suggests that this extended regimen may result in a lower cost per live birth without a significant impact on the health budget, despite offering additional treatments. This comparison answers the question of whether the NZ funding model could be modified to include provision of four IUI-OS cycles in advance of two completed IVF cycles, in a cost-effective manner. Both of these aims could lead to important changes to the provision of public fertility care, with an increase in the number of couples able to be (successfully) treated for unexplained infertility in NZ. This finding will also be of interest to other countries with public funding and also for couples who have to pay for their own fertility treatment.

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development and Nicola Bitossi of Fertility NZ approved the final study protocol.

Authors' roles

All authors were involved in the design of this study and made substantial contributions to this manuscript. All authors critically revised and approved the final version of this manuscript.

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Conflict of interest

All authors report no conflict of interest related to this protocol.

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