The effectiveness of ICSI versus conventional IVF in couples with non-male factor infertility: study protocol for a randomised controlled trial

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STUDY QUESTIONS: Does ICSI result in a higher live birth rate as compared with conventional IVF in couples with non-male factor infertility?

WHAT IS KNOWN ALREADY: ICSI is primarily indicated for severe male factor infertility. While the use of ICSI for couples with non-male factor infertility has been increasing worldwide, this is not supported by data from randomised controlled trials. Evidence from non-randomised studies suggest no benefit from ICSI compared with conventional IVF in non-male factor infertility, if not a harm.

STUDY DESIGN, SIZE, DURATION: This randomised, open-label, multi-centre trial aims to compare the effectiveness of one ICSI cycle and one conventional IVF cycle in infertile couples with non-male factor infertility. A total of 1064 couples will be randomly allocated to an ICSI group and a conventional IVF group. The estimated duration of the study is 30 months.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Eligible couples are those whose husbands’ total sperm count and motility are normal, have undergone \( \leq 2 \) previous IVF/ICSI attempts, use antagonist protocol for ovarian stimulation, agree to have \( \leq 2 \) embryos transferred and are not participating in another IVF study at the same time. Women undergoing IVM cycles, using frozen semen or having a poor fertilisation (\( \leq 25\% \)) in previous cycle will not be eligible. Couples will be randomised to undergo ICSI or conventional IVF (1:1) with ongoing pregnancy resulting in live birth after the first embryo transfer of the started treatment cycle as the primary endpoint. All analyses will be conducted on an intention-to-treat basis. Effect sizes will be summarised as relative risk (RR), with precision evaluated by 95% CIs.

STUDY FUNDING/COMPETING INTEREST(S): All authors declare having no conflict of interests with regards to this trial. This work was supported by a grant from MSD [MISP #57508].

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DATE OF FIRST PATIENT’S ENROLMENT: 16 March 2018.

Key words: ICSI / IVF / non-male factor infertility / randomised controlled trial
Introduction

ART is the cornerstone of modern infertility management, with more than 4 million treatments carried out worldwide between 2008 and 2010 (Dyer et al., 2016). Among all indications for ART treatment, non-male factor infertility is responsible for approximately 50% (Palermo et al., 2017). Traditionally, for these couples, conventional IVF is the method of treatment. However, in the last two decades, the use of ICSI for couples with non-male factor infertility has increased dramatically. Among fresh IVF cycles in the USA, ICSI use increased from 36.4% in 1996 to 76.2% in 2012, with the largest relative increase among cycles without male factor infertility, from 15.4% to 66.9% during the same time period (Boulet et al., 2015).

The rationale for using ICSI in couples with non-male factor infertility is to avoid TFF and to increase the number of embryos available, thus may be increasing the cumulative pregnancy rate. A meta-analysis in 11 studies using sibling oocytes from couples with unexplained infertility found that the pooled relative risk (RR) of TFF was significantly higher with conventional IVF than with ICSI (RR 8.22, 95% CI 4.44–15.23) (Johnson et al., 2013). However, a retrospective study in infertile couples with non-male factor infertility and advanced maternal age showed that there was no difference in fertilisation rate and fertilisation failure (Tannus et al., 2017). In terms of pregnancy, the first randomised controlled trial (RCT) comparing ICSI with conventional IVF was published in 2001, demonstrating that the implantation rate was significantly lower in ICSI compared to conventional IVF (Bhattacharya et al., 2001). There was a trend of lower pregnancy rate per cycle after ICSI as compared to IVF, with the implantation rate even being statistically higher after IVF. Since then, there have been no new large RCTs on this topic, or they have just focused on couples with specific diagnostic categories (Fan et al., 2012; Komsky-Elbaz et al., 2013; Sfontouris et al., 2015). A recent large, observational study based on national data from the USA has demonstrated that in non-male factor cycles, ICSI use was associated with lower rates of implantation compared to conventional IVF (23.0% versus 25.2%, respectively; adjusted RR, 0.93; 95% CI, 0.91–0.95) and live birth (36.5% versus 39.2%, respectively; adjusted RR, 0.95; 95% CI, 0.93–0.97) (Boulet et al., 2015). This is worrisome, as ICSI is an invasive procedure, which bypasses the natural selection barriers of the oocyte with the potential of introducing genetically defective material. This technique also adds more expense and laboratory time than conventional IVF (Bhattacharya et al., 2001). All of this adds to the financial burden already experienced by many couples undergoing fertility treatment. The purpose of this RCT is therefore to compare the effectiveness of ICSI and conventional IVF in couples with non-male factor infertility.

WHAT DOES THIS MEAN FOR PATIENTS?

This study looks at whether ICSI results in a higher live birth as compared with conventional IVF.

ICSI was originally used for couples with severe sperm abnormalities. This technique is more invasive and costly than conventional IVF. However, there is an increasing trend (up to 70% globally) in the use of ICSI for couples with non-male factor infertility, even though there is a lack of data to justify this approach.

In this study, consenting couples who have an indication for assisted reproductive treatment with a normal sperm count and motility will be randomised to ICSI or conventional IVF. Apart from live birth, a number of fertility outcomes as well as maternal safety, pregnancy complications, obstetric and neonatal outcomes will also be assessed. Results from this study can be used to select the most appropriate treatment for couples with infertility.

Materials and Methods

Study design

This trial has a randomised, open-label, multi-centre design. It will be performed at IVFMD, My Duc Hospital and IVFAS, An Sinh Hospital. The study is currently recruiting, and the first patient first visit was on 16 March 2018. The estimated duration of study is 26 months, with final recruitment to be completed by 31 December 2020.

Ethical approval

The protocol (version 1, November 2017) has been approved by the institutional ethical committee (IEC) of partipating centres. To increase the generalisability of the study, the protocol has been amended (version 2, August 2018) in which patients with polycystic ovary syndrome or triggered by GnRH agonist will be included. This amendment was approved by the IEC of My Duc Hospital on 19 September 2018 and An Sinh Hospital on 12 September 2018. The study was registered on ClinicalTrial.gov (NCT03428919) and will be conducted according to the principles outlined in the Declaration of Helsinki and its amendments, in accordance with the medical Research Involving Human Subjects Act, and using Good Clinical Practice.

Participants

Eligible couples are those whose husbands’ total sperm count and motility are normal (World Health Organization, 2010), have undergone ≤2 previous IVF/ICSI attempts, use antagonist protocol for ovarian stimulation, agree to have ≤2 embryos transferred and are not participating in another IVF study at the same time. Women undergoing IVM cycles, using frozen semen or having a poor fertilisation (≤25%) in previous cycle are excluded. To improve the quality of the study, the checklist for how to count sperm properly will be used for the assessment of sperm count and motility (Bjornsdal et al., 2016). However, in this trial, either a dilution of 1:20, 1:5 or 1:2 will be used instead of 1:50, 1:20 or 1:10. We also categorise sperm motility into progressive motility, non-progressive motility or immotile. These deviations are performed according to the World Health Organization laboratory manual for the examination and processing of human semen, fifth edition (World Health Organization, 2010).

Randomisation and masking

Potentially eligible couples will be given the information sheet about the study during their first consultation (2–4 weeks before the start of their menstrual cycle). Screening for eligibility will be performed by treating physicians on the day of oocyte retrieval, after having obtained the semen from the husband. Eligible participants will be invited to a full discussion with investigators about the study and will be given the informed consent form. Couples will have about 1 hour to decide if they agree to participate.
in the study or not. Written informed consent will be obtained by the investigators from all couples prior to enrolment (Supplementary Data). To maximise retention in the trial, consultation will be available to couples to ensure they understand the procedures well and to address any questions or complaints that arose during the study.

Eligible patients that have provided informed consent will be randomised to either ICSI or conventional IVF. Randomisation will be controlled centrally by administrative staffs in the trial centre who are not involved in any treatment procedure. When there is an eligible participant to be enrolled into the study, nurses from the specific site will make a phone call to the trial centre to obtain the allocation of patients according to a computer-generated randomisation list in a 1:1 ratio, with a variable block size of 2, 4 or 8. After randomisation, if a participant wishes to change her assigned protocol, she will be considered as a crossover, but analysed in the group to whom she was assigned (intention-to-treat). Women who choose to transfer more than two embryos after randomisation will be considered as protocol deviations, but remain included in the analysis. Due to the type of interventions, this study will only be blinded to clinicians who perform the embryo transfer.

Interventions

All patients undergoing IVF/ICSI will be treated with a GnRH antagonist protocol. Recombinant FSH (Puregon, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany) will be given on Day 2 or Day 3 of menstrual cycle for 5 days. The starting dose is individualised for each patient based on the following criteria: anti-Müllerian hormone (AMH) < 0.7 ng/mL, dose 300 IU/day, AMH 0.7–2.1 ng/mL, dose 200 IU/day, AMH > 2.1 ng/mL, dose 150 IU/day. After that, clinicians can titrate the dose based on their clinical judgement. Follicular development will be monitored by ultrasound scanning and measurement of estradiol and progesterone levels, starting on Day 5 of stimulation. Scanning and hormonal measurement will be repeated every 2–3 days, depending on the size of follicles. An antagonist (Orgalutran 0.25 mg, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany) is routinely used on Day 5 until the day of triggering. Criteria for triggering, by hCG (Ovitrelle 250 mg, Merck Serono S.p.A., Modugno, Italy) will be the presence of at least three leading follicles of 17 mm. In women with excessive follicular response (>15 follicles >12 mm), 0.2 mg Triptorelin (Diphereline, Ipsen Pharma Biotech, Signes, France) will be used when there are at least two leading follicles of 17 mm. Oocyte retrieval will be performed 36 h after triggering. On the day of oocyte retrieval, after having obtained the semen from the husband, eligible patients will be randomised to the ICSI group or IVF group.

For patients in ICSI group, insemination will be performed by using ICSI, 3–4 h after oocyte retrieval. The cumulus–oocyte complex (COC) will be stripped by using hyaluronidase. Only matured oocytes will be inseminated.

For patients in conventional IVF group, insemination will be performed by conventional IVF. Two hours after retrieval, collected COCs will be inseminated for another 2 h at a concentration of 100 000 motile sperm/ml. Inseminated COCs will be cultured overnight in culture medium.

In both groups, a fertilisation check will be performed under an inverted microscope at 16–18 h after insemination. Embryo evaluation will be performed at a fixed time point 66 ± 2 h after fertilisation, using the Istanbul consensus (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Embryo transfer will be performed on Day 3 under ultrasound guidance. The number of embryos transferred, from one to a maximum of two embryos, will be based on couples’ preference. The remaining Grade 1 and 2 embryos will be frozen. Luteal-phase support will be oral oestradiol valerate (Valiera®; Laboratorios Recalcine SA, Santiago, Chile) 8 mg/day and vaginal progesterone 800 mg/day (Cyclogest®; Actavis UK Ltd, North Devon, United Kingdom) until the 7th week of gestation.

If there are contra-indications for fresh embryo transfer, a freeze-all strategy will be applied, using Cryotech technique (Gandhi et al., 2017). Indications for freeze-all include risk of OHSS, a premature progesterone rise (>1.5 ng/ml), thin endometrium (<7 mm), fluid in the cavity on day of embryo transfer, endometrial polyp and hydrosalpinx that have not been removed before oocyte retrieval.

In the next cycle, the endometrium will be prepared using oral oestradiol valerate (Valiera®; Laboratorios Recalcine SA, Santiago, Chile) 8 mg/day starting from the second or third day of the menstrual cycle. Endometrial thickness will be monitored from Day 6 onwards, and vaginal progesterone (Cyclogest®; Actavis UK Ltd, North Devon, UK) 800 mg/day will be started when endometrial thickness reaches 8 mm or more. A maximum of two embryos will be thawed on the day of embryo transfer, 3 days after the start of progesterone. Two hours after thawing, surviving embryos will be transferred into the uterus under ultrasound guidance.

In both groups, clinicians who perform embryo transfer, either fresh or frozen cycles, will be blinded to the intervention.

Serum hCG will be measured 2 weeks after embryo transfer, and if positive, an ultrasound scan of the uterus will be performed at gestational weeks 7 and 12. At 11–12 weeks of gestation, participants will be referred to the Outpatient clinic, Ob/Gyn Department, My Duc hospital or An Sinh hospital for prenatal care until delivery. At every visit, usually every month until 34 weeks of gestation and every 1–2 weeks thereafter, patients will undergo routine care, as per local protocol. All data from each visit will be documented in the participant’s study profile. When the participant attends for delivery, data on labour and delivery, and any complications experienced by the participant and the neonates will be collected. For those who cannot participate in the prenatal care programme at either My Duc hospital or An Sinh hospital, for any reasons, we will contact the participants via telephone/email monthly until birth to collect data. We also ask these participants to scan the results of each visit in every contact.

Outcome measures

The primary endpoint is live birth after the first embryo transfer of the started treatment cycle. Live birth is defined as the birth of at least one newborn after 24 weeks’ gestation that exhibits any sign of life (twins will be a single count). To allow assessment of the timing of live birth, the rate of ongoing pregnancy at 12 weeks will be used in calculations, conditional on the fact that this ongoing pregnancy results in live birth. Cycles in which no embryo is available for transfer will be considered as failures.

A number of fertility outcomes as well as maternal safety, pregnancy complication, obstetric and perinatal complication, and neonatal complication outcomes will be assessed as secondary endpoints. Full details and definitions are provided in Table I.

Data management and monitoring

Data will be collected using a questionnaire. All data are entered into the database twice. The first data entry is made within a day after embryo transfer. The second is undertaken at the termination of the study. Data from the two entries will be used to check for potential inconsistencies, and any inconsistencies will be adjudicated using the original patient medical record. Data monitoring will be carried out by the principal investigator. Participant privacy will be ensured by allocation of a unique code only available to the local investigator.

Statistical analysis

All analyses will be conducted on an intention-to-treat basis using the R statistical programme (R version 3.5.0; ©2018 The R Foundation for
**Table I  Secondary endpoints and their definition.**

<table>
<thead>
<tr>
<th>Secondary endpoint</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fertility outcomes</strong></td>
<td>Fertilisation rate per oocyte inseminated/injected Fertilisation is defined as the appearance of two PN at 18–20 h per inseminated/injected</td>
</tr>
<tr>
<td>Fertilisation rate per oocyte retrieval</td>
<td>Fertilisation is defined as the appearance of two PN at 18–20 h per oocyte retrieved</td>
</tr>
<tr>
<td>Abnormal fertilisation rate</td>
<td>Abnormal fertilisation rate is defined as the appearance of three PN at 18–20 h after oocyte retrieved and inseminated/injected</td>
</tr>
<tr>
<td>Total fertilisation failure rate</td>
<td>Total fertilisation failure rate is defined as the absence of any zygotes with 2PN at 18–20 h after oocyte retrieved and inseminated/injected</td>
</tr>
<tr>
<td>Embryos on Day 3</td>
<td>Number of embryos on Day 3 after oocyte retrieval day in IVF/ICSI</td>
</tr>
<tr>
<td>Good quality embryo on Day 3</td>
<td>Numbers of embryos on Day 3 with good quality after oocyte retrieval day in IVF/ICSI</td>
</tr>
<tr>
<td>Embryo freezing on Day 3</td>
<td>Number of embryo freezing on Day 3 after oocyte retrieval day in IVF/ICSI</td>
</tr>
<tr>
<td>Live birth from all embryos from the started treatment cycle</td>
<td>Live birth is defined as the birth of at least one newborn after 24 weeks’ gestation that exhibits any sign of life (twin will be a single count)</td>
</tr>
<tr>
<td>Positive pregnancy test</td>
<td>Positive pregnancy test is defined as a serum hCG level greater than 25 mIU/mL 14 days after the first transfer</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>Clinical pregnancy is defined as the presence of at least one gestational sac on ultrasound at 7 weeks’ gestation with the detection of heart beat activity, after the completion of the first transfer</td>
</tr>
<tr>
<td>Ongoing pregnancy*</td>
<td>Ongoing pregnancy is defined as pregnancy with detectable heart rate at 12 weeks’ gestation after the completion of the first transfer</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>Implantation rate is defined as the number of gestational sacs per number of embryos transferred 3 weeks after the first transfer</td>
</tr>
<tr>
<td>Time from randomisation to ongoing pregnancy</td>
<td>Time from randomisation to ongoing pregnancy after completion of the first transfer</td>
</tr>
<tr>
<td><strong>Maternal safety</strong></td>
<td>Symptoms of OHSS At 10 days after hCG injection and 14 days after embryo transfer</td>
</tr>
<tr>
<td>OHSS</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy complications</strong></td>
<td>Ectopic pregnancy is defined as the implantation of a pregnancy confirmed by sonography or laparoscopy at 12 weeks of gestation</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Ectopic nidation of a pregnancy confirmed by sonography or laparoscopy at 12 weeks of gestation</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>Complete loss of clinical pregnancy at 24 weeks of gestation</td>
</tr>
<tr>
<td>Multiple pregnancy rate</td>
<td>Multiple pregnancy rate is explained as two or more gestational sacs or positive heart beats by transvaginal sonography 5 weeks after embryo placement</td>
</tr>
<tr>
<td>Multiple delivery</td>
<td>Multiple delivery is defined as birth of more than one baby beyond 24 weeks</td>
</tr>
<tr>
<td><strong>Obstetric and perinatal complications</strong></td>
<td>Gestational age at delivery Gestational age at delivery</td>
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<tr>
<td>Gestational age at delivery</td>
<td>Gestational age at delivery</td>
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<tr>
<td>Gestational diabetes mellitus</td>
<td>Development of diabetes during pregnancy</td>
</tr>
<tr>
<td>Hypertensive disorders of pregnancy</td>
<td>Hypertensive disorders of pregnancy will include pregnancy induced hypertension, pre-ecampsia and eclampsia at birth</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>Antepartum haemorrhage will include placenta previa, placenta accreta and unexplained</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>Preterm delivery is defined as any delivery at &lt; 24, &lt; 28, &lt; 32, &lt; 37 completed weeks’ gestation</td>
</tr>
<tr>
<td>Spontaneous preterm birth</td>
<td>Spontaneous preterm birth is defined as delivery spontaneously at &lt; 24, &lt; 28, &lt; 32, &lt; 37 completed weeks</td>
</tr>
<tr>
<td>Iatrogenic preterm birth</td>
<td>Iatrogenic preterm birth is defined as delivery non-spontaneously at &lt; 24, &lt; 28, &lt; 32, &lt; 37 completed weeks</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Weight of newborn</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>Low birthweight is defined as &lt; 2500 gm at birth</td>
</tr>
<tr>
<td>Very low birthweight</td>
<td>Very low birthweight is defined as &lt; 1500 gm at birth</td>
</tr>
<tr>
<td>High birthweight</td>
<td>High birthweight is defined as &gt; 4000 gm at birth</td>
</tr>
<tr>
<td>Very high birthweight</td>
<td>Very high birthweight is defined as &gt; 4500 gm at birth</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>Large for gestational age is defined as birthweight &gt; 90th percentile</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>Small for gestational age is defined as birthweight &lt; 10th percentile</td>
</tr>
<tr>
<td><strong>Neonatal complications</strong></td>
<td>Congenital anomaly diagnosed at birth</td>
</tr>
<tr>
<td>Congenital anomaly diagnosed at birth</td>
<td>Any congenital anomaly will be included at birth</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>The admittance of the newborn to NICU At 7 days after birth</td>
</tr>
</tbody>
</table>

*All assessed after completion of the first transfer and at 12 months after randomisation.

OHSS, ovarian hyperstimulation syndrome; NICU, neonatal intensive care unit.
Statistical Computing). Per-protocol analyses may be conducted but these would be considered exploratory only. If a participant withdraws consent, no further data will be analysed. Baseline data will be presented using descriptive statistics (mean and SD for normally distributed variables, or median and interquartile range for skewed variables). Categorical data will be presented as number (%).

The rate of live birth and the associated 95% CI will be estimated and compared between groups using the exact method for binomial proportion. Kaplan–Meier survival curves for the cumulative live birth rates in each treatment group will be constructed. The log rank test and Cox regression model will be used to assess between-group differences in the cumulative pregnancy rates. Differences between groups in secondary outcome variables will be analysed using Student’s-t test or Wilcoxon signed-rank test for normally distributed or skewed variables, and Fisher’s exact test for categorical variables, and reported as RR with 95% CI.

Missing observations for the primary endpoint (ongoing pregnancy resulting in live birth) will be imputed as ‘negative’ irrespective of the reason why data are not recorded. Missing observations for the supportive secondary endpoints (beta hCG, clinical pregnancy, ongoing pregnancy) will be imputed based on the result, which is observed at a later pregnancy assessment. For example, if the outcome of beta-hCG is missing but clinical pregnancy is positive then beta-hCG will be imputed as ‘positive’. For adverse events, missing values will be treated as missing, except for causality, intensity and seriousness of adverse events, where a worst-case approach will be used.

Sample size calculation
The current live birth rate (using ICSI, with two embryos transferred) in IVFMD and IVFAS is 31.5%. To demonstrate a 10% difference for ICSI over IVF, 968 couples (484 in each arm) will be needed (power 0.90, two-sided alpha 5%). To account for an estimated loss to follow-up rate of 10%, the number of patients needed will be 1064 (532 per arm).

Safety
(Serious) Adverse event
The primary investigator will inform participants and the reviewing accredited medical research ethics committee if anything occurs that would suggest that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited medical research ethics committee, except where suspension would jeopardise the participants’ health. The investigator will ensure that all participants are kept informed.

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the intervention. All adverse events reported spontaneously by the subject or observed by the investigator or their staff will be recorded.

A serious adverse event (SAE) is defined as any untoward medical occurrence or effect that results in death, is life threatening (at the time of the event), requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is a new event of the trial likely to affect the safety of the participants such as an unexpected outcome of an adverse reaction. All SAEs will be reported to the accredited ethics committee that approved the protocol, according to the requirements of that committee. All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to a general physician or medical specialist.

Interim analysis
An independent Data Safety Monitoring Committee (DSMC) will be convened (Supplementary Data). The DSMC will assess the ongoing pregnancy because data on live birth will not be available. The DSMC will also review any SAEs that have occurred. Interim analysis will be performed after enrolment of the first 500 participants. The interim analysis will be conducted using a two-sided significant test with the Haybittle–Peto spending function and a Type I error rate of 5% with stopping criteria of \( P < 0.001 \) (Z alpha = 3.29).

Independent study monitoring will be performed monthly by a clinical research associate from the My Duc Hospital Clinical Research Department to ensure adherence to the protocol, International Conference on Harmonisation-Good Clinical Practice, standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, and accuracy and verifiability of case report form entries compared with source data.

Discussion
There is currently a lack of data from RCTs on the live birth rates after ICSI compared with conventional IVF in couples with non-male factor infertility. Strengths of this trial include its randomised, controlled design, which should minimise bias, and a multi-centre design, which enhances the generalisability of the results. The results of this trial will provide evidence on the use of IVF and ICSI in national and international clinical practice.

Supplementary data
Supplementary data are available at Human Reproduction Open online.

Authors’ roles

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Conflict of interest

L.N.V. has received speaker and conference fees from Merck, grant, speaker and conference fees from Merck Sharpe and Dohme, and speaker, conference and scientific board fees from Ferring. T.M.H. has received speaker fees from Merck, Merck Sharpe and Dohme, and Ferring. R.J.N has received grants and conference fees from Merck, grants and speaker fees from Merck Sharp and Dohme, and conference and scientific board fees for Ferring. B.W.M. has acted as a paid consultant to Merck, ObsEva and Guerbet, and is the recipient of grant money from the NHMRC Practitioner Fellowship. Other authors have no conflicts of interest to declare.

References


