




# BMJ Open Individual participant data meta-analysis of trials comparing frozen versus fresh embryo transfer strategy (INFORM): a protocol

Rui Wang <sup>1</sup>, David J McLernon,<sup>2</sup> Shimona Lai,<sup>1</sup> Marian G Showell,<sup>3</sup> Zi-Jiang Chen,<sup>4</sup> Daimin Wei,<sup>4</sup> Richard S Legro,<sup>5</sup> Ze Wang,<sup>4</sup> Yun Sun,<sup>6</sup> Keliang Wu,<sup>4</sup> Lan N Vuong <sup>7</sup>, Pollyanna Hardy,<sup>8</sup> Anja Pinborg,<sup>9</sup> Sacha Stormlund,<sup>9</sup> Xavier Santamaría,<sup>10</sup> Carlos Simón,<sup>10</sup> Christophe Blockeel,<sup>11</sup> Femke Mol,<sup>12</sup> Anna P Ferraretti,<sup>13</sup> Bruce S Shapiro,<sup>14,15</sup> Forest C Garner,<sup>14,15</sup> Rong Li,<sup>16</sup> Christos A Venetis,<sup>17</sup> Ben W Mol <sup>1,18</sup>, Siladitya Bhattacharya,<sup>18</sup> Abha Maheshwari,<sup>19</sup> The INFORM Collaboration

**To cite:** Wang R, McLernon DJ, Lai S, *et al.* Individual participant data meta-analysis of trials comparing frozen versus fresh embryo transfer strategy (INFORM): a protocol. *BMJ Open* 2022;**12**:e062578. doi:10.1136/bmjopen-2022-062578

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-062578>).

Received 04 March 2022  
Accepted 06 June 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

**Correspondence to**  
Dr Rui Wang;  
[r.wang@monash.edu](mailto:r.wang@monash.edu)

## ABSTRACT

**Introduction** Existing randomised controlled trials (RCTs) comparing a freeze-all embryo transfer strategy and a fresh embryo transfer strategy have shown conflicting results. A freeze-all or a fresh transfer policy may be preferable for some couples undergoing in-vitro fertilisation (IVF), but it is unclear which couples would benefit most from each policy, how and under which protocols. Therefore, we plan a systematic review and individual participant data meta-analysis of RCTs comparing a freeze-all and a fresh transfer policy.

**Methods and analysis** We will search electronic databases (Medline, Embase, PsycINFO and CENTRAL) and trial registries (ClinicalTrials.gov and the International Clinical Trials Registry Platform) from their inception to present to identify eligible RCTs. We will also check reference lists of relevant papers. The search was performed on 23 September 2020 and will be updated. We will include RCTs comparing a freeze-all embryo transfer strategy and a fresh embryo transfer strategy in couples undergoing IVF. The primary outcome will be live birth resulting from the first embryo transfer. All outcomes listed in the core outcome set for infertility research will be reported. We will invite the lead investigators of eligible trials to join the individual participant data meta-analysis of trials comparing frozen versus fresh embryo transfer strategy (INFORM) collaboration and share the deidentified individual participant data (IPD) of their trials. We will harmonise the IPD and perform a two-stage meta-analysis and examine treatment-covariate interactions for important baseline characteristics.

**Ethics and dissemination** The study ethics have been granted by the Monash University Human Research Ethics Committee (Project ID: 30391). The findings will be disseminated via presentations at international conferences and publication in peer-reviewed journals.

**PROSPERO registration number** CRD42021296566.

## INTRODUCTION

Infertility affects up to one in seven couples globally.<sup>1, 2</sup> In-vitro fertilisation (IVF) is

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This individual participant data meta-analysis (IPDMA) offers a unique opportunity evaluate outcomes that were impossible in existing aggregate data meta-analysis due to heterogeneous reporting and/or analysis strategies in the primary trials, including time to pregnancy leading to live birth and perinatal outcomes.
- ⇒ This IPDMA has the potential to identify individuals that would benefit most from a freeze-all policy or a fresh transfer policy, and thus provide guidance towards personalised in-vitro fertilisation treatment.
- ⇒ The coordination of international collaboration will promote research transparency and data sharing, making clinical trials more useful for their end-users.
- ⇒ Limitations include (un)availability of data on covariates of interest across trials.

a treatment option for all couples with prolonged unresolved infertility. Over 10 million IVF children have been born since 1978, and over 2.5 million cycles are being performed every year.<sup>3, 4</sup>

About a decade ago, a few small randomised controlled trials (RCTs) suggested that a freeze-all transfer policy may improve IVF success rates, while minimising the risk of ovarian hyperstimulation (OHSS).<sup>5, 6</sup> The scientific rationale includes the avoidance of reduced endometrial receptivity in the fresh cycles, the prevention of late-onset OHSS and the reduction in early-onset OHSS if a gonadotropin-releasing hormone (GnRH) agonist trigger is used.<sup>7</sup> This has led to a global increase in the number of clinics adapting a freeze-all transfer policy for both elective and non-elective indications.<sup>8</sup>



Over the last decade, multiple large RCTs across different countries comparing a strategy of freeze-all versus a fresh embryo transfer have been published. Some RCTs suggested an improvement in live birth rates<sup>5-9,10</sup> while others either found insufficient evidence of a difference between the two options<sup>6,11-14</sup> or a decline in live birth rate.<sup>15</sup> Meanwhile, recent meta-analyses showed that a freeze-all embryo transfer strategy was associated with a lower risk of OHSS, preterm delivery and small for gestational age baby, but a higher risk of a large for gestational age baby and hypertensive disorders of pregnancy, and a higher birth weight.<sup>16,17</sup> These meta-analyses also showed moderate to severe unexplained heterogeneity,<sup>16,17</sup> suggesting study protocols features affected the results of comparisons. Although the precise reasons for findings on these perinatal outcomes are not known, they have profound implications for the long-term health of mothers undergoing IVF as well as their offspring.

Hence, the optimal strategy for each couple is not yet known, and there is an urgent need to provide clear evidence on which couples would benefit most from each policy.<sup>8,18</sup> None of the individual trials is large enough to provide definitive conclusions with any degree of precision especially when it comes to obstetric and perinatal outcomes. The effectiveness of a freeze-all embryo transfer strategy may vary by maternal age, number of oocytes retrieved, stage at which embryos are frozen, endometrial preparation, luteal support protocol, embryo selection/assessment before and after cryopreservation and the stage at which embryos are replaced (cleavage stage or blastocyst), but existing meta-analyses based on published aggregated data are unable to conduct meaningful subgroup analyses due to different reporting strategies of subgroup data in primary trial reports.<sup>17,19</sup> Moreover, time to pregnancy leading to live birth is an important patient-centred outcome but could not be analysed in aggregated data due to the heterogeneous reporting approaches in the primary trials.<sup>17</sup>

We propose to undertake a systematic review and individual participant data meta-analysis (IPDMA) of eligible RCTs to evaluate the effectiveness and safety of a freeze-all transfer strategy versus a fresh embryo transfer strategy in couples undergoing IVF. Our research questions include:

Does a freeze-all embryo transfer strategy differ from a fresh embryo transfer strategy in

- ▶ Live birth rate after the first transfer and in whom?
- ▶ Cumulative live birth rate and shorten time-to-pregnancy leading to live birth?
- ▶ Maternal safety during IVF treatment?
- ▶ Obstetric and perinatal complications?

## METHODS AND ANALYSIS

### Search strategy

Comprehensive literature searches using an appropriate combination of index terms and free words will be conducted to identify published, ongoing and unpublished randomised trials assessing the clinical effectiveness of freezing all embryos followed by thawed frozen

embryo transfer compared with fresh embryo transfer for couples undergoing IVF.

Various electronic databases will be searched from their date of inception to the present day, these include: Medline (1946 to present), Embase (1980 to present) and PsycINFO (1806 to present) (Ovid platform), CENTRAL via The Cochrane Register of Studies Online (inception to present, Web platform) and The Cochrane Gynaecology and Fertility Group Specialised Register (inception to present, ProCite platform). Key clinical trial registries including ClinicalTrials.gov and the WHO International Clinical Trials Registry portal will also be searched (web platforms). The comprehensive strategy for this IPDMA is based on the search strategy of the latest Cochrane systematic review on this topic,<sup>14</sup> which was run from the date of inception of the databases to 23 September 2020. Therefore, we will run our database searches from 23 September 2020 to present. In this way we will ensure that we include all RCTs from inception to present.

The reference lists of relevant trails will be examined. Recent conference proceedings of key professional organisations and trial registers from all continents will also be scrutinised. Trial investigators who have agreed to share their data and take part in the IPDMA will be asked for information on any additional trial reports. No language or publication date restrictions will be applied to the searches. The detailed search strategy is listed in online supplemental appendix 1.

### Eligibility criteria

Only RCTs (published or unpublished) comparing the clinical effectiveness of a freeze-all versus a fresh embryo transfer strategy in couples undergoing IVF will be eligible for inclusion. RCTs on preimplantation genetic testing (PGT) will be excluded. For multiarm RCTs involving both PGT and non-PGT, the non-PGT arms will be included. The following eligibility criteria will be followed:

- ▶ Population: women undergoing IVF, using their own oocytes; for trials including both couples with both autologous oocytes and oocyte donations, couples with oocytes donation will be excluded.
- ▶ Intervention: elective freezing of all suitable embryos followed by thawed frozen embryo transfer.
- ▶ Comparison group: fresh embryo transfer followed by thawed frozen embryo transfer.
- ▶ Outcome measures: the core outcome set for infertility research and consensus definitions of these outcomes<sup>20,21</sup> will be used (indicated with \* below), with additional outcomes of interest listed below. All outcomes will be measured based on the first embryo transfer, except for cumulative live birth and time to pregnancy leading to live birth, where multiple episodes of embryo transfers resulting from the same oocyte retrieval cycle in same couple will be included.

### Primary outcome

\*Live birth resulting from the first embryo transfer. Live birth resulting from spontaneous pregnancy after randomisation before the first embryo transfer will also be included.<sup>20</sup>

### Secondary outcomes (refer to the first pregnancy unless specified)

#### Pregnancy outcomes

- ▶ \*Clinical pregnancy (a pregnancy diagnosed by ultrasonographic examination of at least one fetus with a discernible heartbeat)<sup>20</sup>;
- ▶ Pregnancy (defined as positive pregnancy test at 11–17 days after embryo transfer);
- ▶ \*Pregnancy loss (including ectopic pregnancy, miscarriage, stillbirth, termination of pregnancy)<sup>20</sup>;
- ▶ \*Multiple pregnancy<sup>20</sup>;
- ▶ \*Gestational age at delivery (weeks of gestation);
- ▶ Healthy baby (defined as term (>37 weeks) singleton live birth with appropriate weight for gestation. Appropriate weight will be determined by plotting weight against the gestational age on the standardised ethnicity-based growth charts).

#### Obstetric outcomes

- ▶ Gestational diabetes.
- ▶ Hypertensive disorders of pregnancy (comprising pregnancy induced hypertension; pre-eclampsia and eclampsia) as reported by individual investigators.
- ▶ Antepartum haemorrhage (placenta praevia, placenta accrete and other antepartum haemorrhage).
- ▶ Postpartum haemorrhage.

#### Other maternal safety outcomes

- ▶ Moderate or severe OHSS.

### Neonatal outcomes

- ▶ \*Birth weight
  - Small for gestational age
  - Large for gestational age
- ▶ \*Neonatal mortality
- ▶ \*Major congenital anomaly

### Cumulative outcomes

- ▶ Cumulative live birth (only the first live birth resulting from the same oocyte retrieval cycle after randomisation will be included);
- ▶ Time to pregnancy leading to live birth (resulting from the same oocyte retrieval cycle after randomisation). The time of randomisation will be the starting time point. For RCTs where randomisation occurs before oocytes retrieval, the start time of this outcome will be truncated at a comparable time to other RCTs.

### Study selection

Two members of the team will independently assess eligibility of studies identified through the search. Disagreements will be resolved by involving a third member of the team. Investigators of included trials will not be involved in the assessments of their own trials. Study selection will be performed and managed in an online platform, Covidence.<sup>22</sup>

### Establishment of the INFORM collaboration

We have already established contacts with the principal investigators of these trials and invited them to participate in this study and form an international collaboration: the *Individual participant data meta-analysis of trials comparing frozen versus fresh embryo transfer strategy (INFORM) collaboration*. Table 1 lists the trial groups

**Table 1** Trial groups in the *Individual participant data meta-analysis of trials comparing frozen versus fresh embryo transfer strategy (INFORM) collaboration* up to February 2022

Trial	Location	Status	Sample size
31	Italy	Published	125
NCT00963625 <sup>5</sup>	USA	Published	137
NCT00963079 <sup>6</sup>	USA	Published	122
NCT01841528 <sup>9</sup>	China	Published	1508
NCT02471573 <sup>12</sup>	Vietnam	Published	782
ChiCTR-IOR-14005406 <sup>11</sup>	China	Published	2157
NCT01954758 <sup>32</sup>	Spain	Published	458
ChiCTR-IOR-14005405 <sup>10</sup>	China	Published	1650
NCT02148393 <sup>33</sup>	Belgium	Published	212
34	China	Published	100
NCT02746562 <sup>13</sup>	Denmark	Published	460
NTR3187 <sup>15</sup>	Netherlands	Published	205
ISCTRN-61225414 <sup>14</sup>	UK	Published	619
ACTRN 12616000643471	Australia	Ongoing	400





identified during the pilot search that have joined the collaboration.

### Data collection, acquisition and cleaning

We will seek to collect data from all participants included in eligible RCTs. All primary investigators will be asked to share their deidentified trial IPD electronically using encrypted or protected data transfer procedures (File-Share via Monash Secure Data Enclaves platform) after signing a data usage agreement. Data from individual datasets will remain the property of the primary trial investigators who have provided them. The core team of researchers at Monash University will be responsible for the collection, handling, checking and analysis of IPD. A data variable list is presented in online supplemental appendix 2.

Data will be accepted in an electronic format, with variables and categories either adequately labelled within the dataset or accompanied by a separate dictionary. Comprehensive details of units or coding used will be requested, including how missing or not applicable values were dealt with. If any parts of the data are unclear, clarification will be sought from the relevant trials' investigators. Trial protocols will also be requested.

Once all the data are collected, the definition and coding of variables will be assessed for compatibility. The original data from all trials will be stored into a single database for analysis. A unique trial identification variable will be created to identify individual trials within the pooled dataset. The data will be checked with respect to range, internal consistency, missing or extreme values, errors and consistency with the published reports. Trial details, such as randomisation methods, characteristics of intervention, outcome measures and missing data will be crosschecked against published reports, trial protocols and data collection schedules. Inconsistencies or missing data will be discussed with the individual investigators and attempts will be made to resolve any problems by consensus. Completeness of the data will be checked and where data are found to have missing values, the relevant trial's investigators will be asked to provide reasons and check whether the actual values are available.

All anonymised data received from the investigators of included trials will be treated as sensitive data and stored securely in Monash Secure Data Enclaves platform, which is a software-defined, secure and centralised private cloud infrastructure managed by Monash University. Identifiable information sent by the trial's investigators (eg, names and addresses of participants) will not be accepted. All data will be subject to the Data Protection regulations and laws. The data will only be used for the purpose set out in the research protocol for this project and stored for 5 years beyond the life of this project.

The planned timeline for data transfer is February 2023. For ongoing studies that cannot provide data by then, they will be included in future update.

### Risk of bias and overall certainty of evidence assessment

The risk of bias of each trial will be assessed using the revised risk of bias tool for RCTs (ROB 2), including the following individual five domains and an overall assessment: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result.<sup>23</sup> Two reviewers will independently assess the risk of bias of included trials. Any disagreement between reviewers will be resolved by discussion or through consultation with a third member of the project team. If necessary, additional information from the trials' investigators will be sought to improve the accuracy of risk of bias assessment.

The overall certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach consisting of five domains consideration of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.

### Statistical analysis

All analyses will be based on IPD from all included RCTs. The primary analysis for all primary and secondary outcomes will be by intention to treat (ITT), that is, per woman randomised. Secondary analyses will be performed to include the clinically relevant denominators such as: per total number of women with a pregnancy after embryo transfer, for miscarriage; and per total number of babies born, for birth weight and congenital anomalies. For neonatal outcomes, the unit of analysis in the ITT analysis will also be the mother in the primary analysis and in cases of multiple pregnancy where the infants' outcomes differed, the worst outcome will be used. This reflects the negative impacts of any neonatal complication among multiple pregnancies on the families from a patient's perspective. In secondary analyses of neonatal outcomes, the unit of analysis will be the infant.

To estimate the effect of freeze-all compared with fresh embryo transfer, a two-stage IPD meta-analysis will be performed.<sup>24</sup> The first stage will involve analysing the IPD separately in each study in order to obtain aggregate data (ie, the treatment effect in each study). Binary outcomes (eg, live birth) will be analysed using Poisson regression models in order to estimate risk ratios. Continuous outcomes (eg, birth weight) will be analysed using linear regression models. The overall estimated mean and SD by treatment group will be presented along with the mean difference in treatment effect and accompanying 95% CI. All models will be adjusted for participant level predictors (eg, female age and body mass index). The second stage will involve using random effects meta-analysis with restricted maximum likelihood methods to estimate the average treatment effect across trials, followed by the Hartung-Knapp-Sidik-Jonkman approach to estimate the confidence intervals.<sup>25</sup> The study-specific risk ratio and overall risk ratio with 95% CIs will be presented graphically using a forest plot. For time-to-event outcomes, Cox Proportional Hazards regression will be used but if not

applicable, other appropriate methods will be used.<sup>26</sup> The heterogeneity statistics  $I^2$  and  $\tau^2$  will be reported.

A two-stage IPD meta-analysis will be the preferred approach. But in circumstances where there are RCTs with very small numbers of events or zero event for some outcomes, a one-stage approach will be used. Nevertheless, we intend to repeat the meta-analysis of the primary outcome using a one-stage approach as a sensitivity analysis to check for robustness. If data do not meet the assumptions of the model, transformations or alternative models will be considered. Publication bias across trials will be visualised using a contour-enhanced funnel plot. In the case of participants with some missing data for variables within trials, multiple imputation methods will be used as appropriate. Participants with non-compliant group allocation will be considered as per the group randomised in ITT analysis and will be excluded from the per protocol analysis. To evaluate IPD availability bias, we will compare summary estimates from studies providing IPD and those not providing or providing only incomplete IPD. A detailed statistical analysis plan will be developed by the project team and agreed on by the collaboration before statistical analysis. Statistical analysis will be performed in Stata V.16.1 (StataCorp, USA) or later versions, and IPDMA will be performed using 'ipdmetan'<sup>27</sup> and 'ipdforest'<sup>28</sup> suites.

### Subgroup analysis or treatment covariate interaction

We will follow the current recommendations for examining the interactions between treatment effect and participant-level covariates in IPDMA, including nonlinear relationships between continuous covariates and treatment effects.<sup>29 30</sup> The following treatment-covariate interactions (subgroup effects) will be assessed for the primary.<sup>8</sup> All continuous variables will be considered as continuous variables without categorisation and non-linear interactions will also be considered.

#### Participant-level covariates

- ▶ Maternal age
- ▶ Serum antimullerian hormone levels
- ▶ Antral follicle count
- ▶ Stage embryo transfer (cleavage/blastocyst)\*
- ▶ Quality of embryo(s) transferred
- ▶ Number of embryos transferred
- ▶ Number of oocytes retrieved
- ▶ Number of good quality embryos available on day 3
- ▶ Progesterone level on the day of human chorionic gonadotropin (hCG) trigger
- ▶ Polycystic ovary syndrome (PCOS/WHO group II-anovulation (cause of infertility)
- ▶ Previous IVF failure.

\*These could be a postrandomisation variable in some studies.

We will also consider the following treatment-level covariates. As these covariates either occur after randomisation or are relevant to the intervention group (freeze-all) only, the findings will be considered exploratory only. If

the variables are not available at participant level, they will be treated as centre-level or trial-level covariate in the analysis.

- ▶ Stage of embryo cryopreservation
- ▶ Method of embryo cryopreservation
- ▶ Endometrial preparation protocol for FET (natural vs artificial)
- ▶ Luteal support protocol (progesterone type, dose, duration).

### Sensitivity analysis

A sensitivity analysis will be performed, excluding trials judged to be at high risk of bias. To assess the impact of non-adherence to the randomised treatment allocation (ie, women who were randomised to receive thawed frozen embryo transfer, receiving fresh embryo transfer—non-compliers), a per protocol analysis will be performed. To test the robustness of the findings, a one-stage IPDMA will also be performed. All sensitivity analyses will be performed for the primary outcome.

### Patient and public involvement (PPI)

We have patient and public representatives involved in this IPDMA. This has been integral to the design of the proposed IPDMA with input from Kate Brian (previous Women's Voices Lead at the Royal College of Obstetrics and Gynaecology), Gwenda Burns (CEO of Fertility Network UK) and Karin Hammarberg (The Victorian Assisted Reproductive Treatment Authority). PPI representatives were involved in the inception of the idea and development of the research protocol. Patient representatives have (a) confirmed the critical importance of the proposed IPDMA in generating results which will improve clinical care for couples undergoing IVF and (b) helped to prioritise our clinical outcomes and key subgroups. Ongoing PPI will be integrated into our research and aim to provide value via the following: (a) continuing involvement of all PPI collaborators throughout the course of the project, including interpretation of results and report preparation as well as (b) involvement in the dissemination of research findings.

### DISCUSSION

This IPDMA offers a unique opportunity evaluate both effectiveness and safety outcomes based on individual patient characteristics, some of which were impossible in existing aggregate data meta-analysis due to heterogeneous reporting and/or analysis strategies in the primary reports. These outcomes include time to pregnancy leading to live birth and perinatal outcomes. This project will be timely due to the growing relevance of a major unanswered clinical question with exponentially increasing demand at a time when multiple RCTs have either been published recently or are due to be completed soon. In addition, this IPDMA will help us identify individuals that would benefit most from a freeze-all policy or a fresh transfer policy, and thus provide guidance towards

personalised IVF treatment. The coordination of international collaboration will also promote research transparency and data sharing in our research area, making clinical trials more useful for their end-users.

#### Author affiliations

- <sup>1</sup>Department of Obstetrics and Gynaecology, Monash University, Clayton, VIC, Australia
- <sup>2</sup>Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
- <sup>3</sup>Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand
- <sup>4</sup>Centre for Reproductive Medicine, Shandong University, Jinan, Shandong, China
- <sup>5</sup>Department of Obstetrics and Gynecology and Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA
- <sup>6</sup>Shanghai Key Laboratory for Assisted Reproduction and Reproductive Genetics, Center for Reproductive Medicine, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
- <sup>7</sup>Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam
- <sup>8</sup>National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
- <sup>9</sup>Fertility Clinic, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
- <sup>10</sup>Igenomix Foundation, INCLIVA Health Research Institute, Valencia, Spain
- <sup>11</sup>Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium
- <sup>12</sup>Centre for Reproductive Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
- <sup>13</sup>Reproductive Medicine Unit, SISMeR, Bologna, Emilia-Romagna, Italy
- <sup>14</sup>Department of Obstetrics and Gynecology, Kirk Kerkorian School of Medicine, Las Vegas, NV, USA
- <sup>15</sup>Fertility Center of Las Vegas, Las Vegas, NV, USA
- <sup>16</sup>Centre for Reproductive Medicine, Peking University Third Hospital, Beijing, China
- <sup>17</sup>Centre for Big Data Research in Health & School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia
- <sup>18</sup>School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK
- <sup>19</sup>Aberdeen Centre of Reproductive Medicine, NHS Grampian, Aberdeen, UK

**Twitter** Rui Wang @ruiwangmd, David J McLernon @davemclernon and Femke Mol @femmie75

**Acknowledgements** We would like to thank other members of the INFORM Collaboration who contribute to the protocol: Kate Brian (previous Women's Voices Lead at the Royal College of Obstetrics and Gynaecology, RCOG), Gwenda Burns (CEO of Fertility Network UK) and Karin Hammarberg (The Victorian Assisted Reproductive Treatment Authority, VARTA).

**Collaborators** The INFORM Collaboration: Rui Wang, David J McLernon, Shimona Lai, Marian G Showell, Zi-Jiang Chen, Daimin Wei, Richard S Legro, Ze Wang, Yun Sun, Keliang Wu, Lan N Vuong, Pollyanna Hardy, Anja Pinborg, Sacha Stormlund, Xavier Santamaría, Carlos Simón, Christophe Blockeel, Femke Mol, Anna P Ferraretti, Bruce S Shapiro, Forest C Garner, Rong Li, Christos A Venetis, Ben W Mol, Siladitya Bhattacharya, Kate Brian, Gwenda Burns, Karin Hammarberg, Abha Maheshwari.

**Contributors** Study conception and design: RW, DJM, MGS, BWM, SB and AM. Acquisition of data: SL, Z-JC, DW, RSL, ZW, YS, KW, LNV, PH, AP, SS, XS, CS, NT, CB, FM, APF, BSS, FCG, RL, CAV. Analysis: RW, DJM, SL, and AM. Drafting of the manuscript: RW and AM. Interpretation and critical revision of the article: DJM, MGS, SL, Z-JC, DW, RSL, ZW, YS, KW, LNV, PH, AP, SS, XS, CS, NT, CB, FM, APF, BSS, FCG, RL, CAV, BWM and SB.

**Funding** The study is funded by an Australian National Health and Medical Research Council (NHMRC) Emerging Leadership Investigator Grant (GNT2009767).

**Competing interests** RW reports grants from the NHMRC and NHMRC Centre for Research Excellence in Women's Health in Reproductive Life (CRE WHIRL). LNV reports personal fees from Merck, Merck Sharpe and Dohme, Ferring, outside the submitted work. AP reports grants and personal fees from Gedeon Richter, Ferring Pharmaceuticals and Merck A/S and personal fees from IBSA, outside the submitted work. CB reports grants and personal fees from Gedeon Richter, Ferring Pharmaceuticals, Merck A/S and Organon, and personal fees from IBSA

and Abbott outside the submitted work. CS is a co-inventor of Igenomix SL and Head of Scientific Advisory Board at Igenomix SL. BWM is supported by a NHMRC Investigator grant (GNT1176437). BWM reports personal fees from ObsEva and Merck, and travel support from Merck, outside the submitted work. SB is the Editor in Chief of Human Reproduction Open. AM reports grants from HTA/NHHR, travel/meeting support from Ferring and Pharmsure and participation in a Ferring advisory board. All other authors do not have competing interests to declare.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study. No datasets were generated for this publication as this is a protocol.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Rui Wang <http://orcid.org/0000-0002-6622-8134>  
Lan N Vuong <http://orcid.org/0000-0001-6529-6912>  
Ben W Mol <http://orcid.org/0000-0001-8337-550X>

#### REFERENCES

- Datta J, Palmer MJ, Tanton C, *et al*. Prevalence of infertility and help seeking among 15 000 women and men. *Hum Reprod* 2016;31:2108–18.
- Zhou Z, Zheng D, Wu H, *et al*. Epidemiology of infertility in China: a population-based study. *BJOG* 2018;125:432–41.
- Fausser BC. Towards the global coverage of a unified registry of IVF outcomes. *Reprod Biomed Online* 2019;38:133–7.
- ESHRE. ART fact sheet, 2022. Available: <https://www.eshre.eu/Press-Room/Resources> [Accessed 11 Feb 2022].
- Shapiro BS, Daneshmand ST, Garner FC, *et al*. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. *Fertil Steril* 2011;96:344–8.
- Shapiro BS, Daneshmand ST, Garner FC, *et al*. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. *Fertil Steril* 2011;96:516–8.
- Evans J, Hannan NJ, Edgell TA, *et al*. Fresh versus frozen embryo transfer: backing clinical decisions with scientific and clinical evidence. *Hum Reprod Update* 2014;20:808–21.
- Blockeel C, Campbell A, Cotichio G, *et al*. Should we still perform fresh embryo transfers in ART? *Hum Reprod* 2019;34:2319–29.
- Chen Z-J, Shi Y, Sun Y, *et al*. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. *N Engl J Med* 2016;375:523–33.
- Wei D, Liu J-Y, Sun Y, *et al*. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. *Lancet* 2019;393:1310–8.
- Shi Y, Sun Y, Hao C, *et al*. Transfer of fresh versus frozen embryos in ovulatory women. *N Engl J Med* 2018;378:126–36.



- 12 Vuong LN, Dang VQ, Ho TM, *et al.* IVF transfer of fresh or frozen embryos in women without polycystic ovaries. *N Engl J Med* 2018;378:137–47.
- 13 Stormlund S, Sopa N, Zedeler A, *et al.* Freeze-all versus fresh blastocyst transfer strategy during in vitro fertilisation in women with regular menstrual cycles: multicentre randomised controlled trial. *BMJ* 2020;370:m2519.
- 14 Maheshwari A, Bell JL, Bhide P, *et al.* Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze). *Hum Reprod* 2022;37:476–87.
- 15 Wong KM, van Wely M, Verhoeve HR, *et al.* Transfer of fresh or frozen embryos: a randomised controlled trial. *Hum Reprod* 2021;36:998–1006.
- 16 Maheshwari A, Pandey S, Amalraj Raja E, *et al.* Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? *Hum Reprod Update* 2018;24:35–58.
- 17 Zaat T, Zagers M, Mol F, *et al.* Fresh versus frozen embryo transfers in assisted reproduction. *Cochrane Database Syst Rev* 2021;2:CD011184.
- 18 Eapen A, Sparks A. Improved outcomes following frozen embryo transfer does not provide a "universal license to chill". *Fertil Steril* 2018;110:847–8.
- 19 Roque M, Haahr T, Geber S, *et al.* Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes. *Hum Reprod Update* 2019;25:2–14.
- 20 Duffy JMN, Bhattacharya S, Bhattacharya S, *et al.* Standardizing definitions and reporting guidelines for the infertility core outcome set: an international consensus development study† double dagger. *Hum Reprod* 2020;35:2735–45.
- 21 Duffy JMN, AlAhwany H, Bhattacharya S, *et al.* Developing a core outcome set for future infertility research: an international consensus development study† double dagger. *Hum Reprod* 2020;35:2725–34.
- 22 Covidence. *Covidence systematic review software, veritas health innovation.* Melbourne: Melbourne, Australia. www.covidence.org
- 23 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
- 24 Tierney JF, Vale C, Riley R, *et al.* Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. *PLoS Med* 2015;12:e1001855.
- 25 Burke DL, Ensor J, Riley RD. Meta-Analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* 2017;36:855–75.
- 26 de Jong VMT, Moons KGM, Riley RD, *et al.* Individual participant data meta-analysis of intervention studies with time-to-event outcomes: a review of the methodology and an applied example. *Res Synth Methods* 2020;11:148–68.
- 27 Fisher DJ. Two-Stage individual participant data meta-analysis and generalized forest plots. *Stata J* 2015;15:369–96.
- 28 Kontopantelis E, Reeves D. A short guide and a forest plot command (ipdforest) for one-stage meta-analysis. *Stata J* 2013;13:574–87.
- 29 Riley RD, Debray TPA, Fisher D, *et al.* Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: statistical recommendations for conduct and planning. *Stat Med* 2020;39:2115–37.
- 30 Fisher DJ, Carpenter JR, Morris TP, *et al.* Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017;356:j573.
- 31 Ferraretti AP, Gianaroli L, Magli C, *et al.* Elective cryopreservation of all pronucleate embryos in women at risk of ovarian hyperstimulation syndrome: efficiency and safety. *Hum Reprod* 1999;14:1457–60.
- 32 Simón C, Gómez C, Cabanillas S, *et al.* A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. *Reprod Biomed Online* 2020;41:402–15.
- 33 Santos-Ribeiro S, Mackens S, Popovic-Todorovic B, *et al.* The freeze-all strategy versus agonist triggering with low-dose hCG for luteal phase support in IVF/ICSI for high responders: a randomized controlled trial. *Hum Reprod* 2020;35:2808–18.
- 34 Yang S, Pang T, Li R, *et al.* The individualized choice of embryo transfer timing for patients with elevated serum progesterone level on the HCG day in IVF/ICSI cycles: a prospective randomized clinical study. *Gynecol Endocrinol* 2015;31:355–8.

## Appendix 1 Search strategy

CENTRAL via the Cochrane Register of Studies Online (CRSO)

- #1 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES
- #2 (assisted reproduct\* techn\*):TI,AB,KY
- #3 embryo\*:TI,AB,KY
- #4 blastocyst\*:TI,AB,KY
- #5 (vitro fertili?ation):TI,AB,KY
- #6 (intracytoplasmic sperm injection\*):TI,AB,KY
- #7 (ivf or icsi):TI,AB,KY
- #8 (ovari\* adj2 stimulation):TI,AB,KY
- #9 (in vitro adj2 maturation\*):TI,AB,KY
- #10 MESH DESCRIPTOR Infertility EXPLODE ALL TREES
- #11 (infertil\* or subfertil\*):TI,AB,KY
- #12 ((elevated or high or raise\* or rise) adj2 progesterone):TI,AB,KY
- #13 MESH DESCRIPTOR Ovarian Hyperstimulation Syndrome EXPLODE ALL TREES
- #14 (ovarian hyperstimulation syndrome):TI,AB,KY
- #15 OHSS:TI,AB,KY
- #16 (implantation failure\*):TI,AB,KY
- #17 ( preimplantation genetic screening):TI,AB,KY
- #18 (high responder\*):TI,AB,KY
- #19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13  
OR #14 OR #15 OR #16 OR #17 OR #18
- #20 MESH DESCRIPTOR Cryopreservation EXPLODE ALL TREES
- #21 MESH DESCRIPTOR Vitrification EXPLODE ALL TREES
- #22 MESH DESCRIPTOR Freezing EXPLODE ALL TREES
- #23 ((cryopreservat\* or cryofixation or cryonic suspension)):TI,AB,KY
- #24 (freez\* or frozen):TI,AB,KY
- #25 Vitrif\*:TI,AB,KY



- #26 Thaw\*:TI,AB,KY
- #27 (cryopreserv\* or cryofix\* ):TI,AB,KY
- #28 cryonic :TI,AB,KY
- #29 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
- #30 #19 AND #29

## Appendix 2 Variable list

Variable	Variable type	Notes
<b>IDs</b>		
Centre ID		For multi-centre trials only
<b>Randomisation</b>		
Randomisation	Categorical	Frozen/fresh
Date of randomisation	Continuous	DD-MM-YYYY
<b>Demographics/baseline</b>		
Female age	Continuous	In years
Ethnicity	Categorical	
Duration of infertility	Continuous	In months
Type of infertility	Categorical	Primary/secondary
Female BMI	Continuous	Kg/m <sup>2</sup>
	Continuous	
	Or	
Menstrual cycle	categorical	Days Or regular/irregular
Cause of infertility:	Categorical	Yes/no for each cause
1 Ovulatory	Categorical	
2 Tubal	Categorical	
3 Male	Categorical	
4 Unexplained	Categorical	
5 Endometriosis	Categorical	
PCOS/WHO II anovulation	Categorical	Yes/no
Smoker	Categorical	Current/past/never smoker
IVF cycle number	Continuous	1/2/3/...
Baseline AMH levels	Continuous	Ng/ml (1ng/ml= 7.1429pmol/L)
Baseline antral follicle count	Continuous	
<b>Ovarian stimulation</b>		
Ovarian stimulation protocol	Categorical	Long/short/ultrashort/antagonist
Total dose of gonadotrophins	Continuous	IU
Trigger	Categorical	Agonist/hCG/dual trigger
Progesterone level on day of HCG	Continuous	ng/ml (1ng/ml=3.18 nmol/L)
<b>Oocyte collection</b>		
Number of oocytes collected	Continuous	
Date of oocyte collection	Continuous	DD-MM-YYYY
<b>Fertilisation</b>		
Insemination method	Categorical	IVF/ICSI/split
Number of 2PN	Continuous	

Number of good quality embryos	Continuous	defined by ACE/BFS scoring- 6 to 8 cells minimum on day 3
<b>Embryo transfer</b>		
Actual intervention received	Categorical	Fresh/frozen
Date of embryo transfer	Continuous	YY-MM-YYYY
Stage of embryo transfer	Categorical	cleavage or blastocyst
Number of embryo transferred	Continuous	0/1/2/3
Quality of each transferred embryo	Categorical	Embryo quality
Endometrial thickness on the day of hCG	Continuous	mm (or on the last USG prior to ET for the frozen group)
Endometrial pattern	Categorical	trilaminar, opaque, not measured
<b>Embryo freezing</b>		
Number of spare embryos frozen	Continuous	For the fresh group only
Number of embryos frozen	Continuous	For the frozen group only
Stage of freezing	Categorical	cleavage or blastocyst
Method of freezing	Categorical	Vitrification/slow freezing
Endometrial preparation	Categorical	For the frozen group only, natural/modified/HRT-short/HRT-long
Number of embryos thawed	Continuous	
Luteal support (progesterone type)	Categorical	No/IM/Oral/Vaginal/Dydrogesterone/Mixed/Other
Does of progesterone per day	Continuous	
Duration of progesterone	Continuous	Days
Additional notes	String	
<b>Fertility outcomes</b>		
Live birth	Categorical	Yes/no
Healthy baby	Categorical	Yes/no (defined as term (>37 weeks) singleton live birth with appropriate weight for gestation. Appropriate weight will be determined by plotting weight against the gestational age on the standardised ethnicity-based growth charts)
Pregnancy	Categorical	Yes/no (hCG positive)
Clinical pregnancy	Categorical	Yes/no (Viable pregnancy confirmed by ultrasound)
Pregnancy loss:	Categorical	Yes/no
- ectopic pregnancy	Categorical	Yes/no
- miscarriage	Categorical	Yes/no
- stillbirth	Categorical	Yes/no
- termination of pregnancy	Categorical	Yes/no
Multiple pregnancy:	Categorical	Yes/no
Twin	Categorical	Yes/no

High-order (triplet or more)	Categorical	Yes/no
Gestational age at delivery	Continuous	Days (or x weeks + y days)
<b>Obstetric outcomes</b>		
Hypertensive disorders of pregnancy	Categorical	Yes/no (comprising pregnancy induced hypertension, pre-eclampsia and eclampsia)
- preeclampsia	Categorical	Yes/no
Antepartum haemorrhage	Categorical	Yes/no
- placenta praevia	Categorical	Yes/no
- placenta accrete	Categorical	Yes/no
- unexplained	Categorical	Yes/no
Postpartum haemorrhage	Categorical	Yes/no
<b>Other maternal safety outcomes:</b>		
OHSS	Categorical	No/mild/moderate/severe (RCOG green top guidance)
<b>Neonatal outcomes#</b>		
Birthweight	Continuous	Grams
Neonatal mortality	Categorical	Yes/no
Major congenital anomaly	Categorical	Yes/no
- if yes, specify		Detailed description
Admission to neonatal intensive care unit	Categorical	Yes/no
<b>Cumulative outcomes (till the first live delivery)*</b>		
Cumulative live birth	Categorical	Yes/no
Date of the last embryo transfer or the embryo transfer resulting in live birth	Continuous	DD-MM-YYYY
<b>Follow up</b>		
Withdrew consent	Categorical	Categorical
- if yes, date	Continuous	DD-MM-YYYY
Loss to follow up	Categorical	Categorical
- if yes, date	Continuous	DD-MM-YYYY

Footnotes: #For multiple birth, neonatal outcomes will be collected for each infant separately.