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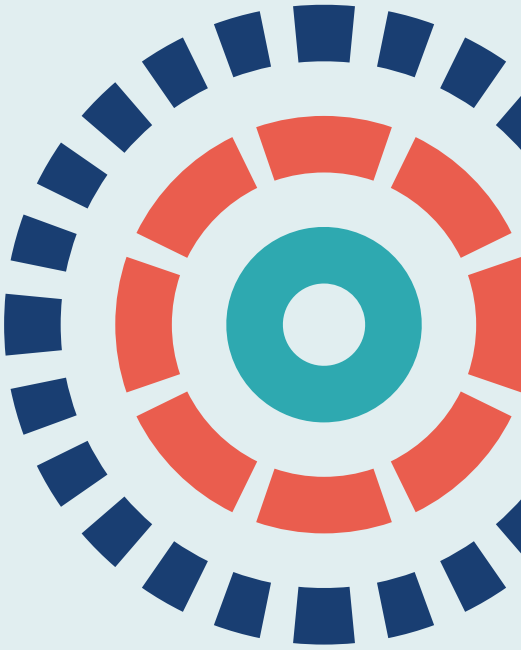

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Transfer of thawed frozen embryo versus fresh embryo to improve the healthy baby rate in women undergoing IVF: the E-Freeze RCT

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Abstract

Transfer of thawed frozen embryo versus fresh embryo to improve the healthy baby rate in women undergoing IVF: the E-Freeze RCT

Abha Maheshwari,[1*] Vasha Bari,[2] Jennifer L Bell,[2] Siladitya Bhattacharya,[1] Priya Bhide,[3] Ursula Bowler,[2] Daniel Brison,[4] Tim Child,[5] Huey Yi Chong,[1] Ying Cheong,[6] Christina Cole,[2] Arri Coomarasamy,[7] Rachel Cutting,[8] Fiona Goodgame,[2] Pollyanna Hardy,[2] Haitham Hamoda,[9] Edmund Juszczak,[2,10] Yacoub Khalaf,[11] Andrew King,[2] Jennifer J Kurinczuk,[2] Stuart Lavery,[12] Clare Lewis-Jones,[13] Louise Linsell,[2] Nick Macklon,[14,15] Raj Mathur,[16] David Murray,[2] Jyotsna Pundir,[17] Nick Raine-Fenning,[18] Madhurima Rajkohwa,[19] Lynne Robinson,[20] Graham Scotland,[1] Kayleigh Stanbury[2] and Stephen Troup[21] on behalf of the E-Freeze Trial Collaborative Group

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Background: Freezing all embryos, followed by thawing and transferring them into the uterine cavity at a later stage (freeze-all), instead of fresh-embryo transfer may lead to improved pregnancy rates and fewer complications during in vitro fertilisation and pregnancies resulting from it.

Objective: We aimed to evaluate if a policy of freeze-all results in a higher healthy baby rate than the current policy of transferring fresh embryos.

Design: This was a pragmatic, multicentre, two-arm, parallel-group, non-blinded, randomised controlled trial.

Setting: Eighteen in vitro fertilisation clinics across the UK participated from February 2016 to April 2019.

Participants: Couples undergoing their first, second or third cycle of in vitro fertilisation treatment in which the female partner was aged < 42 years.

Interventions: If at least three good-quality embryos were present on day 3 of embryo development, couples were randomly allocated to either freeze-all (intervention) or fresh-embryo transfer (control).

Outcomes: The primary outcome was a healthy baby, defined as a live, singleton baby born at term, with an appropriate weight for their gestation. Secondary outcomes included ovarian hyperstimulation, live birth and clinical pregnancy rates, complications of pregnancy and childbirth, health economic outcome, and State–Trait Anxiety Inventory scores.

Results: A total of 1578 couples were consented and 619 couples were randomised. Most non-randomisations were because of the non-availability of at least three good-quality embryos ($n = 476$). Of the couples randomised, 117 (19%) did not adhere to the allocated intervention. The rate of non-adherence was higher in the freeze-all arm, with the leading reason being patient choice. The intention-to-treat analysis showed a healthy baby rate of 20.3% in the freeze-all arm and 24.4% in the fresh-embryo transfer arm (risk ratio 0.84, 95% confidence interval 0.62 to 1.15). Similar results were obtained using complier-average causal effect analysis (risk ratio 0.77, 95% confidence interval 0.44 to 1.10), per-protocol analysis (risk ratio 0.87, 95% confidence interval 0.59 to 1.26) and as-treated analysis (risk ratio 0.91, 95% confidence interval 0.64 to 1.29). The risk of ovarian hyperstimulation was 3.6% in the freeze-all arm and 8.1% in the fresh-embryo transfer arm (risk ratio 0.44, 99% confidence interval 0.15 to 1.30). There were no statistically significant differences between the freeze-all and the fresh-embryo transfer arms in the live birth rates (28.3% vs. 34.3%; risk ratio 0.83, 99% confidence interval 0.65 to 1.06) and clinical pregnancy rates (33.9% vs. 40.1%; risk ratio 0.85, 99% confidence interval 0.65 to 1.11). There was no statistically significant difference in anxiety scores for male participants (mean difference 0.1, 99% confidence interval −2.4 to 2.6) and female participants (mean difference 0.0, 99% confidence interval −2.2 to 2.2) between the arms. The economic analysis showed that freeze-all had a low probability of being cost-effective in terms of the incremental cost per healthy baby and incremental cost per live birth.

Limitations: We were unable to reach the original planned sample size of 1086 and the rate of non-adherence to the allocated intervention was much higher than expected.

Conclusion: When efficacy, safety and costs are considered, freeze-all is not better than fresh-embryo transfer.

Trial registration: This trial is registered as ISRCTN61225414.

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Report Supplementary Material 2 E-Freeze Economic Questionnaire

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/AEFU1104).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

24/7	24 hours per day, 7 days per week
ACE	The Association of Clinical Embryologists
AE	adverse event
ANC	antenatal care
ASHE	Annual Survey of Hours and Earnings
BMI	body mass index
CACE	complier-average causal effect
CI	confidence interval
CLBR	cumulative live birth rate
CRF	case report form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eCRF	electronic case report form
E-Freeze	elective freeze
GDM	gestational diabetes mellitus
GnRH	gonadotropin-releasing hormone
HCG	human chorionic gonadotropin
HFEA	Human Fertilisation and Embryology Authority
HRG	Heathcare Resource Group
HRT	hormone replacement therapy
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICSI	intracytoplasmic sperm injection
IPD	individual patient data
IPD-MA	individual patient data meta-analysis
IQR	interquartile range
ITT	intention to treat
IVF	in vitro fertilisation
MD	mean difference
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NPEU	National Perinatal Epidemiology Unit
OHSS	ovarian hyperstimulation syndrome
PI	principal investigator
PIL	participant information leaflet
PMG	Project Management Group
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
STAI	State–Trait Anxiety Inventory
TSC	Trial Steering Committee

Plain English summary

During in vitro fertilisation, eggs and sperm are mixed in a laboratory to create embryos. An embryo is placed in the womb 2–5 days later (fresh-embryo transfer) and the remaining embryos are frozen for future use. Initial research suggested that freezing all embryos followed by thawing and replacing them a few weeks later could improve treatment safety and success. Although these data were promising, the data came from small studies and were not enough to change practice and policy.

We conducted a large, multicentre, clinical trial to evaluate the two strategies: fresh-embryo transfer compared with later transfer of frozen embryos. We also compared the costs of both strategies during in vitro fertilisation treatment, pregnancy and delivery.

This study was conducted across 18 clinics in the UK from 2016 to 2019, and 619 couples participated. Couples were allocated to one of two strategies: immediate fresh-embryo transfer or freezing of all embryos followed later by transfer of frozen embryo. The study's aim was to find out which type of embryo transfer gave participants a higher chance of having a healthy baby.

We found that freezing all embryos followed by frozen-embryo transfer did not lead to a higher chance of having a healthy baby. There were no differences between strategies in the number of live births, the miscarriage rate or the number of pregnancy complications. Fresh-embryo transfer was less costly from both a health-care and a patient perspective.

A routine strategy of freezing all embryos is not justified given that there was no increase in success rates but there were extra costs and delays to embryo transfer.

Scientific summary

The study operated to a strict pre-agreed protocol and statistical analysis plan.

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In vitro fertilisation (IVF) involves several steps. Initially, hormones are used to stimulate the ovaries to produce eggs, which are harvested surgically. Next, embryos are created in a laboratory by mixing eggs with sperm by either putting them together or injecting sperm directly into an egg (i.e. intracytoplasmic sperm injection). Embryos are grown in culture for a few days before being transferred into the uterus (i.e. fresh-embryo transfer) on day 3 (the cleavage stage) or day 5 (the blastocyst stage). Despite improvements in technology, success rates remain low (i.e. 25% live birth rate). Systematic reviews have shown poorer maternal and perinatal outcomes in pregnancies following IVF, particularly after fresh-embryo transfer [Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update* 2012;**18**:485–503; Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. *Fertil Steril* 2012;**98**:368–77.e9]. The process of IVF also incurs a risk of ovarian hyperstimulation syndrome, which can cause serious maternal morbidity and, rarely, mortality. It has been suggested that avoiding fresh-embryo transfer by freezing all embryos, followed by thawing and subsequent transfer into the uterus at a later stage (frozen-embryo transfer), may lead to improved pregnancy rates and fewer complications. However, the existing evidence from three small randomised trials (and the resulting meta-analysis) was considered inadequate to justify a radical change in practice to a freeze-all policy [Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Can fresh-embryo transfers be replaced by cryopreserved-thawed embryo transfers in assisted reproductive cycles? A randomized controlled trial. *J Assist Reprod Genet* 2010;**27**:357–63; Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. 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, Aguirre M, Hudson C, Thomas S. 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**:516–18].

Objective

The primary objective of the trial was to determine if a policy of freezing all embryos, followed by frozen-embryo transfer, resulted in a higher healthy baby rate than the current policy of transferring fresh embryos.

The secondary objectives of the trial were to assess if a policy of freezing all embryos, followed by frozen-embryo transfer, led to fewer complications associated with IVF treatment and pregnancy, and greater cost-effectiveness from a health service perspective than the current policy of transferring fresh embryos.

Methods

Study design

The elective freeze (E-Freeze) trial was a pragmatic, multicentre, two-arm, parallel-group, non-blinded, randomised controlled trial conducted in the UK.

Setting

The trial was conducted in 18 clinics in England and Scotland.

Participants

Inclusion criteria

- Female partner aged between ≥ 18 and < 42 years at the start of treatment (i.e. start of ovarian stimulation).
- Couples who were undergoing their first, second or third cycle of IVF treatment.
- Both partners were resident in the UK.
- Both partners provided written informed consent.
- At least three good-quality embryos were available {as determined by nationally agreed criteria [Cutting R, Morroll D, Roberts SA, Pickering S, Rutherford A, BFS and ACE. Elective single embryo transfer: guidelines for practice British Fertility Society and Association of Clinical Embryologists. *Hum Fertil* (*Camb*) 2008;**11**:131–46]} on day 3 following fertilisation.

Exclusion criteria

- Use of donor gametes.
- Planned preimplantation genetic testing.
- Planned elective freezing of all embryos for clinical reasons (e.g. severe risk of ovarian hyperstimulation/fertility preservation).
- Couples had been previously randomised to the E-Freeze trial.

Interventions

In the standard-care arm (i.e. the fresh-embryo transfer arm), women underwent fresh-embryo transfer in accordance with local protocols.

In the intervention arm (freeze-all), all good-quality embryos were frozen in accordance with local protocols, followed by frozen-embryo transfer later.

One-to-one randomisation was undertaken, minimising for age, duration of infertility, type of infertility, type of insemination and number of good-quality embryos.

Outcomes

Primary outcome

- Healthy baby (defined as term born, singleton, live birth, with an appropriate weight for their gestation).

Secondary outcomes

- Maternal safety.
- Complications of pregnancy and delivery.
- Measures of clinical effectiveness.
- Measures of the clinical effectiveness of the process of freezing embryos.
- Health economic measures.
- Evaluation of emotional state.

Statistics and analysis plan

Sample size

With 90% power and a two-sided 5% level of statistical significance, 1086 women (543 in each arm) were required to show an absolute risk difference in the primary outcome of 8% (from 17% to 25%) between fresh-embryo transfer and frozen-embryo transfer strategies. An expert panel of clinicians considered a difference of at least 8% to be clinically important enough to recommend a change in clinical practice, considering the extra time, effort and cost involved in freezing all embryos.

Descriptive analysis

The flow of participants through each stage of the trial was summarised by trial arm. Demographic factors and clinical characteristics were summarised for all participants at trial entry and separately for those who delivered. Counts and percentages were reported for categorical variables, means (with standard deviations) were reported for normally distributed continuous variables, and medians (with interquartile ranges) were reported for other continuous variables.

Comparative analysis

The primary analysis for all primary and secondary outcomes was by intention to treat. Secondary analyses were performed to include the clinically relevant denominators, such as the total number of women with a positive pregnancy test after embryo transfer (for miscarriage); the total number of pregnant women with an ongoing pregnancy resulting in delivery (for pregnancy complications); and the total number of babies born (for birthweight and congenital anomalies). For neonatal secondary outcomes, the unit of analysis in the intention-to-treat analysis was the mother, and in cases of multiple pregnancy where the infants' outcomes differ, the worst outcome was reported.

Risk ratios and confidence intervals were calculated using log-binomial regression model or a Poisson regression model with a robust variance estimator. Analyses were adjusted for all minimisation factors where possible. Both unadjusted and adjusted risk ratios were presented, with the primary inference being based on the adjusted estimates. Linear regression was used for normally distributed continuous outcomes and quantile regression was used for skewed continuous outcomes.

Prespecified subgroup analyses for the primary outcome were:

1. woman's age
2. fertility clinic
3. cleavage compared with blastocyst embryo transfer
4. single compared with multiple embryo transfer
5. number of previous embryo transfers.

Among those receiving frozen-embryo transfer, the primary outcome was also summarised by the subgroups:

1. natural compared with hormone replacement cycles
2. vitrification compared with slow freezing.

For the primary outcome, 95% confidence intervals were used for all analyses; for the secondary outcomes, 99% confidence intervals were used.

The economic analysis assessed costs to the health service from randomisation to embryo transfer, and to delivery for those achieving pregnancy. Costs to participants and their partners were collected from randomisation to embryo transfer. Following an intention-to-treat approach, cost-effectiveness was expressed in terms of the incremental cost per healthy baby and the incremental cost per additional live birth for freeze-all compared with fresh-embryo transfer. The analyses were performed with and without the inclusion of pregnancy-related costs. Non-parametric bootstrapping was used to characterise uncertainty surrounding the difference in the combined costs and effects between the strategies, and further modelling was conducted to extrapolate expected cumulative costs and outcomes following the transfer of the remaining frozen embryos for those failing to achieve a live birth with the index transfer.

Additional analyses

The following prespecified analyses were carried out for the primary outcome only:

- per-protocol analysis – restricted to those who complied with allocated intervention
- as-treated analysis– grouping couples according to allocation actually received
- complier-average causal effect analysis.

Results

A total of 1578 couples consented, of whom 619 were randomised (fresh-embryo transfer arm, $n = 310$; freeze-all arm, $n = 309$). Most non-randomisations ($n = 959$) were because of the non-availability of three good-quality embryos ($n = 476$). Of the couples randomised, 117 (19%) did not adhere to the allocated intervention. Non-adherence was higher in the freeze-all arm (31.3%) than in the fresh-embryo transfer arm (6.8%), with the most common reason being patient choice. There were nine withdrawals from the study in total: seven in the freeze-all arm and two in the fresh-embryo transfer arm.

Primary outcome

The intention-to-treat analysis showed that the healthy baby rate was 20.3% in the freeze-all arm and 24.4% in the fresh-embryo transfer arm (risk ratio 0.84, 95% confidence interval 0.62 to 1.15). Similar results were obtained using complier-average causal effect analysis (risk ratio 0.77, 95% confidence interval 0.44 to 1.10), per-protocol analysis (risk ratio 0.87, 95% confidence interval 0.59 to 1.26) and as-treated analysis (risk ratio 0.91, 95% confidence interval 0.64 to 1.29). There was no evidence of any differences in the healthy baby rate across age groups (< 35, 35 to < 40 and ≥ 40 years), whether or not a previous embryo transfer had been performed (0 or ≥ 1), whether it was cleavage or blastocyst transfer, or whether one or two embryos were transferred.

Secondary outcomes

There were no statistically significant differences in the live birth rates (28.3% vs. 34.3%; risk ratio 0.83, 99% confidence interval 0.65 to 1.06) and clinical pregnancy rates (33.9% vs. 40.1%; risk ratio 0.85, 99% confidence interval 0.65 to 1.11) in the freeze-all arm compared with the fresh-embryo transfer arm.

There were no significant differences between the two arms in any of the obstetrics and perinatal outcomes (i.e. hypertensive disorders of pregnancy, antepartum haemorrhage, preterm delivery, very preterm delivery, onset of labour, mode of delivery, low birthweight, high birthweight, low weight for gestational age, high weight for gestational age and congenital anomalies). There was no statistical difference between the arms in anxiety scores among male participants (mean difference 0.1, 99% confidence interval −2.4 to 2.6) or female participants (mean difference 0.0, 99% confidence interval −2.2 to 2.2).

A total of 88.6% (248/280) of embryos survived the freezing–thawing process.

Health economic outcomes

Following adjustment for minimisation criteria, the mean post-randomisation treatment costs (inclusive of ovarian hyperstimulation) were £1395 (95% confidence interval £1294 to £1505) per woman randomised to the fresh-embryo transfer arm and £1576 (95% confidence interval £1514 to £1642) for each of those randomised to the freeze-all arm. The mean between-group difference was £181 (95% confidence interval £60 to £292). Based on the estimated difference in the healthy live birth rate (−0.039, 95% confidence interval −0.101 to 0.027), fresh-embryo transfer was found to dominate frozen-embryo transfer because it was, on average, less costly and more effective. Considering the joint uncertainty surrounding the estimated differences in costs and effects, the probability of fresh-embryo transfer being preferred on grounds of cost-effectiveness was > 89% across all thresholds of willingness to pay per additional healthy live birth.

When antenatal care and delivery costs were included in the cost-effectiveness analysis, the freeze-all strategy was, on average, less costly owing to a smaller number of pregnancies and live births (−75, 95% confidence interval −623 to 461). However, fresh-embryo transfer retained the higher probability of being cost-effective above a willingness-to-pay threshold of £1921 per additional healthy live birth. Furthermore, when cumulative costs and outcomes associated with the transfer of the remaining frozen embryos were simulated using a Markov model, fresh-embryo transfer was found to be, on average, less costly and more effective, even with the inclusion of antenatal care and delivery costs. The same pattern of results was observed when live births were used as the measure of effectiveness.

The difference in treatment costs was found to be sensitive to the application of more conservative costs for monitoring ultrasound scans prior to frozen-embryo transfer, but the overall cost-effectiveness findings remained stable, with fresh-embryo transfer retaining a substantially higher probability of being cost-effective in terms of the incremental cost per healthy baby and live birth.

Safety and adverse events

The risk of ovarian hyperstimulation was 3.6% in the freeze-all arm compared with 8.1% in the fresh-embryo transfer arm, with a risk ratio of 0.44 (99% confidence interval 0.15 to 1.30). There were 30 reported adverse events; none was related to the intervention.

Discussion

The results of this trial showed that a general policy of freezing all embryos, followed by frozen-embryo transfer, did not increase the chance of having a healthy baby. The health economic analysis confirmed that freezing all embryos, followed by frozen-embryo transfer, is not a cost-effective strategy.

There was no statistical difference in ovarian hyperstimulation syndrome by freezing all embryos in this trial. In addition, live birth rate, clinical pregnancy rates and pregnancy, and neonatal complications showed no difference.

This was a pragmatic trial that recruited from multiple clinics; hence, the results are immediately applicable. There were minimal withdrawals from the trial and data collection was almost complete.

The trial was limited by non-adherence to the allocated intervention in the freeze-all arm, but the additional analyses showed that this was unlikely to have altered the results.

Owing to evolving clinic policies, there has been an increase in the proportion of treatments using freeze-all in preference to fresh-embryo transfer. This trial provides timely evidence for challenging this trend, unless there is a clinical indication, such as significant risk of ovarian hyperstimulation.

Several other trials from across the world were published while the E-Freeze trial was planned and conducted. Our results are in line with those of randomised controlled trials from other countries; for example, one trial has shown a reduction in the live birth rate (Wong KM, van Wely M, Verhoeve HR, Kaaijk EM, Mol F, van der Veen F, *et al.* Transfer of fresh or frozen embryos: a randomised controlled trial. *Hum Reprod* 2021;**36**:998–1006) and three trials have shown no difference by routinely freezing all embryos compared with fresh-embryo transfer (Vuong LN, Dang VQ, Ho TM, Huynh BG, Ha DT, Pham TD, *et al.* IVF transfer of fresh or frozen embryos in women without polycystic ovaries. *N Engl J Med* 2018;**378**:137–47; Shi Y, Sun Y, Hao C, Zhang H, Wei D, Zhang Y, *et al.* Transfer of fresh versus frozen embryos in ovulatory women. *N Engl J Med* 2018;**378**:126–136; and Stormlund S, Sopa N, Zedeler A, Bogstad J, Prætorius L, Nielsen HS, *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). To the best of our knowledge, E-Freeze is the first trial to assess the healthy baby rate as the primary outcome, as both safety and efficacy are important.

Further work is required to identify which subgroups of couples may benefit the most from a freeze-all strategy. This may be possible by undertaking individual patient data meta-analysis of the existing trials across the world. We also plan to conduct further follow-up of participants to look at the cumulative live birth rate (i.e. all babies from one egg collection episode) between the two arms, as well as longer-term outcome of babies born.

Conclusion

When efficacy, safety and costs are considered, freeze-all is not better than fresh-embryo transfer.

Trial registration

This trial is registered as ISRCTN61225414.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 25. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

The study operated to a strict pre-agreed protocol, which has been published.[1]

Parts of this chapter have been reproduced with permission from the published protocol, Maheshwari *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Infertility is common, affecting one in seven couples in the UK.[2] The National Institute for Health and Care Excellence (NICE) recommends in vitro fertilisation (IVF) as the definitive treatment for prolonged unresolved infertility.[3] The number of IVF treatments in the UK has continued to rise each year, from 6609 in 1999 to > 64,000 in 2013, resulting in > 20,000 pregnancies.[4]

In vitro fertilisation

In vitro fertilisation treatment involves a number of consecutive steps. Initially, each woman is given external hormone injections to develop multiple ovarian follicles. The growth of these follicles is monitored by serial transvaginal ultrasound scans and, when these follicles reach maturity, the eggs within them are harvested surgically. Retrieved eggs are mixed with sperm by one of two methods: IVF, where motile sperm are placed surrounding the eggs, or intracytoplasmic sperm injection (ICSI), where a single sperm is selected and injected into the egg. Eggs mixed with sperm are then incubated to create embryos. Conventionally, these embryos are allowed to develop in the laboratory for a few days before one or two of them are selected for transfer into the uterus (i.e. fresh-embryo transfer) on day 3 (the cleavage stage) or day 5 (the blastocyst stage). Additional embryos are frozen and stored for replacement at a later date without the need for ovarian stimulation (i.e. frozen-embryo transfer).

Concerns with in vitro fertilisation

Despite being a widely used treatment in the UK and around the world, there are a number of concerns about conventional IVF.

Static success rates

In vitro fertilisation success rates remain modest, with a mean live birth rate of 25% per treatment involving a fresh-embryo transfer. Data for three consecutive years (2010 to 2012) from the American[4] and European registries[5] suggest that there was no improvement in IVF live birth rates over the 3-year period.

Ovarian hyperstimulation syndrome

Exogenous hormones used for ovarian stimulation are associated with a risk of ovarian hyperstimulation syndrome (OHSS), which is exacerbated if a woman becomes pregnant following fresh-embryo transfer. Moderate to severe OHSS is a complication unique to IVF treatment, occurring in around 1–5% of treatments,[6] and often requiring in-patient care, resulting in significant NHS costs. Severe OHSS is associated with significant morbidity (including ascites, pleural and pericardial effusion, respiratory failure and intensive care admission) and, rarely, death.

Poor obstetric and perinatal outcomes

Pregnancies resulting from IVF are associated with a higher rate of maternal and perinatal complications than pregnancies resulting from spontaneous conception. A systematic review[7] has shown that babies, even singletons, conceived following IVF are more likely than babies conceived without IVF treatment to die during the perinatal period [risk ratio (RR) 1.87, 95% confidence interval (CI) 1.48 to 2.37], to be delivered preterm (RR 1.54, 95% CI 1.47 to 1.62), to have a low birthweight (RR 1.65, 95% CI 1.56 to 1.75) and to have congenital anomalies (RR 1.67, 95% CI 1.33 to 2.09). Women who become pregnant as a result of IVF are more likely than those who become pregnant as a result of spontaneous conception to develop pre-eclampsia (RR 1.49, 95% CI 1.39 to 1.59), bleeding in pregnancy (RR 2.49, 95% CI 2.30 to 2.69) and diabetes (RR 1.48, 95% CI 1.33 to 1.66) and to require a caesarean section (RR 1.56, 95% CI 1.51 to 1.60).

Although the absolute number of women with OHSS and pregnancy-related complications associated with IVF is relatively small, the increasing number of women receiving IVF[4] has meant that the NHS burden of dealing with its short- and long-term complications is a serious and growing problem.

A possible cause of suboptimal live birth rates, as well as adverse maternal and perinatal outcomes, following IVF is the impact of the exogenous hormones used for ovarian stimulation on the lining of the uterine cavity. High levels of oestrogen produced by the ovary in response to this treatment affect uterine receptivity, reducing the chances of successful implantation and placentation. Suboptimal placentation may lead to obstetric and perinatal complications. It has been suggested that avoiding embryo transfer when the uterus is less receptive could improve success rates and reduce complications in pregnancy and delivery. Such a strategy also reduces the risk of OHSS by ensuring that a pregnancy does not occur in the presence of hyperstimulated ovaries.

Evidence supporting frozen-embryo transfer

It is already known that the risk of severe OHSS is greatly reduced by a policy of freezing all embryos, followed by frozen-embryo transfer, compared with fresh-embryo transfer.[8] A systematic review of observational data[9] showed that babies (singletons) conceived from frozen embryos have a reduced risk of perinatal morbidity (RR 0.68, 95% CI 0.48 to 0.96) and preterm delivery (RR 0.84, 95% CI 0.78 to 0.90), making IVF safer and more effective for women and babies.

Preliminary data from small randomised trials from the Islamic Republic of Iran[10] and the USA[11,12] in 2015 suggested that a strategy of not replacing embryos when they are created, but freezing them, followed by transferring thawed embryos into the uterus at a later date, improves pregnancy rates. A meta-analysis of data from these three randomised controlled trials (RCTs)[8] has shown higher pregnancy rates following frozen-embryo transfer (odds ratio 1.32, 95% CI 1.10 to 1.59).

However, these existing trials have a number of significant limitations:

- They reported implausibly high pregnancy rates (e.g. 84% per embryo transfer), which are far in excess of those reported by national and international registries.[4,5]
- Key outcomes, including healthy baby, live birth, costs, safety and acceptability, were not measured by any of the trials.
- They were limited in terms of design, with highly selected populations, inadequate sample sizes and per-protocol analysis rather than intention to treat (ITT) and conduct, as all of the trials involved co-interventions that were not accounted for in the analysis.

One of the publications[10] has been retracted on the grounds of serious methodological flaws. Hence, the evidence base, comprising two small trials, was not sufficiently robust to support a radical change in clinical practice. In addition, the results of these trials could not be directly applied to a UK setting

because of very different regulatory and funding arrangements. There was, therefore, an urgent need to perform a definitive RCT in the UK evaluating elective freezing of embryos, followed by subsequent thawed frozen-embryo transfer, in terms of clinical effectiveness and cost-effectiveness.

Objective

Primary objective

The primary objective of the trial was to determine if a policy of freezing embryos, followed by thawed frozen-embryo transfer, results in a higher healthy baby rate than the current policy of transferring fresh embryos.

Secondary objectives

The secondary objectives of the trial were to assess if a policy of freezing embryos, followed by thawed frozen-embryo transfer, compared with the current policy of transferring fresh embryos, results in:

- fewer complications associated with IVF treatment and pregnancy
- greater cost-effectiveness from a health service and broader societal perspective.

Chapter 2 Methods

The study operated to a strict pre-agreed protocol[1] and statistical analysis plan (SAP),[13] both of which have been published.

Design

The elective freeze (E-Freeze) trial was a pragmatic, multicentre, two-arm, parallel-group, non-blinded RCT conducted in the UK, comparing the freezing of all suitable embryos, followed by frozen-embryo transfer, with the current policy of fresh-embryo transfer. We undertook both clinical effectiveness and economic analysis. Details of the economic analysis are reported in *Chapter 4*.

Ethics approval and research governance

The E-Freeze trial protocol was approved by the North of Scotland Research Ethics Service (NoSRES) Committee (study reference 15/NS/0114). Local approval and site-specific assessments were obtained from each participating site. The trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Registry as ISRCTN61225414.

Participants

Participants were couples undergoing their first, second or third cycle of IVF/ICSI treatment in the participating clinics in the UK.

Inclusion criteria

- The female partner was aged between ≥ 18 and < 42 years at the start of treatment (i.e. start of ovarian stimulation).
- Couples were undergoing their first, second or third cycle of IVF/ICSI treatment, where a cycle is defined as egg collection following ovarian stimulation.
- Both partners were resident in the UK.
- Both partners were able to provide written informed consent.
- They had at least three good-quality embryos [as defined by the Association of Clinical Embryologists (ACE)[14]] on day 3 after egg collection (note that the day of egg collection is counted as day 0). Good-quality embryos on day 3 were defined as those with 6–8 cells of grade 3/3 or above using the agreed national grading scheme.[14]

At the start of the trial, only the first cycle was included. However, after discussion with the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Monitoring Board, it was agreed that couples having their second or third cycle could also be included. This change to the eligibility criteria took effect from 12 April 2018.

A list of all amendments are described in *Appendix 1*.

Exclusion criteria

- Couples were using donor gametes.
- Pre-implantation genetic testing was planned.
- Elective freezing of all embryos was planned for medical reasons (e.g. severe risk of OHSS).
- Couples had been previously randomised to E-Freeze.

Setting

The trial was conducted in 18 IVF units across the UK. A list of all participating sites is presented in *Appendix 2*.

Participant selection and enrolment

Identifying participants

Potentially eligible couples were identified from clinic case notes. An invitation letter and participant information leaflet (PIL) were mailed to eligible couples prior to their clinic appointment. A PIL was also provided at patient information/open evenings attended by couples preparing for their IVF/ICSI treatment. This was usually at least 24 hours prior to their clinic appointment. Eligible couples were approached by a clinician involved in their care and were invited to participate in the trial. Those interested in participating were able to discuss the study with a research nurse on the same day or at a later date.

Consenting participants

Informed consent from both partners was obtained by an appropriately delegated member of the study team. Contact details and baseline characteristics that were necessary for randomisation were recorded by the research nurse immediately after consent was obtained. Consent forms were signed by both partners; however, this could be undertaken at two different time points, as not all appointments were attended by both partners. This could be undertaken at their clinic appointment or at a subsequent visit until the procedure of egg collection; all consent forms had to be signed before the procedure of egg collection took place (*Figure 1*).

Couples who may have previously consented to take part in E-Freeze during their first or second cycle of IVF were still eligible to participate in E-Freeze if they had not been previously randomised into the trial. For couples who had previously consented but had not been randomised onto the trial, informed consent was reobtained for any participation during future cycles and a new study number was generated.

After consent, each partner completed a short questionnaire on how they were feeling emotionally (see *Report Supplementary Material 1*). Each participant sealed their questionnaire in an envelope after completion and questionnaires were destroyed (unopened) if the couple did not proceed to randomisation.

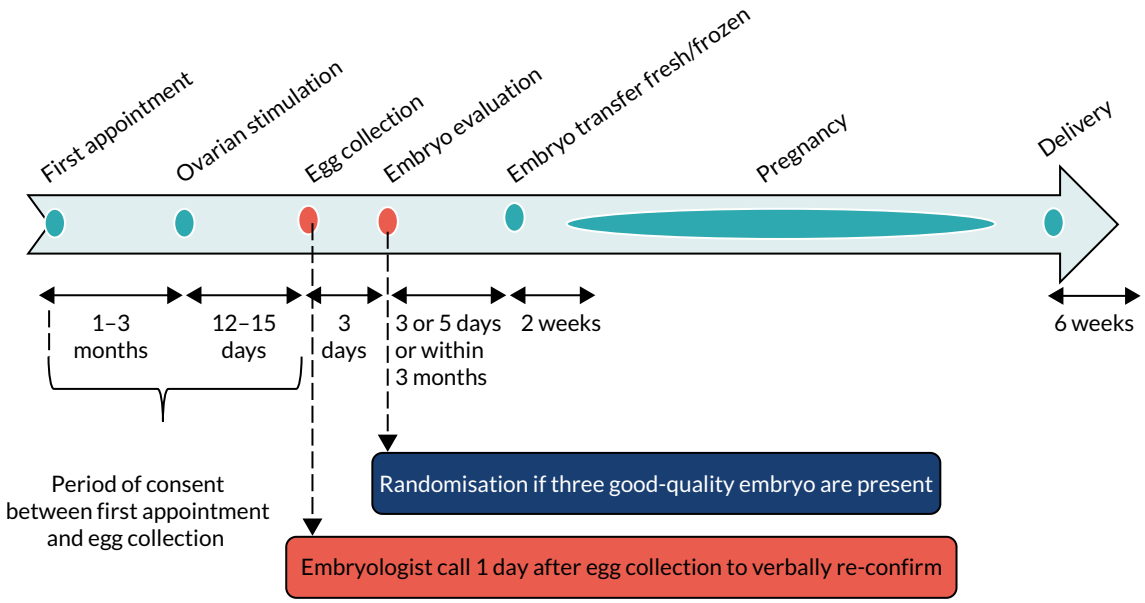


FIGURE 1 Process and timescale for consent and randomisation.

The data needed for randomisation were recorded in the bespoke consent and randomisation program developed by the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit (CTU) at the University of Oxford (Oxford, UK).

Confirmation of consent

A routine telephone call was made to couples 1 day after egg collection to inform them of the outcome of fertilisation (see *Figure 1*). Consent was confirmed during this routine telephone call from the embryologist or research delegate.

Screening for final eligibility

A final eligibility check was carried out on day 3 post egg retrieval. Couples with a minimum of three good-quality embryos were eligible for randomisation to receive either fresh-embryo transfer (i.e. the fresh-embryo transfer arm) or freezing of all good-quality embryos, followed by subsequent transfer of thawed embryos within 3 months (i.e. the freeze-all arm) (*Figure 2*).

Good-quality embryos on day 3 were defined as those with 6–8 cells grade 3/3 or above using the agreed national grading scheme based on guidance from ACE in the UK.[14]

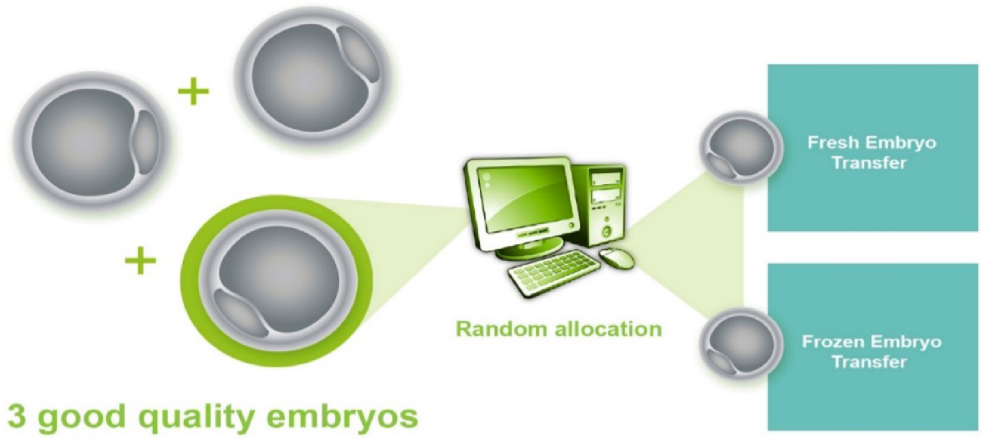


FIGURE 2 Final eligibility criteria.

Randomisation

Randomisation was performed after the creation of embryos, 3 days post egg collection, once all eligibility criteria were established, including ensuring that three or more good-quality embryos were available. This minimised the randomisation-to-intervention time interval as embryos were transferred at either the cleavage or the blastocyst stage (i.e. day 3 or 5 after egg collection, respectively). Couples were randomised (in an allocation ratio of 1 : 1) to a strategy of either fresh-embryo transfer or freezing of embryos, followed by thawing and replacement at a later date (typically 4–6 weeks later and almost always within 3 months of egg collection). Randomisation was undertaken by the research nurse or a delegated member of the research team using a secure web-based centralised system [with 24 hours per day, 7 days per week (24/7) telephone back-up, 365 days per year] hosted by the NPEU CTU (University of Oxford), ensuring allocation concealment. The randomisation employed a minimisation algorithm to balance across the following factors: fertility clinic, woman's age (at the time of start of treatment, i.e. ovarian stimulation), primary/secondary infertility, self-reported duration of infertility, method of insemination (IVF, ICSI or a combination of both) and number of previous egg collections (i.e. cycles).

Communication of randomisation to couples

As part of routine practice, the embryologist contacted the couple by telephone to let them know the quality of their embryos (on day 3 after egg collection). The embryologist or research delegate confirmed to couples whether or not they fulfilled the final inclusion criteria (three or more good-quality embryos on day 3) and which arm they had been randomised to at the time of their routine telephone call on day 3. The research nurse then contacted the couple if they had not fulfilled the inclusion criteria to answer any queries and offer follow-up in the clinic.

Treatment plan

This study was a pragmatic, multicentre, two-arm, parallel-group, non-blinded RCT to evaluate the clinical effectiveness of the proposed intervention using the most rigorous gold-standard experimental methodology in real-life conditions. All clinical elements of IVF/ICSI treatment, apart from the randomised interventions, were carried out in accordance with local protocols. Blinding of the allocated intervention was not possible in this trial because of the nature of the treatments and statutory requirements of the regulatory body the Human Fertilisation and Embryology Authority (HFEA).[15] The process is detailed in the subsequent sections.

Standard-care arm

Women underwent fresh-embryo transfer at the cleavage or blastocyst stage in accordance with local protocols.

Intervention arm

All good-quality embryos were frozen in accordance with local protocols. Couples who were randomised to the freeze-all arm were contacted by the research nurse or research delegate within 3 working days post randomisation and arrangements were made for frozen-embryo transfer within 3 months of the egg retrieval process. This could involve a few visits to hospital for blood tests and ultrasounds to prepare the endometrium prior to embryo transfer.

At embryo transfer (in both arms), couples were asked to complete a short questionnaire to assess the additional costs related to the treatment (see *Report Supplementary Material 2*) and to repeat the emotions questionnaire (see *Report Supplementary Material 1*) that they filled in when they provided consent.

Ineligible and non-recruited participants

Details of all consenting couples were entered in a dedicated secure online database. It was anticipated that a proportion of those consented may not proceed to randomisation; the reasons for this were recorded (if available) and included the non-availability of three good-quality embryos on day 3. Couples not proceeding to randomisation were offered the most appropriate standard treatment. All clinics have access to supportive counselling as a requirement of the regulatory authority.

Follow-up

All randomised women carried out a pregnancy test 2 weeks (± 3 days) after embryo transfer. All women who had a positive pregnancy test at 2 weeks (± 3 days) underwent a transvaginal ultrasound scan afterwards (i.e. at 6–8 weeks of gestation) to identify the presence of a gestational sac with a fetal heartbeat, signifying an ongoing pregnancy.

Women who had an ongoing pregnancy were contacted by their research nurse (by telephone) to record pregnancy events and outcomes at 12 and 28 weeks of gestation and, again, at approximately 6 weeks after delivery. Outcomes presenting at ≥ 6 weeks post delivery were not recorded. All women who conceive by IVF/ICSI are followed up by their IVF centres routinely, as there is a mandatory requirement to report early-pregnancy outcomes, as well as delivery outcomes, including stillbirth, congenital anomalies and perinatal mortality, to the regulatory body (HFEA). Usually, this information is provided to each IVF clinic by the couples themselves. Alternatively, clinic staff contact couples by telephone to collect this information and report it to HFEA. In addition to data collected for reporting to HFEA, data were collected over the telephone at 12 and 28 weeks, and collected using questionnaires at embryo transfer for this trial.

Those who had a negative pregnancy test were not followed up any further as part of this trial.

Figure 3 presents a flow chart that explains the flow of participants through the trial.

Outcomes

Primary outcome

The primary outcome was a healthy baby. A healthy baby was defined as a live, singleton baby born at term (between 37 and 42 completed weeks of gestation), with an appropriate weight for gestation (i.e. weight between the 10th and the 90th centile for that gestation, based on standardised charts).

Secondary outcomes

The secondary outcomes were separated into maternal safety, complications of pregnancy and delivery, measures of clinical effectiveness, measures of effectiveness of the process of freezing embryos, and health economic outcome measures.

Maternal safety outcome

- Ovarian hyperstimulation syndrome, defined and classified as per the Royal College of Obstetricians and Gynaecologists (RCOG)'s Green-Top Guidelines.[6]

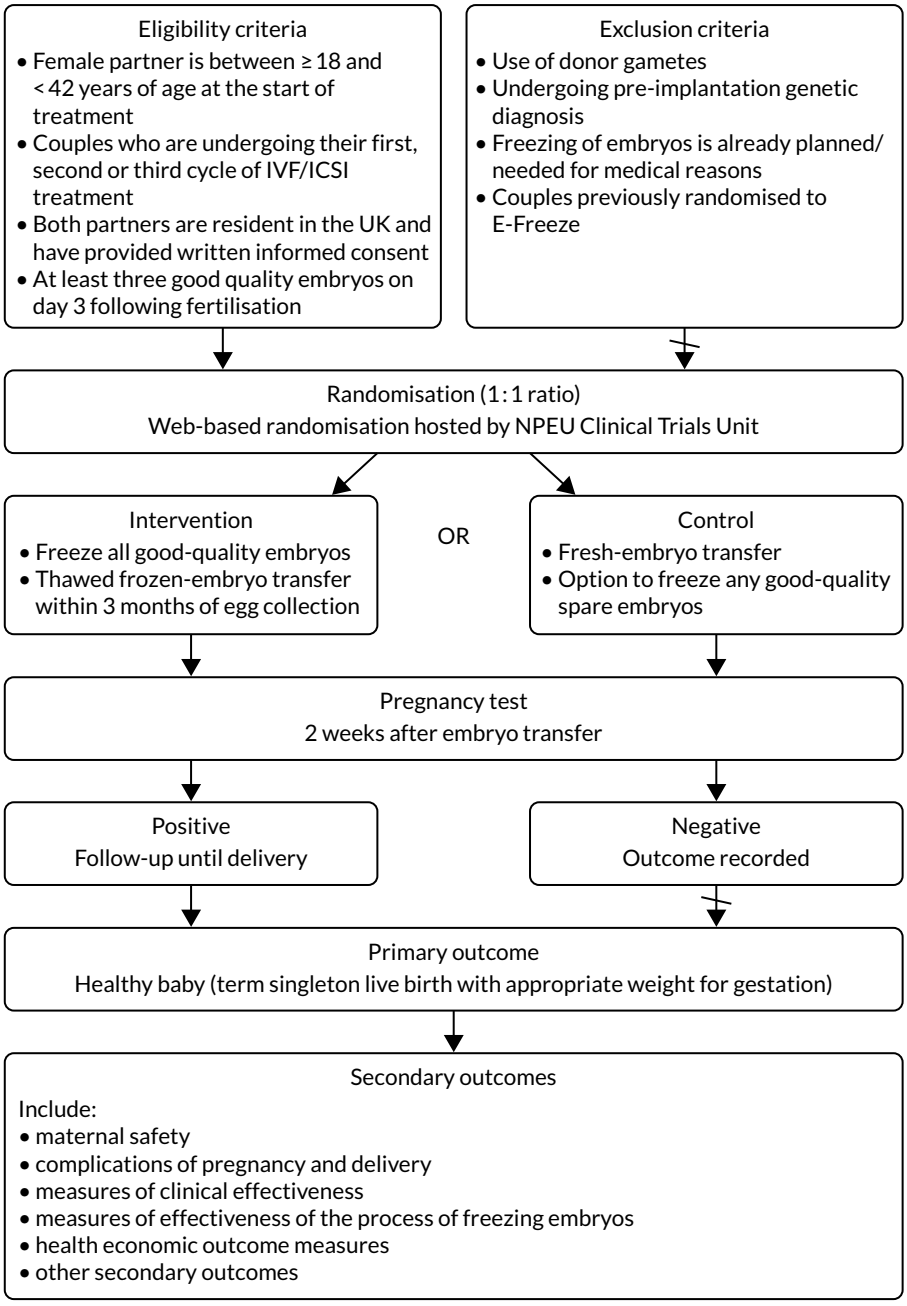


FIGURE 3 Flow chart for the study.

Complications of pregnancy and delivery outcomes

- Vanishing twin or triplet (defined as more fetal heartbeats than babies born, more gestational sacs than babies born or more gestational sacs than fetal heartbeats).
- Miscarriage rate (defined as pregnancy loss prior to age of viability, i.e. 24 weeks of gestation).
- Ectopic pregnancy.
- Termination.
- Gestational diabetes mellitus (GDM).
- Multiple pregnancy (defined as more than one fetal heartbeat or more than one gestational sac).
- Multiple births (including live and stillbirths).
- Hypertensive disorders of pregnancy (e.g. chronic hypertension, pregnancy-induced hypertension, pre-eclampsia and eclampsia).

- Most severe hypertensive disorder experienced (from least to worst severe: chronic hypertension, pregnancy-induced hypertension, pre-eclampsia and eclampsia).
- Antepartum haemorrhage (i.e. any bleeding per vaginam after 28 weeks of pregnancy, including placenta praevia and placental abruption).
- Onset of labour (i.e. spontaneous, induced or planned caesarean section).
- Mode of delivery for each baby (i.e. normal vaginal delivery, instrumental vaginal delivery or caesarean section).
- Preterm delivery (defined as delivery at < 37 completed weeks of gestation).
- Very preterm delivery (defined as delivery at < 32 completed weeks of gestation).
- Low birthweight (defined as weight of < 2500 g at birth).
- Very low birthweight (defined as weight of < 1500 g at birth).
- High birthweight (defined as weight of > 4000 g at birth).
- High birthweight for gestational age (defined as birthweight > 90th centile for gestational age at delivery, based on standardised charts).
- Low birthweight for gestational age (defined as birthweight < 10th centile for gestational age at delivery, based on standardised charts).
- Congenital anomaly/birth defect (all congenital anomalies/birth defects identified to be included).
- Perinatal mortality (stillbirth or late, as well as early, neonatal deaths, up to 28 days after birth).

Measures of clinical effectiveness outcomes

- Live birth rate (this is a live birth episode, i.e. twins were counted as one birth).
- Singleton live birth rate.
- Singleton live birth rate at term.
- Singleton baby with appropriate weight for gestation.
- Pregnancy rate (defined as positive pregnancy test at 2 weeks ± 3 days after embryo transfer).
- Clinical pregnancy rate (defined as the presence of at least one fetal heartbeat at ultrasound between 6 and 8 weeks' gestation; ectopic pregnancy counts as a clinical pregnancy and multiple gestational sacs count as one clinical pregnancy).

Measures of the effectiveness of the process of freezing embryos outcomes

- Total number of embryos frozen, thawed and transferred for all randomised couples.
- Proportion of thawed embryos that were then transferred for all randomised couples.
- No embryos survived thawing, leading to no embryo transfer.

Health economic outcome measures

- Cost to the health service of treatment, pregnancy and delivery care.
- Modelled long-term costs of health and social care, and broader societal costs.

Other secondary outcomes

- Evaluation of emotional state (for both the female and the male partners).

Data collection

Data were collected at various time points, as shown in *Figure 4*. Data for both clinical and economic outcomes were collected using bespoke electronic case report forms (eCRFs) and entered directly into the study's OpenClinica, version 3.0 (Waltham, MA, USA), electronic database by the centre's research staff and trial team. Data were single entered only and, at the point of entry, the data underwent a number of checks to verify the validity and missingness of the data captured.

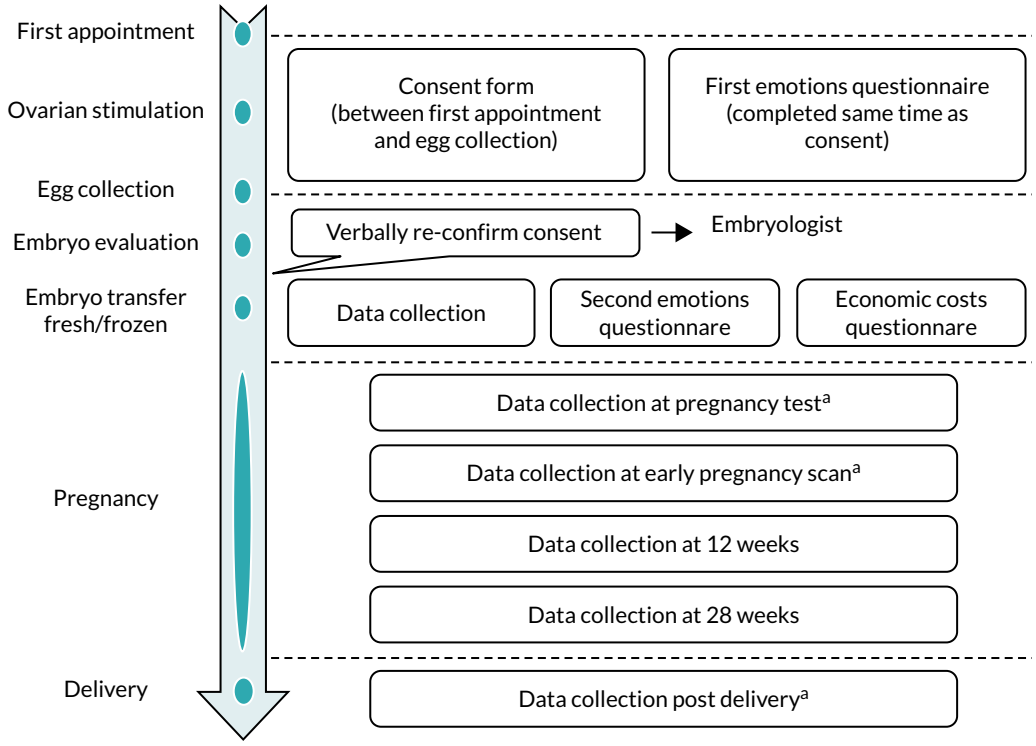


FIGURE 4 Stages of data collection. a, Part of routine care.

After consent and at embryo transfer, each partner completed a short paper-based questionnaire (see *Report Supplementary Material 1*) asking them how they were feeling. This was based on the State–Trait Anxiety Inventory (STAI).[16]

A short questionnaire was provided to each partner for them to record the details of time and travel expenses accrued during their treatment as part of the economic evaluation (see *Report Supplementary Material 2*). This was completed at the time of embryo transfer.

Sample size

Sample size calculation

The proposed primary outcome for this trial was novel and is not currently reported by IVF clinics or national regulatory bodies. This meant that a number of assumptions were made to determine the expected event rate in the fresh-embryo transfer arm (receiving current standard treatment, i.e. fresh-embryo transfer).

Prior to commencing the trial, the most recent data from the HFEA,[4] which collects data on all IVF cycles from all clinics in the UK, showed that 25% of all women undergoing one episode of IVF treatment involving a fresh-embryo transfer have a live birth and 20% have singleton live births. These values were for women of all age groups, not necessarily for women fulfilling the inclusion criteria for this trial in terms of the number of good-quality embryos in their IVF cycle. The live birth rate for first, second and third cycles was similar.[4] No data were available regarding the primary outcome for this study: the healthy baby rate (i.e. live singletons born between 37 and 42 weeks, with appropriate weight for gestation). For our trial population, we anticipated that the fresh-embryo transfer arm event rate was likely to be $< 25\%$ and possibly as low as 17%.

To provide relevant information regarding the event rate expected in the fresh-embryo transfer arm, we surveyed 10 IVF centres that expressed an interest in the study, collecting data on the number of live births in women aged < 42 years who were undergoing their first IVF treatment in 2012. The average live birth episode rate from this survey was 31% (95% CI 25% to 37%). Accurate data on the healthy baby rate in those with at least three good-quality embryos were not available. Although the live birth rate is expected to be higher in women with at least three good-quality embryos (who are likely to have a better prognosis), we anticipated that the healthy baby rate in our trial population would be towards the lower end of the CI, that is around 25%, taking into account the higher risk of preterm delivery and babies who are small for their gestational age following IVF.[9]

The following assumptions were made for the sample size calculation.

We assumed a healthy baby rate of between 17% and 25% in women who were eligible for the trial (i.e. aged < 42 years, with three good-quality embryos) undergoing standard care (i.e. fresh-embryo transfer). Taking into account the extra time, effort and potential expense involved in freezing embryos, and the delay in embryo transfer of up to 3 months, a difference of at least 8% in absolute terms was considered to be clinically important by an expert panel of clinicians to recommend a change in clinical practice. With 90% power and using a two-sided, 5% level of statistical significance, a total of 1086 couples (i.e. 543 couples in each arm) would be required to be able to detect an absolute difference of 8% (from 17% to 25%) and 9% (from 25% to 34%) in the healthy baby rate in the fresh-embryo transfer arm and the freeze-all arm, respectively.

It is a regulatory requirement for clinics in the UK to report live birth outcomes (including number, weight and gestation) after all embryo transfers; hence, loss to follow-up was not anticipated. Therefore, we did not take into account loss to follow-up for these sample size calculations.

It was anticipated that a proportion of those who consented may not reach randomisation (e.g. those who did not have three good-quality, day 3 embryos or who required all embryos to be frozen for medical reasons); therefore, a larger number of participants would need to be consented. It was anticipated that the number of participants who did not have three good-quality embryos would be 50% out of those consented.

Statistical analysis

A detailed SAP was agreed and published[13] prior to data lock. The analysis and presentation of results followed the most up-to-date recommendations of the Consolidated Standards of Reporting Trials (CONSORT) group.[17]

Descriptive analysis

The flow of participants through each stage of the trial was summarised by trial arm. Demographic factors and clinical characteristics were summarised for all couples at trial entry, and separately for couples who delivered. Counts and percentages were reported for categorical variables, means [with standard deviations (SDs)] were reported for normally distributed continuous variables, and medians [with interquartile ranges (IQRs)] were reported for other continuous variables. No tests of statistical significance were performed and CIs were not calculated for differences between randomised arms on any baseline variable.

Primary analysis

All participants were analysed in the arms to which they were assigned, regardless of deviation from the protocol or treatment received under the ITT analysis principle. To perform the analyses for all outcomes on the ITT analysis population, the couple was included in the denominator once for all outcomes regardless of whether a pregnancy or a live birth occurred. Where this was a perinatal

outcome, the woman was included once in the denominator. For neonatal secondary outcomes, the unit of analysis in the ITT analysis was the mother, and in cases of multiple pregnancy for which the infants' outcomes differ, the worst outcome was reported.

Binary outcomes were analysed using a log-binomial regression model or a Poisson regression model with a robust variance estimator if the binomial model failed to converge. Linear regression was used for normally distributed continuous outcomes and quantile regression was used for skewed continuous outcomes. All comparative analyses were adjusted for the minimisation factors where possible. Fertility clinic was treated as a random effect in the models, where possible, and all other factors were treated as fixed effects. Both unadjusted and adjusted estimates are presented, but the primary inference is based on the adjusted analyses.

Comparative analyses entailed calculating the adjusted RR and 95% CI for the primary outcome, adjusted RRs and 99% CIs for all binary secondary outcomes, adjusted mean differences (MDs) and 99% CIs for normally distributed continuous secondary outcomes, or median differences and 99% CIs for skewed continuous secondary outcome variables. To account for the number of hypothesis tests performed, 99% CIs were used for all analyses of the secondary outcomes.

Customised birthweight centiles to calculate low weight for gestational age and high weight for gestational age were based on an existing, published, British model.[18]

The following secondary outcomes were described only, and no formal statistical analysis comparing the arms was conducted:

- chronic hypertension, pregnancy-induced hypertension, pre-eclampsia and eclampsia
- most severe hypertensive disorder experienced (from least to worst severe: chronic hypertension, pregnancy-induced hypertension, pre-eclampsia and eclampsia).

Secondary analysis

The primary analysis for all primary and secondary outcomes was by ITT. Secondary analyses were performed to include clinically relevant denominators, such as the total number of women with a positive pregnancy test at 2 weeks ± 3 days after embryo transfer (for miscarriage), the total number of pregnant women with an ongoing pregnancy resulting in delivery (for pregnancy complications) and the total number of babies born (for birthweight and congenital anomalies). The adjusted analyses per total number of babies also accounted for the anticipated correlation in outcomes between multiple births. The rate of embryos not surviving after thawing (per embryo thawed) was reported for the intervention arm only.

Subgroup analysis

We performed subgroup analyses of the primary outcome on the following, as prespecified in the SAP:[13]

- fertility clinic
- woman's age (at the time of start of treatment, i.e. ovarian stimulation): < 35, 35 to < 40 and ≥ 40 years
- blastocyst-stage compared with cleavage-stage embryo transfer
- single embryo transfer compared with multiple embryo transfer
- number of previous embryo transfers: 0 compared with ≥ 1 (the groups 0, 1–3 and ≥ 4 were prespecified, but were reduced to two groups in the analysis because of low frequencies).

The consistency of the effect of type of embryo transfer across specific subgroups of couples was assessed for the primary outcome using the statistical test of interaction, in addition to the adjusted model. The results are presented in forest plots, with RRs, 95% CIs and the results of the interaction test.

In addition, for those receiving frozen-embryo transfer, the primary outcome was summarised for the following subgroups using numbers and percentages only:

- natural cycles compared with hormone replacement cycles
- vitrification compared with slow freezing.

Additional analysis

The following prespecified analyses were carried out for the primary outcome only:

- per protocol – restricted to those who complied with the allocated intervention
- as treated – grouping couples according to the intervention that they actually received (i.e. those randomised to frozen-embryo transfer but who received fresh-embryo transfer were in the fresh-embryo transfer arm in this analysis)
- complier-average causal effect (CACE) analysis.

To assess the impact of non-compliance with the randomised allocation, that is women randomised to the frozen arm receiving fresh-embryo transfer (non-compliers), a CACE analysis was conducted. This analytic technique provides a robust estimate of the treatment effect among compliant participants.[19,20]

The baseline characteristics of women randomised to the freeze-all arm were reported by compliance status, and the unadjusted event rate for the primary outcome was calculated for the observed compliers and non-compliers in the freeze-all arm. The CACE analysis assumed that the proportion of non-compliers in the fresh-embryo transfer arm (i.e. couples in the fresh-embryo transfer arm who would not have complied had they been randomised to the freeze-all arm) was the same as the proportion of non-compliers in the freeze-all arm. It also assumed that the event rate among the non-compliers in the freeze-all arm was the same as the event rate among the non-compliers in the fresh-embryo transfer arm. Applying these two assumptions, the unadjusted event rate for the primary outcome was calculated for the would-be compliers and would-be non-compliers in the fresh-embryo transfer arm. The unadjusted CACE RR with 95% CIs for the primary outcome was calculated using the event rates for compliant groups only (i.e. the observed compliers in the freeze-all arm and the would-be compliers in the fresh-embryo transfer arm). The CIs for the CACE-estimated RRs were calculated using bootstrapping methods.[21]

Analysis of emotions questionnaire

The emotions questionnaires at randomisation and post embryo transfer captured responses to the STAI.[16] The response at randomisation was used as a covariate in an analysis of covariance (ANCOVA) model. Hypothesis testing investigated if there was a post-embryo transfer difference in the means of the two treatment arms after adjustment for responses at randomisation. To avoid bias, maximise the power of the study and obey the ITT principle, the missing-indicator method[22] was used to replace missing baseline scores. This method replaces all missing baseline observations with the same value and an extra indicator variable is added to the model to indicate whether or not the value for that variable is missing. For any partially completed questionnaires, if one or two items were omitted, then the prorated score was obtained by calculating the mean weighted score for the completed items, multiplying by 20 and rounding to the next whole number. If three or more items were omitted, then the whole questionnaire was analysed as missing. Models were fitted separately for the female and male partners.

Economic evaluation

A formal economic evaluation was undertaken to assess the cost-effectiveness of the alternative approaches to treatment used in the trial.

The resource use and costs were primarily estimated from a health and personal social services perspective. However, personal time and travel costs associated with any additional treatment-related visits that were not part of standard, routine data collection were also estimated using a short questionnaire administered at the time of embryo transfer (see *Report Supplementary Material 2*). This was completed by both partners.

Trial data collected using eCRFs were used to capture participant-level resource use associated with treatment up to the trial end points of delivery or failure to become pregnant following the initial transfer. The appropriate unit costs were used to value resource use events recorded in the case report forms (CRFs). The detailed methods of economic evaluation are described in *Chapter 4*.

Adverse event reporting

A Data Monitoring Committee (DMC) was established to ensure the independent monitoring of the data and the well-being of study participants. The DMC periodically reviewed study progress and outcomes, as well as reports of unexpected serious adverse events (SAEs). The DMC made recommendations regarding the continuance of the study or modification of the study protocol.

Adverse events

As per the protocols of the trial unit, an adverse event (AE) was defined as any untoward medical occurrence in a participant, which did not, necessarily, have to have a causal relationship with the intervention. Owing to the high incidence of AEs routinely expected in this patient population (e.g. abnormal laboratory findings, new symptoms), only those AEs identified as serious were recorded for the trial.

Serious adverse events

A SAE was any untoward medical occurrence that:

- resulted in death
- was life-threatening
- required participant hospitalisation or prolongation of existing hospitalisation
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was an important medical event.

The term ‘severe’ was often used to describe the intensity (i.e. severity) of a specific event; however, the event itself may have been of relatively minor medical significance. This was not the same as ‘serious’, which was based on participant/event outcome or action criteria, usually associated with events that posed a threat to a participant’s life or functioning.

The term ‘life-threatening’ in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe. Medical and scientific judgement was exercised in deciding whether or not an AE was serious in other situations.

Foreseeable serious adverse events

Foreseeable SAEs were events that were expected in the patient population or as a result of the routine care/treatment of a patient. The events were foreseeable in women or couples undergoing IVF treatment and, therefore, did not need to be reported as SAEs. Data on foreseeable SAEs were collected on the eCRF as part of routine data collection.

The foreseeable events relating to the female partner or couple were:

- OHSS
- miscarriage
- hypertensive disorders of pregnancy
- antepartum haemorrhage
- GDM
- multiple pregnancy
- no embryos surviving thawing.

The foreseeable events relating to the baby when born were:

- low birthweight
- very low birthweight
- low weight for gestational age
- high weight for gestational age
- preterm delivery
- very preterm delivery.

Unforeseeable serious adverse events

An unforeseeable SAE was any event that met the definition of a SAE and was not detailed as foreseeable. The following unforeseeable SAEs were reported:

- maternal death
- stillbirth
- congenital anomaly detected antenatally or postnatally
- neonatal death.

Unforeseeable SAEs were reported up to 6 weeks post delivery. They were reported to the NPEU CTU as soon as possible after staff at the site became aware of the event. The SAEs were reported in one of the following ways:

1. Using the clinical database OpenClinica – only staff with access to OpenClinica could report SAEs in this way; site staff were required to print the OpenClinica SAE form and obtain the information and signature of the study clinician carrying out the causality assessment. The completed and signed SAE form was e-mailed or faxed to the NPEU CTU. NPEU CTU staff were automatically informed by e-mail of any SAEs reported electronically.
2. By completing a SAE form that was e-mailed or faxed to the NPEU CTU. Paper copies were available with the trial documentation to enable anyone to report a SAE. Guidance for the research site was provided on the paper SAE reporting form.
3. If it was not possible to report a SAE using the methods detailed in points 1 and 2, the unforeseeable SAE could be reported by telephone and the SAE form was completed by staff at the NPEU CTU.

If any additional information regarding the SAEs became available, this was detailed on a new SAE form and e-mailed or faxed to the NPEU CTU or reported electronically using OpenClinica. The SAE forms were sent to the sponsor by the NPEU CTU as soon as possible after they were received. The chief investigator assessed whether or not a SAE was 'related' (i.e. resulting from administration of any of the research procedures) and 'unforeseeable' in relation to those procedures. Any reports of related and unforeseeable SAEs were submitted to the following places, in line with the protocols of the trial unit: the North of Scotland Research Ethics Committee (which gave a favourable opinion of the study), the sponsor and the centre at which the SAE occurred within 15 working days of the

chief investigator becoming aware of the event. All recorded SAEs were reviewed by the DMC at regular intervals. The chief investigator informed all principal investigators (PIs) concerned of relevant information that adversely affected the safety of the participants.

Governance and monitoring

To ensure oversight and governance of the trial, a DMC and a Trial Steering Committee (TSC) were established, and a Project Management Group (PMG) was responsible for the day-to-day running of the trial.

Trial Steering Committee

The role of the TSC was to provide overall supervision of the study. The TSC monitored the progress of the study and conduct, and advised on its scientific credibility. The TSC considered and acted, as appropriate, on the recommendations of the DMC and, ultimately, carried the responsibility for deciding whether or not the trial needed to be stopped on grounds of safety or efficacy.

The TSC consisted of an independent chairperson and two other independent members. The committee members were deemed to be independent if they were not involved in study recruitment and were not employed by any organisation directly involved in the study's conduct. Representatives from Fertility Network (London, UK) (patient/public involvement groups), the chief investigator and other investigators/co-applicants were joined by observers from the NPEU CTU. A TSC charter was prepared in advance of and agreed on at the first TSC meeting to document how the committee operated.

Data Monitoring Committee

A DMC that was independent of the applicants and the TSC reviewed the progress of the trial at frequent intervals and provided advice on the conduct of the trial to the TSC, which reported to the HTA programme manager. The committee periodically reviewed study progress and outcomes. The timing and content of the DMC reviews were detailed in a DMC charter, which was agreed on at its first meeting.

Project Management Group

The study was supervised on a day-to-day basis by the PMG. This group reported to the TSC, which had overall responsibility for the conduct of the study. The core PMG met regularly (i.e. at least monthly). The Co-Investigators Group (CIG) met at regular intervals during the trial, and comprised all co-applicants and the members of the core PMG. The full membership of the committees is listed in *Appendix 5*.

Trial management

The trial co-ordinating centre was the NPEU CTU, University of Oxford, where the trial manager was based. The NPEU CTU was responsible for trial oversight; information technology (IT) system/functions, such as randomisation, clinical and administrative databases; all programming and statistical analyses; servicing both the DMC and the TSC; and, in collaboration with the chief investigator and the local research nurse, the general day-to-day running of the study, including the recruitment of sites and training of staff. A 24/7 (365 days per year) emergency helpline was available for out-of-hours queries related to the trial. The economic analysis was conducted at the University of Aberdeen (Aberdeen, UK).

Risk assessment and monitoring

A study risk assessment and monitoring plan was completed as part of the development of this study by the NPEU CTU. This risk assessment and monitoring plan was reviewed at regular intervals during the study to ensure that appropriate and proportionate monitoring activity was performed.

Patient and public involvement

Patients and the public were involved at every step of the trial. At the conception of the trial, the Chief Executive of Fertility Network UK, Mrs Claire Lewis Jones, was consulted. She was involved in every meeting from the submission of the outline application to the NIHR HTA programme and the full application. Once funding was awarded, patient involvement continued during the design of the protocol and all patient facing information, including leaflets. Multiple members of Fertility Network UK were involved in publicising the trial, especially when recruitment was suboptimal and non-compliance was higher than expected. Patient representatives advised on recruitment strategies and the conduct of the trial at each step. They were part of both the DMC and the TSC. They were consulted when the inclusion criteria were amended from first cycle of IVF/ICSI to first, second and third cycle. We also took their advice when it was recommended to stop the trial, as communication to participants was crucial at that time. Patient representatives have been fully involved in the interpretation of the results, writing of this report and dissemination strategies.

Chapter 3 Results

Between February 2016 and April 2019, 1578 participants consented and 619 couples were randomised: 310 to the fresh-embryo transfer arm and 309 to the freeze-all arm (*Figure 5*). One couple in the fresh-embryo transfer arm and two in the intervention arm withdrew consent to use their data; hence, the ITT analysis included 309 participants in the fresh-embryo transfer arm and 307 participants in the freeze-all arm.

Recruitment and retention

When the trial initially started, in 2016, only the first cycle of IVF/ICSI was included. Owing to suboptimal recruitment (and after discussion with the funders), it was agreed that we could include the second and third cycles as well (decided on 12 April 2018).

A total of 1578 couples provided consent to be enrolled in the trial. The time between consent and randomisation varied from 10 to 80 days, with a mean of 55.5 days. A total of 959 (60.8%) couples who provided consent were not randomised; the main reason for this (49.6%) was not meeting the final eligibility criterion of at least three good-quality embryos on day 3. Other reasons are described in the flow chart in *Figure 5*. Some couples ($n = 25$) became pregnant spontaneously during the time between consent and randomisation.

The proportion of couples not randomised after providing consent remained constant throughout the trial (*Figure 6*), even after changing the inclusion criteria to incorporate second- and third-cycle treatments.

The monthly recruitment figures lagged behind target and plateaued after October 2018 (*Figure 7*). On 9 November 2018, the DMC recommended to the TSC that the trial should be halted, owing to the shortfall in recruitment and the high level of non-adherence. Following this recommendation, a joint meeting of the TSC and DMC was convened on 17 January 2019, with an independent chairperson because of disagreement between the TSC and the DMC, to agree scenarios for a monitoring meeting. After a monitoring meeting with the NIHR HTA programme on 29 January 2019, it was agreed that the trial would stop recruitment on 30 April 2019. It was felt that continuing the trial further would yield no benefit, as an adequate sample size was unlikely given the slow recruitment, compounded by non-adherence, which was particularly evident in the intervention arm (see *Table 1*).

One-fifth of couples included in the analysis (117/616, 19%) did not adhere to their allocated intervention: 21 out of 309 (6.8%) in the fresh-embryo transfer arm and 96 out of 307 (31.3%) in the freeze-all arm. Non-adherence varied across clinics, with the rate in the intervention arm ranging from 0% to 86%. One clinic had a for-cause monitoring visit and was closed early in its recruitment, with non-adherence reaching almost 100%.

Table 1 shows the reasons for non-adherence in the trial arms. The most common reason for non-adherence in the freeze-all arm was patient choice (72% of those who did not receive their allocated intervention).

Recruitment by sites

Eighteen clinics across the UK signed up for the trial. Only 13 clinics randomised any participants, of which four randomised > 50 participants. The number of recruited participants from each clinic is presented in *Table 2*.

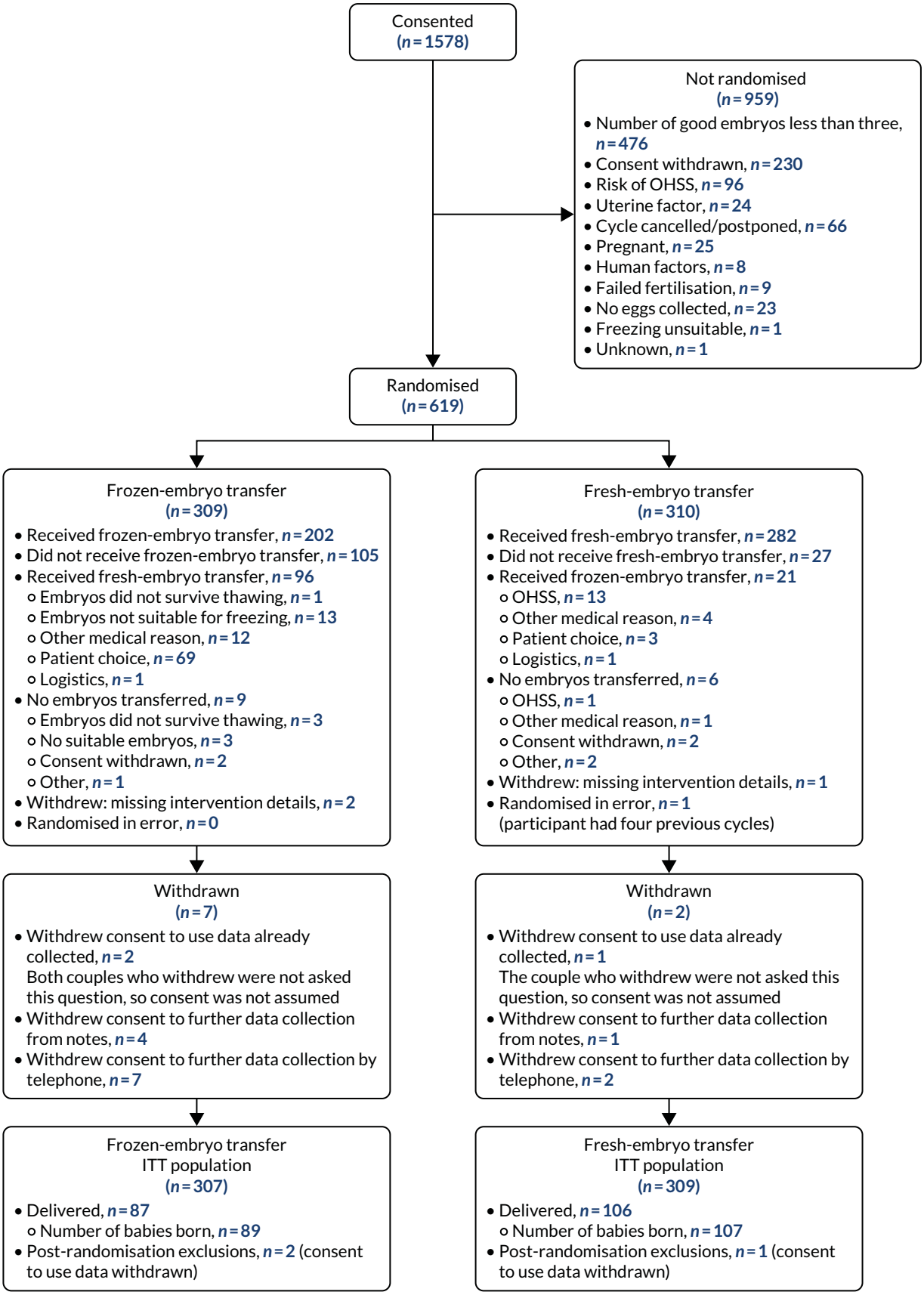


FIGURE 5 Flow of participants. Reproduced from Maheshwari *et al.*,[23] Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze), *Human Reproduction*, 2022, deab279, by permission of European Society of Human Reproduction and Embryology.

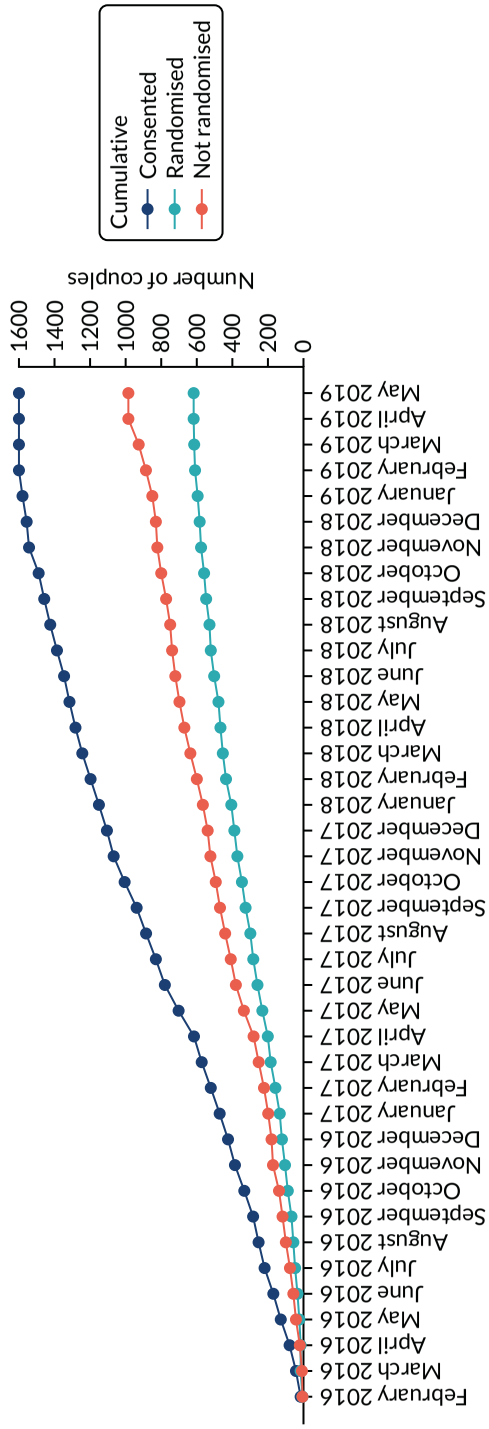
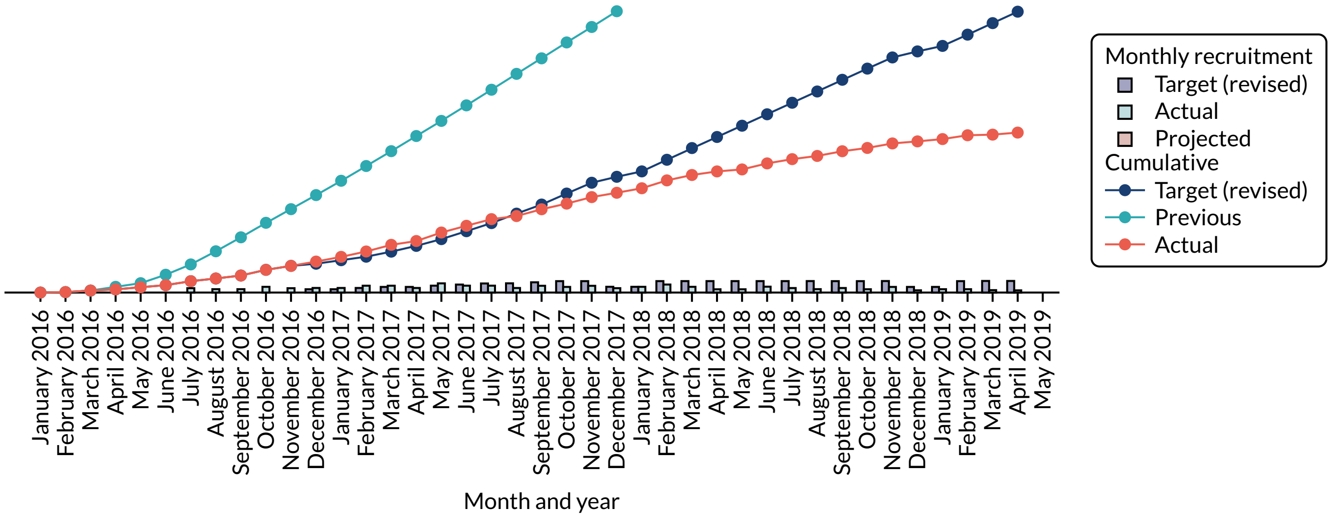


FIGURE 6 Proportion of consented and randomised participants.



Target monthly recruitment												11	11	16	19	22	25	31	32	34
Actual monthly recruitment	0	2	6	5	8	9	14	9	13	22	14	16	17	23	23	17	33	26	25	16
Projected monthly recruitment																				
Target cumulative total												113	124	140	159	181	206	237	269	303
Actual cumulative total	0	2	8	13	21	30	44	53	66	88	102	118	135	158	181	198	231	257	282	298
Per cent of target												104	109	113	114	109	112	108	105	98

Target monthly recruitment	38	41	43	22	22	44	44	44	44	44	44	44	44	44	44	22	22	44	44	44
Actual monthly recruitment	26	21	26	15	18	30	20	13	12	22	17	11	17	12	18	8	11	13	5	6
Projected monthly recruitment																				
Target cumulative total	341	382	425	447	469	513	557	601	645	689	733	777	821	865	909	931	953	997	1041	1085
Actual cumulative total	324	345	371	386	404	434	454	467	479	501	518	529	546	558	576	584	595	608	613	619
Per cent of target	95	90	87	86	86	85	82	78	74	73	71	68	67	65	63	63	62	61	59	57

FIGURE 7 Final recruitment figures.

TABLE 1 Adherence to intervention

Clinical characteristics	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Received frozen-embryo transfer, *n* (%)	202 (65.8)	21 (6.8)
Time from egg collection to frozen-embryo transfer (days), median (IQR)	63 (33–97)	105 (84–138)
Received frozen-embryo transfer within 3 months of egg collection,[a] *n* (%)	145 (71.8)	7 (33.3)
Received fresh-embryo transfer, *n* (%)	96 (31.3)	282 (91.3)
Reason embryo transfer type is different from allocation, *n* (%)	96	21
Embryos did not survive after thawing	1 (1.0)	0 (0.0)
OHSS	0 (0.0)	13 (61.9)
Not suitable to freeze	13 (13.5)	0 (0.0)
Other medical reason	12 (12.5)	4 (19.0)
Patient choice	69 (71.9)	3 (14.3)
Logistics	1 (1.0)	1 (4.8)
Received no embryo transfer, *n* (%)	9 (2.9)	6 (1.9)
Reason no embryos were transferred, *n* (%)	9	6
Embryos did not survive after thawing	3 (33.3)	0 (0.0)
OHSS	0 (0.0)	1 (16.7)
No suitable embryos	3 (33.3)	0 (0.0)
Other medical reason	0 (0.0)	1 (16.7)
Consent withdrawn	2 (22.2)	2 (33.3)
Other	1 (11.1)	2 (33.3)

a Where 3 months = 92 days.

TABLE 2 Recruitment per site

	Number of participants (%)	
Fertility clinic[a]	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
1	11 (3.6)	11 (3.6)
2	14 (4.6)	11 (3.6)
3	90 (29.3)	92 (29.8)
4	49 (16.0)	48 (15.5)
5	31 (10.1)	30 (9.7)
6	21 (6.8)	29 (9.4)
7	11 (3.6)	11 (3.6)
8	24 (7.8)	23 (7.4)
9	7 (2.3)	7 (2.3)
10	10 (3.3)	8 (2.6)
11	29 (9.4)	30 (9.7)
12	1 (0.3)	1 (0.3)
13	9 (2.9)	8 (2.6)

a Minimisation criterion.

Data missingness

As is clear from *Figures 8* and *9*, there were very few missing data for all clinical outcomes. The emotions questionnaires were completed at consent and, again, at embryo transfer. The return rate was 97% for the first emotions questionnaire and > 70% for the second emotions questionnaire. Patients also completed an economics questionnaire, which had a return rate of > 70%.

Statistical analyses

Baseline comparability of randomised arms

The demographic and clinical characteristics at trial entry are described for all couples in the ITT population by trial arm.

Demographic characteristics at consent

Demographic characteristics at consent are described in *Table 3*.

Age

The mean (SD) age of the female partner was 34.7 (3.8) years in the freeze-all arm and 34.6 (3.6) years in the fresh-embryo transfer arm. Most women (95.1%) were aged < 40 years and half (50.3%) were aged < 35 years. Age was a minimisation criterion.

Ethnicity

Women's ethnicity was included in the eCRFs only part-way through the trial, on 12 April 2017. All attempts were made to collect these data retrospectively, but data were missing for some couples who were recruited prior to this date (freeze-all arm, $n = 6$; fresh-embryo transfer arm, $n = 11$). Most participants were of white ethnic background (80.2%) and 11.9% were Asian. A small proportion in both arms were of black, mixed or other ethnic backgrounds.

Woman's smoking status

Regarding smoking status, 89.9% of women in the freeze-all arm and 91.3% in the fresh-embryo transfer arm had never smoked. A small proportion were previous smokers (9.8% in the freeze-all arm and 8.4% in the fresh-embryo transfer arm).

Woman's body mass index

The mean body mass index (BMI) of the female partner was 24.1 kg/m^2 (SD 3.4 kg/m^2) in the freeze-all arm and 24.1 kg/m^2 (SD 3.2 kg/m^2) in the fresh-embryo transfer arm. Just over 60% were in the healthy weight category (as per internationally agreed criteria).[24] Almost one-third of female participants were overweight and 4.2% were obese. Overall, 95.3% had a BMI of < 30 kg/m^2.

Type of infertility

Most women (77.2% in the freeze-all arm and 78% in the fresh-embryo transfer arm) had primary infertility. One-fifth had secondary infertility in both arms (22.8% vs. 22% in the freeze-all and fresh-embryo transfer arms, respectively). The type of infertility was a minimisation criterion.

Previous pregnancies

Over two-thirds of the participants (69.7% in the freeze-all arm vs. 71.2% in the fresh-embryo transfer arm) had had no previous pregnancy. In both arms, most participants (> 95%) had not had a previous live birth.

Main cause of infertility

The male factor and unexplained infertility constituted > 70% of the causes of infertility (72.0% in the freeze-all arm and 75.4% in the fresh-embryo transfer arm), followed by ovulatory factor (13.0% in the

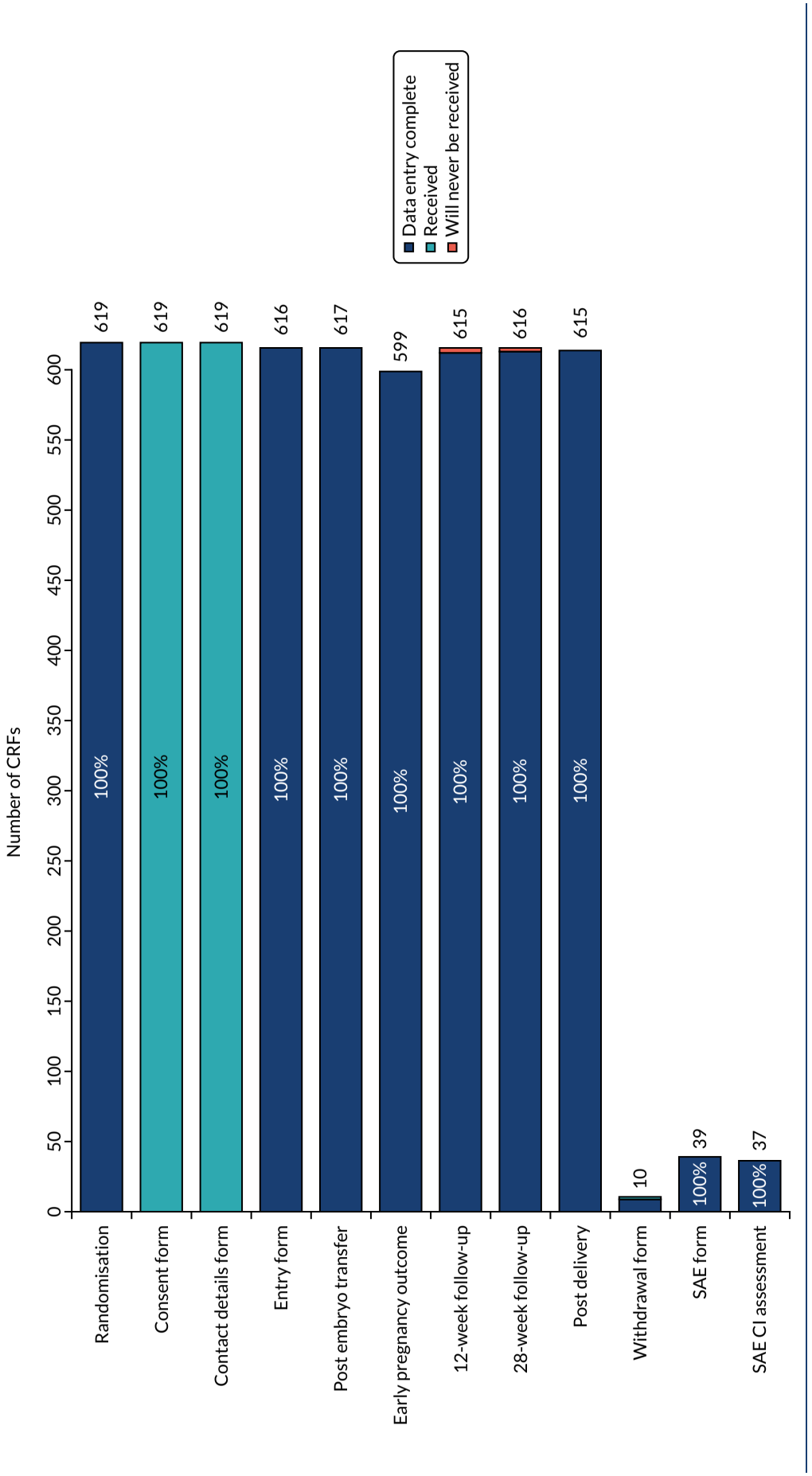


FIGURE 8 Data missingness on CRFs.

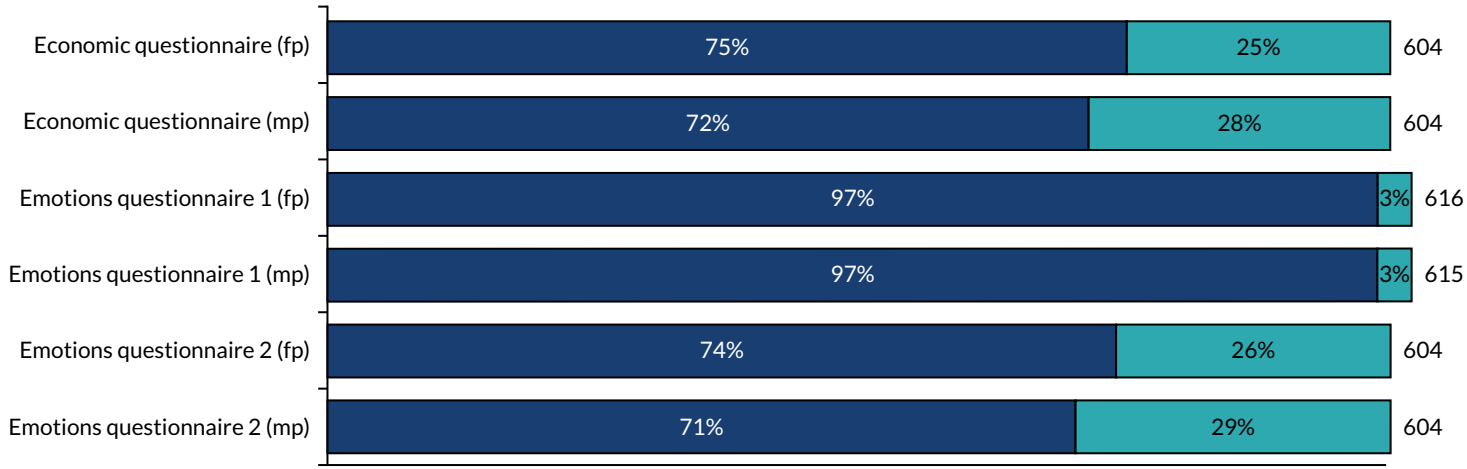


FIGURE 9 Data missingness for patient-completed questionnaires. fp, female participant; mp, male participant.

TABLE 3 Demographic characteristics at consent

Characteristic	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Woman's age at ovarian stimulation (years)		
< 35, *n* (%)	153 (49.8)	157 (50.8)
35 to < 40, *n* (%)	137 (44.6)	139 (45.0)
≥ 40, *n* (%)	17 (5.5)	13 (4.2)
Mean (SD)	34.7 (3.8)	34.6 (3.6)
Woman's ethnicity, *n* (%)		
White	237 (82.0)	221 (78.4)
Black	8 (2.8)	13 (4.6)
Asian	28 (9.7)	40 (14.2)
Mixed	6 (2.1)	5 (1.8)
Other	10 (3.5)	3 (1.1)
Not known	12	16
Missing	6	11
Woman's smoking status, *n* (%)		
Never smoked	276 (89.9)	282 (91.3)
Past smoker	30 (9.8)	26 (8.4)
Current smoker	1 (0.3)	1 (0.3)
Woman's BMI (kg/m^2)		
Underweight (< 18.5), *n* (%)	5 (1.6)	5 (1.6)
Healthy weight (18.5–24.9), *n* (%)	195 (63.7)	187 (60.7)
Overweight (25–29.9), *n* (%)	91 (29.7)	102 (33.1)
Obese (30–34.9), *n* (%)	12 (3.9)	14 (4.5)
Very obese (> 35), *n* (%)	3 (1.0)	0 (0.0)
Mean (SD)	24.1 (3.4)	24.1 (3.2)
Missing, *n*	1	1
Type of infertility, *n* (%)		
Primary	237 (77.2)	241 (78.0)
Secondary	70 (22.8)	68 (22.0)
Woman's previous pregnancies, *n* (%)		
0	214 (69.7)	220 (71.2)
1	65 (21.2)	63 (20.4)
2	18 (5.9)	16 (5.2)
> 2	10 (3.3)	10 (3.2)
Woman's previous live births, *n* (%)		
0	292 (95.1)	295 (95.5)
1	15 (4.9)	12 (3.9)
2	0	2 (0.6)

continued

TABLE 3 Demographic characteristics at consent (*continued*)

Characteristic	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Main cause of infertility, *n* (%)		
Ovulatory	40 (13.0)	32 (10.4)
Tubal	29 (9.4)	27 (8.7)
Endometriosis	13 (4.2)	11 (3.6)
Unexplained	119 (38.8)	131 (42.4)
Male factor, *n* (%)	102 (33.2)	102 (33.0)
Uterine	1 (0.3)	0 (0.0)
Low ovarian reserve	2 (0.7)	4 (1.3)
Other	1 (0.3)	2 (0.6)
Duration of infertility (months)		
< 12, *n* (%)	3 (1.0)	3 (1.0)
12 to < 24, *n* (%)	31 (10.1)	37 (12.0)
24 to < 36, *n* (%)	106 (34.5)	99 (32.0)
36 to < 48, *n* (%)	80 (26.1)	81 (26.2)
48 to < 60, *n* (%)	37 (12.1)	38 (12.3)
≥ 60, *n* (%)	50 (16.3)	51 (16.5)
Median (IQR)	36 (24–48)	36 (24–48)

Note
'Not know' and 'missing' values have not been included in the percentages throughout this table.

freeze-all arm and 10.4% in the fresh-embryo transfer arm). In both arms, a large proportion of participants had unexplained infertility (38.8% in the freeze-all arm and 42.4% in the fresh-embryo transfer arm).

Duration of infertility (months)

The median (IQR) duration of infertility was 36 months (24–48 months) in both arms. Overall, 28.6% of patients had a duration of infertility of > 48 months.

The demographic characteristics of participants randomised to the freeze-all arm were similar whether or not they complied with the allocated intervention.

Characteristics of treatment pre randomisation

The characteristics of the IVF treatment pre randomisation are described in *Table 4*. All proportions were similar in both arms unless specified.

Stimulation regimen and dose

The most common protocol used was an antagonist protocol (used in 58.8%), followed by a long protocol (used in 22.2%). The total stimulation dose was similar, with a mean dose of 2542 (SD 1257) international units (IUs). Most participants (> 80%) had human chorionic gonadotrophin (HCG) as a final booster injection, followed by dual trigger (10.2%) and, in a small proportion of participants, agonist trigger.

TABLE 4 Clinical characteristics pre randomisation

Characteristic	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Endometrial scratch performed, *n* (%)	4 (1.3)	3 (1.0)
Stimulation regimen used, *n* (%)	299 (97.4)	301 (97.4)
Long	73 (23.8)	64 (20.7)
Short	42 (13.7)	48 (15.5)
Ultrashort	7 (2.3)	4 (1.3)
Antagonist	177 (57.7)	185 (59.9)
Total stimulation dose of FSH (IUs), mean (SD)	2540 (1257)	2543 (1259)
Adjuvants used (non-exclusive), *n* (%)	9 (2.9)	7 (2.3)
Aspirin	0 (0.0)	1 (0.3)
Heparin	3 (1.0)	0 (0.0)
Steroids	2 (0.7)	1 (0.3)
Growth hormone	7 (2.3)	6 (1.9)
DHEA	0 (0.0)	1 (0.3)
Blood test performed on day of trigger injection, *n* (%)	135 (44.0)	142 (46.0)
Trigger injection used, *n* (%)		
Agonist	19 (6.2)	28 (9.1)
Dual trigger	31 (10.1)	32 (10.4)
HCG	257 (83.7)	249 (80.6)
Total number of eggs collected		
3–5, *n* (%)	14 (4.6)	16 (5.2)
6–9, *n* (%)	73 (23.8)	77 (24.9)
10–15, *n* (%)	141 (45.9)	121 (39.2)
> 15, *n* (%)	79 (25.7)	95 (30.7)
Median (IQR)	12 (9–16)	12 (9–17)
Method of insemination,[a] *n* (%)		
IVF	158 (51.5)	159 (51.5)
ICSI	139 (45.3)	138 (44.7)
Split (IVF and ICSI)	10 (3.3)	12 (3.9)
Number of eggs fertilised normally (two pronuclei)		
3–5, *n* (%)	69 (22.5)	69 (22.3)
6–9, *n* (%)	139 (45.3)	137 (44.3)
10–15, *n* (%)	76 (24.8)	81 (26.2)
> 15, *n* (%)	23 (7.5)	22 (7.1)
Median (IQR)	8 (6–11)	8 (6–11)
Time lapse used, *n* (%)	124 (40.4)	126 (40.8)

continued

TABLE 4 Clinical characteristics pre randomisation (*continued*)

Characteristic	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Good-quality embryos created on day 3		
3 or 4, *n* (%)	131 (42.7)	112 (36.2)
5 or 6, *n* (%)	70 (22.8)	84 (27.2)
7–10, *n* (%)	80 (26.1)	88 (28.5)
> 10, *n* (%)	26 (8.5)	25 (8.1)
Median (IQR)	5 (3–7)	5 (4–8)
Number of previous egg collections,[a] *n* (%)		
0	284 (92.5)	286 (92.6)
1	19 (6.2)	17 (5.5)
2	4 (1.3)	5 (1.6)
≥ 3	0 (0.0)	1 (0.3)
Number of previous embryo transfers, *n* (%)		
0	284 (92.5)	288 (93.2)
1–3	22 (7.2)	20 (6.5)
≥ 4	1 (0.3)	1 (0.3)

DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; IU, international unit.
a Minimisation criterion.

Adjuvants

Most treatments did not have add-ons or adjuvants, including endometrial scratch. A total of ≈ 40% used time lapse as the incubator, but this was similar in both arms.

Number of eggs collected

The median (IQR) number of eggs collected was 12 (range 9–16 eggs), with > 10 eggs collected from 70.8% of participants and > 15 eggs collected from 28.2%; in the case of 30 participants, fewer than six eggs were collected.

Method of insemination

The eggs and sperm were mixed by IVF or ICSI, with an almost equal split between the two methods (IVF, 51.5%; ICSI, 45%). The method of insemination was a minimisation criterion.

Number of embryos

The median number of embryos created was 8 (IQR 6–11), with 45 couples having more than 15 embryos. The median number of good-quality embryos created on day 3 was 5 (IQR 3–7) in the freeze-all arm and 5 (IQR 4–8) in the fresh-embryo transfer arm. The number of good-quality embryos created on day 3 was a minimisation criterion.

Number of previous treatments

Despite the inclusion of second and third cycles, most couples recruited had not previously undergone egg collection (92.5%) or embryo transfer (92.9%).

The clinical pre-randomisation characteristics of those randomised to the freeze-all arm were similar whether or not they complied with the allocated intervention.

Clinical characteristics post randomisation

The clinical characteristics of the embryo and the endometrium, which were collected post randomisation, are described for the ITT population by trial arm in *Table 5*.

Of those randomised, 298 out of 307 participants underwent embryo transfer in the freeze-all arm and 303 out of 309 participants underwent embryo transfer in the fresh-embryo transfer arm. Most transfers (93.8%) were at the blastocyst stage. Overall, > 80% of participants in both arms underwent single embryo transfer; the remaining participants had two embryos, except for one participant, who had three embryos.

TABLE 5 Clinical characteristics post randomisation

Characteristic	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Had embryo transfer, effective, *n*	298	303
Stage of embryo at transfer, *n* (%)		
Cleavage (day 3)	11 (3.7)	14 (4.6)
Cleavage (day 4)	5 (1.7)	6 (2.0)
Blastocyst (day 5)	270 (90.6)	281 (92.7)
Blastocyst (day 6)	12 (4.0)	1 (0.3)
< 3 days	0 (0.0)	1 (0.3)
Number of embryos transferred		
1, *n* (%)	249 (83.6)	247 (81.5)
2, *n* (%)	–	55 (18.2)
3, *n* (%)	49 (16.4)	1 (0.3)
Median (IQR)	1 (1–1)	1 (1–1)
Number of remaining frozen embryos after transfer[a]		
0, *n* (%)	68 (22.8)	61 (20.1)
1, *n* (%)	46 (15.4)	52 (17.2)
2, *n* (%)	55 (18.5)	55 (18.2)
≥ 3, *n* (%)	129 (43.3)	135 (44.6)
Median (IQR)	2 (1–4)	2 (1–4)
Endometrial appearance, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 167; fresh-embryo transfer, effective *N* = 169)		
Triple layer	152 (96.2)	157 (96.3)
No triple layer	6 (3.8)	6 (3.7)
Unknown	140	140
Endometrial thickness (mm), mean (SD) (mean is of effective *N*: frozen, effective *N* = 188; fresh-embryo transfer, effective *N* = 189)	9.3 (1.9)	10.2 (2.3)
Not recorded, *n*	119	120

a For fresh-embryo transfer, the remaining embryos that were not transferred are then frozen for future cycles. For frozen-embryo transfer, the remaining embryos that were not thawed remain frozen.

The endometrial appearance was recorded in only half of the cases in both arms; in 96.3% of these cases, it was triple layer, with a mean thickness of > 9.3 mm (SD 1.9 mm) in the freeze-all arm and 10.2 mm (SD 2.3 mm) in the fresh-embryo transfer arm.

The number of embryos remaining frozen (i.e. spare embryos) after the first embryo transfer was similar in both arms (median 2, IQR 1–4); 78.5% of couples had at least one remaining embryo frozen after embryo transfer.

The clinical characteristics post randomisation of those randomised to the freeze-all arm were similar whether or not they complied with the allocated intervention.

Post-randomisation characteristics of those who received frozen-embryo transfer

As shown in *Table 6*, 202 couples in the freeze-all arm and 21 couples in the fresh-embryo transfer arm received frozen-embryo transfer. Most couples had embryos frozen by vitrification (88.1% in the freeze-all arm and 95.2% in the fresh-embryo transfer arm). Most embryos were frozen at the blastocyst stage. The median number of embryos frozen among those who underwent frozen-embryo

TABLE 6 Post-randomisation characteristics of those who received frozen-embryo transfer

Characteristic	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Received frozen transfer, *n*	202	21
Method of embryo freezing, *n* (%)		
Vitrification	178 (88.1)	20 (95.2)
Slow freezing	24 (11.9)	1 (4.8)
Number of embryos frozen		
1, *n* (%)	16 (7.9)	1 (4.8)
2, *n* (%)	34 (16.8)	2 (9.5)
≥ 3, *n* (%)	152 (75.2)	18 (85.7)
Median (IQR)	4 (3 to 6)	4 (4 to 6)
Number of embryos thawed		
1, *n* (%)	162 (80.2)	18 (85.7)
2, *n* (%)	34 (16.8)	2 (9.5)
≥ 3, *n* (%)	6 (3.0)	1 (4.8)
Median (IQR)	1 (1 to 1)	1 (1 to 1)
Number of embryos thawed and discarded		
1, *n* (%)	15 (7.4)	0
2, *n* (%)	2 (1.0)	1 (4.8)
≥ 3, *n* (%)	1 (0.5)	0
Median (IQR)	0 (0 to 0)	0 (0 to 0)
Number of embryos thawed and refrozen, *n* (%)		
≥ 3	1 (0.5)	0

TABLE 6 Post-randomisation characteristics of those who received frozen-embryo transfer (*continued*)

Characteristic	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Number of embryos remaining frozen		
0, *n* (%)	28 (13.9)	1 (4.8)
1, *n* (%)	33 (16.3)	4 (19.0)
2, *n* (%)	40 (19.8)	1 (4.8)
≥ 3, *n* (%)	101 (50.0)	15 (71.4)
Median (IQR)	3 (1 to 4)	3 (2 to 5)
Method of endometrial preparation for transfer, *n* (%)		
Natural cycle	6 (3.0)	6 (28.6)
Natural cycle with HCG	4 (2.0)	0
Artificial cycle with oestrogen and progesterone	130 (64.4)	7 (33.3)
Artificial cycle with oestrogen and progesterone and downregulation with GnRH agonist	47 (23.3)	6 (28.6)
Artificial cycle with oestrogen, progesterone and antagonist	14 (6.9)	2 (9.5)
Other	1 (0.5)	0
Time from egg collection to embryo freezing, *n* (%)		
Cleavage (day 3)	14 (6.9)	0
Cleavage (day 4)	3 (1.5)	0
Blastocyst (day 5)	175 (86.6)	19 (90.5)
Blastocyst (day 6)	10 (5.0)	1 (4.8)
< 3 days	0	1 (4.8)

GnRH, gonadotropin-releasing hormone.

transfer was 4 (IQR 3–6). The median number of embryos thawed was one. One-fifth (19.8%) of those randomised to the freeze-all arm and 14.3% of those randomised to the fresh-embryo transfer arm who underwent frozen transfer had more than one embryo thawed. Very few embryos were thawed and discarded (i.e. this occurred in a total of 19 couples). The most common method used for endometrial preparation was artificial cycle with oestrogen and progesterone, or downregulation with gonadotropin-releasing hormone (GnRH) agonist.

Primary outcome

Intention-to-treat analysis

The ITT analysis (*Table 7*) showed that the healthy baby rate (i.e. term singleton live birth with appropriate weight for gestation) was 20.3% in the freeze-all arm and 24.4% in the fresh-embryo transfer arm ($p = 0.28$). There was no statistical difference with/without adjustment of confounding factors (adjusted RR 0.84, 95% CI 0.62 to 1.15). The proportion of singletons born was 27.7% in the freeze-all arm and 34.0% in the fresh-embryo transfer arm. The proportion of babies born at term was 25.4% in the freeze-all arm and 30.2% in fresh-embryo transfer arm. Similarly, the proportion with an appropriate weight for gestation was 22.5% in the freeze-all arm and 26.9% in the fresh-embryo transfer arm.

TABLE 7 Primary outcome

Outcome	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR (95% CI)		*p*-value
			Unadjusted	Adjusted[a]	
Singleton baby born at term with an appropriate weight for gestation, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 308)	62 (20.3)	75 (24.4)	0.83 (0.62 to 1.12)	0.84 (0.62 to 1.15)	0.275
Missing, *n*	1	1			
Singleton, *n* (%)	85 (27.7)	105 (34.0)			
Born at term, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 307; fresh-embryo transfer, effective *N* = 308)	78 (25.4)	93 (30.2)			
Missing, *n*	0	1			
Appropriate weight for gestation, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 308)	69 (22.5)	83 (26.9)			
Missing, *n*	1	1			

a Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).

Sensitivity analysis by compliance status of the freeze-all arm

When the analysis for the primary outcome was undertaken by compliance status of those randomised to the freeze-all arm, there was no difference in the outcome healthy baby rate between those who complied and those who did not comply with the allocated intervention (21.3% vs. 20.0%, respectively) (*Table 8*).

Sensitivity analysis: complier-average causal effect

The CACE RR was 0.77 (0.204/0.264). This was calculated for participants with no missing primary outcome data.

TABLE 8 Sensitivity analysis: primary outcome by compliance status of freeze-all arm

Outcome	Treatment received, *n* (%)	
	Frozen-embryo transfer (*N* = 202)	Fresh-embryo transfer (*N* = 96)
Singleton baby born at term with an appropriate weight for gestation	43 (21.3)	19 (20.0)
Missing	0	1
Singleton	56 (27.7)	29 (30.2)
Born at term	52 (25.7)	26 (27.1)
Appropriate weight for gestation	46 (22.8)	23 (24.2)
Missing	0	1

Percentage is of effective *N*: frozen, effective *N* = 202; fresh-embryo transfer, effective *N* = 95.

The values in *Table 9* are calculated for the would-be non-compliers and would-be compliers of the fresh-embryo transfer arm, assuming the same non-compliance rate and event rate as the non-compliers of the freeze-all arm.[20] The CACE RR suggests that there is no difference in the healthy baby rate between the two arms.

Exploratory analysis on primary outcome

In both arms, the healthy baby rate did not differ depending on whether the analysis was restricted to those who had received the allocated intervention ($p = 0.45$) or the analysis was undertaken as treated ($p = 0.59$) (*Table 10*).

TABLE 9 Sensitivity analysis: CACE

As per compliance status	Freeze-all arm ($N = 306$)			Fresh-embryo transfer arm ($N = 308$)		CACE RR (95% CI)
	Compliance, *n* (%)	Primary outcome (*n*/*N*)	Event rate (%)	Primary outcome (*n*/*N*)	Event rate (%)	
Compliers	211 (69.0)	43/211	20.4	56/212	26.4	0.77 (0.44 to 1.10)
Non-compliers	95 (31.0)	19/95	20.0	19/96	20.0	
Total		62/306	20.3	75/308	24.4	

TABLE 10 Exploratory analysis for the primary outcome

Analysis	Freeze-all arm	Fresh-embryo transfer arm	RR (95% CI)		*p*-value
			Unadjusted	Adjusted[a]	
Restricted per-protocol					
Total couples, excluding those who did not receive their allocated intervention, *n*	202	282			
Singleton baby born at term with appropriate weight for gestation, *n* (%) (percentage is of effective *N*: frozen, effective $N = 202$; fresh-embryo transfer, effective $N = 281$)	43 (21.3)	70 (24.9)	0.85 (0.61 to 1.19)	0.87 (0.59 to 1.26)	0.453
Missing, *n*	0	1			
As treated					
Total couples receiving each allocation, *N*	223	378			
Singleton baby born at term with appropriate weight for gestation, *n* (%) (percentage is of effective *N*: frozen, effective $N = 202$; fresh-embryo transfer, effective $N = 376$)	48 (21.5)	89 (23.7)	0.91 (0.67 to 1.24)	0.91 (0.64 to 1.29)	0.593
Missing, *n*	0	2			

a Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).

Subgroup analysis

The prespecified subgroup analysis for the primary outcome of healthy baby rate was undertaken based on the age of the female partner, number of previous embryo transfers, stage and number of embryos, and fertility clinic. As shown in *Figure 10*, there was no statistical difference in the healthy baby rate in different age groups (< 35, 35 to < 40 and > 40 years), number of previous embryo transfers (0 or ≥ 1), whether the transfer was undertaken at the cleavage or blastocyst stage, or whether one or two embryos were transferred (*Table 11*). There was a difference in the healthy baby rate between clinics; however, this is unlikely to be meaningful because of the very small numbers recruited by most clinics. Exploratory analyses were undertaken for method of endometrial preparation and type of freezing. Most frozen-embryo transfers were hormonally mediated and most embryos were frozen by vitrification.

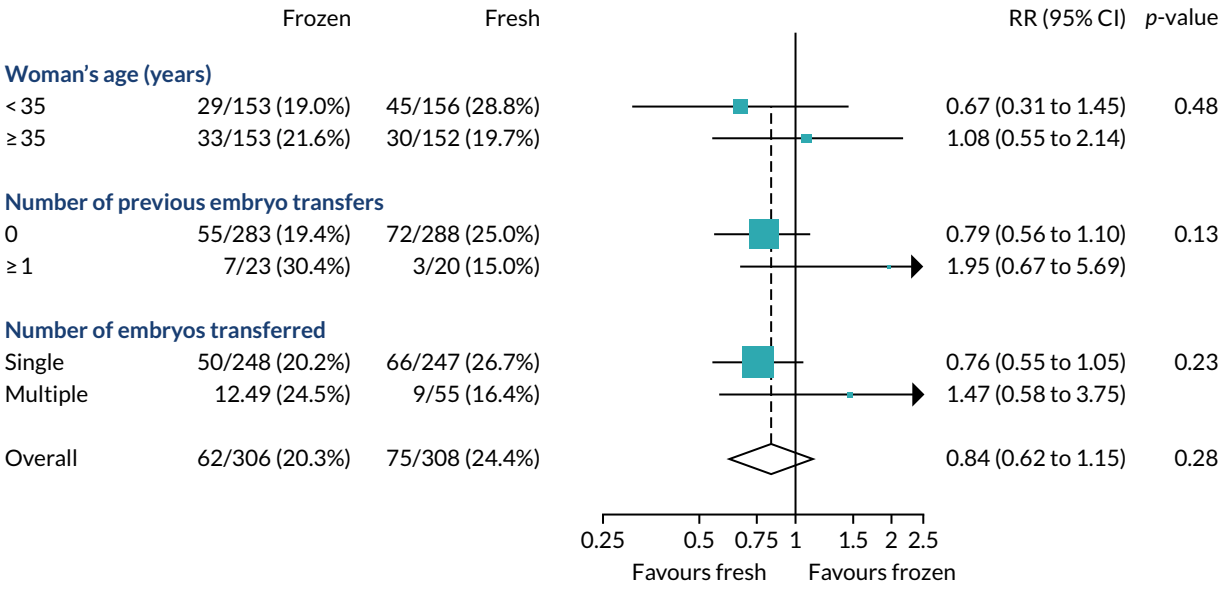


FIGURE 10 Subgroup analysis of the primary outcome. Adjusted for minimisation factors at randomisation. *p*-values from test of heterogeneity. Reproduced from Maheshwari *et al.*,[23] Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze), *Human Reproduction*, 2022, deab279, by permission of European Society of Human Reproduction and Embryology.

TABLE 11 Subgroup analyses for the primary outcome

Subgroup analysis	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR[a] (95% CI)	Interaction *p*-value
Woman's age (years), *n*/*N* (%)				0.100
< 35	29/153 (19.0)	45/156 (28.8)	0.67 (0.31 to 1.45)	
35 to < 40	32/136 (23.5)	28/139 (20.1)	1.15 (0.60 to 2.18)	
≥ 40	1/17 (5.9)	2/13 (15.4)	0.41 (0.04 to 4.10)	
Fertility clinic, *n*/*N* (%)				< 0.001
1	2/11 (18.2)	4/11 (36.4)	0.45 (0.11 to 1.78)	
2	2/13 (15.4)	3/11 (27.3)	0.60 (0.12 to 3.00)	
3	15/90 (16.7)	22/92 (23.9)	0.67 (0.37 to 1.20)	

TABLE 11 Subgroup analyses for the primary outcome (*continued*)

Subgroup analysis	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR[a] (95% CI)	Interaction *p*-value
4	9/49 (18.4)	14/48 (29.2)	0.68 (0.33 to 1.44)	
5	5/31 (16.1)	9/30 (30.0)	0.54 (0.20 to 1.42)	
6	7/21 (33.3)	6/29 (20.7)	1.62 (0.65 to 4.02)	
7	4/11 (36.4)	1/11 (9.1)	4.46 (0.55 to 36.01)	
8	3/24 (12.5)	4/23 (17.4)	0.73 (0.18 to 2.93)	
9	2/7 (28.6)	2/7 (28.6)	0.87 (0.18 to 4.20)	
10	0/10 (0.0)	2/8 (25.0)	–	
11	11/29 (37.9)	7/30 (23.3)	1.77 (0.79 to 3.97)	
12	1/1 (100.0)	0/1 (0.0)	–	
13	1/9 (11.1)	1/7 (14.3)	0.88 (0.07 to 10.75)	
Previous embryo transfers, *n*/*N* (%)				0.132
0	55/283 (19.4)	72/288 (25.0)	0.79 (0.56 to 1.10)	
≥ 1	7/23 (30.4)	3/20 (15.0)	1.95 (0.67 to 5.69)	
Stage of embryo at transfer, *n*/*N* (%)				0.821
Cleavage	1/16 (6.3)	1/20 (5.0)	1.16 (0.08 to 16.52)	
Blastocyst	61/281 (21.7)	73/281 (26.0)	0.84 (0.61 to 1.16)	
Missing, *n*	9	7		
Embryos transferred				0.227
Single, *n*/*N* (%)	50/248 (20.2)	66/247 (26.7)	0.76 (0.55 to 1.05)	
Multiple, *n*/*N* (%)	12/49 (24.5)	9/55 (16.4)	1.47 (0.58 to 3.75)	
Missing, *n*	9	6		
Received frozen-embryo transfer, *n*	202	21		
Method of endometrial preparation for transfer				
Natural cycle, *n*/*N* (%)	0/10 (0.0)	0/6 (0.0)		
Hormone replacement cycle, *n*/*N* (%)	43/191 (22.5)	5/15 (33.3)		
Missing, *n*	1	0		
Method of embryo freezing, *n*/*N* (%)				
Vitrification	37/178 (20.8)	5/20 (25.0)		
Slow freezing	6/24 (25.0)	0/1 (0.0)		
Overall, *n*/*N* (%)	62/306 (20.3)	75/308 (24.4)	0.84 (0.62 to 1.15)	0.275
Missing, *n*	1	1		

a Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).

Secondary outcomes

Maternal safety: ovarian hyperstimulation syndrome

The risk of OHSS was lower in the freeze-all arm (3.6%) than in the fresh-embryo transfer arm (8.1%); however, this difference did not reach statistical significance (RR 0.44, 99% CI 0.15 to 1.30). The severity of OHSS was mild to moderate in the freeze-all arm, whereas six (1.9%) women had severe OHSS in the fresh-embryo transfer arm (*Table 12*).

Measures of clinical effectiveness

Table 13 presents the measures of clinical effectiveness.

TABLE 12 Maternal safety: OHSS

OHSS	Freeze-all arm (*N* = 307), *n* (%)	Fresh-embryo transfer arm (*N* = 309), *n* (%)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Women with OHSS	11 (3.6)	25 (8.1)	0.44 (0.18 to 1.10)	0.44 (0.15 to 1.30)
Severity				
Mild	6 (2.0)	7 (2.3)		
Moderate	5 (1.6)	12 (3.9)		
Severe	0 (0.0)	6 (1.9)		

a Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).

TABLE 13 Measures of clinical effectiveness

Measure	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Live birth episode, *n* (%)	87 (28.3)	106 (34.3)	0.83 (0.61 to 1.13)	0.83 (0.65 to 1.06)
Singleton baby, *n* (%)	85 (27.7)	105 (34.0)	0.81 (0.60 to 1.11)	0.82 (0.64 to 1.06)
Singleton baby born at term, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 307; fresh-embryo transfer, effective *N* = 308)	78 (25.4)	93 (30.2)	0.84 (0.60 to 1.18)	0.85 (0.67 to 1.08)
Missing, *n*	0	1		
Singleton baby with appropriate weight for gestation, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 308)	68 (22.2)	83 (26.9)	0.82 (0.57 to 1.19)	0.83 (0.55 to 1.26)
Missing, *n*	1	1		
Pregnancy test 2 weeks after embryo transfer, *n* (%)				
Positive	139 (45.3)	154 (49.8)	0.91 (0.73 to 1.13)	0.91 (0.77 to 1.08)
Negative	159 (51.8)	149 (48.2)		

TABLE 13 Measures of clinical effectiveness (*continued*)

Measure	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Clinical pregnancy, *n* (%)	104 (33.9)	124 (40.1)	0.84 (0.64 to 1.11)	0.85 (0.65 to 1.11)
EPS performed, *n* (%)	129 (42.0)	139 (45.0)		
Ongoing pregnancy, *n/N* (%)	104/129 (80.6)	123/139 (88.5)		
Ectopic pregnancy, *n/N* (%)	3/129 (2.3)	5/139 (3.6)		
Pregnancy of unknown location, *n/N* (%)	3/129 (2.3)	0/139		
Miscarriage, *n/N* (%)	19/129 (14.7)	11/139 (7.9)		
EPS not performed, *n* (%)	178 (58.0)	170 (55.0)		
Pregnancy lost before date of scan, *n/N* (%)	10/178 (5.6)	15/139 (8.8)		
No embryo transfer or negative pregnancy test, *n/N* (%)	165/178 (92.7)	155/139 (91.2)		
Other, *n/N* (%)	3/178 (1.7)	0/139 (0.0)		

EPS, early-pregnancy scan.
a Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).

There was no significant difference in the live birth rate between the freeze-all arm and the fresh-embryo transfer arm (28.3% vs. 34.3%; adjusted RR 0.83, 99% CI 0.65 to 1.06).

The singleton baby rate was 27.7% in the freeze-all arm and 34.0% in the fresh-embryo transfer arm, but the difference was not statistically significant (adjusted RR 0.82, 99% CI 0.64 to 1.06).

The rate of singleton babies born at term was 25.4% in the freeze-all arm and 30.2% in the fresh-embryo transfer arm. There was no statistically significant difference (adjusted RR 0.85, 99% CI 0.67 to 1.08). The details of gestational age were missing for one baby in the fresh-embryo transfer arm.

The rate of singleton babies with an appropriate weight for their gestational age was 22.2% in the freeze-all arm and 26.9% in the fresh-embryo transfer arm. There was no statistically significant difference (adjusted RR 0.83, 99% CI 0.55 to 1.26). Details were missing for one baby in each arm.

The rate of positive pregnancy tests was 45.3% in the freeze-all arm and 49.8% in the fresh-embryo transfer arm. There was no statistically significant difference (adjusted RR 0.91, 99% CI 0.77 to 1.08).

The clinical pregnancy rate was 33.9% in the freeze-all arm and 40.1% in the fresh-embryo transfer arm. There was no statistically significant difference (adjusted RR 0.85, 99% CI 0.65 to 1.11).

Complications of pregnancy and delivery

Tables 14 (ITT analysis) and *15* (clinically relevant denominators) present the complications in pregnancy and delivery. All complications in pregnancy and delivery are described in text with the clinically relevant denominator.

TABLE 14 Complications of pregnancy and delivery: ITT analysis

Complication	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Vanishing twin/triplet, *n* (%)	4 (1.3)	4 (1.3)	1.01 (0.16 to 6.15)	–
Pregnancy loss, *n* (%)				
Miscarriage	44 (14.3)	40 (12.9)	1.11 (0.66 to 1.87)	1.09 (0.72 to 1.66)
Early (< 12 weeks' gestation)	34 (79.1)	34 (85.0)		
Late (12 to < 24 weeks' gestation)	9 (20.9)	6 (15.0)		
Gestational age unknown	1	0		
Ectopic	3 (1.0)	6 (1.9)	0.50 (0.08 to 3.07)	–
Termination	2 (0.7)	2 (0.6)	1.01 (0.08 to 13.12)	–
Pregnancy of unknown location	3 (1.0)	0 (0.0)		
GDM, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 305; fresh-embryo transfer, effective *N* = 306)	4 (1.3)	4 (1.3)	1.00 (0.16 to 6.13)	–
Missing	2	3		
Multiple pregnancy, *n* (%)	8 (2.6)	5 (1.6)	1.61 (0.38 to 6.89)	–
Multiple births, *n* (%)	2 (0.7)	1 (0.3)	2.01 (0.09 to 46.88)	–
Hypertensive disorder, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 305; fresh-embryo transfer, effective *N* = 306)	8 (2.6)	7 (2.3)	1.15 (0.31 to 4.28)	–
Chronic hypertension	0 (0.0)	1 (0.3)		
Pregnancy-induced hypertension	4 (1.3)	5 (1.6)		
Pre-eclampsia	5 (1.6)	1 (0.3)		
Eclampsia	0 (0.0)	0 (0.0)		
Missing	2	3		
Most severe hypertensive disorder experienced, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 305; fresh-embryo transfer, effective *N* = 306)				
Chronic hypertension	0 (0.0)	1 (0.3)		
Pregnancy-induced hypertension	3 (1.0)	5 (1.6)		
Pre-eclampsia	5 (1.6)	1 (0.3)		
Eclampsia	0 (0.0)	0 (0.0)		
Missing	2	3		
Antepartum haemorrhage (non-exclusive), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 304; fresh-embryo transfer, effective *N* = 306)	12 (3.9)	13 (4.2)	0.93 (0.34 to 2.55)	–
Placenta praevia	1 (0.3)	4 (1.3)		
Placental abruption	2 (0.7)	1 (0.3)		
Other	4 (1.3)	6 (2.0)		
Unexplained	6 (2.0)	4 (1.3)		
Missing	3	3		

TABLE 14 Complications of pregnancy and delivery: ITT analysis (*continued*)

Complication	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Onset of labour, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 303; fresh-embryo transfer, effective *N* = 307)				
Spontaneous	28 (9.2)	50 (16.3)	0.57 (0.32 to 1.00)	0.57 (0.33 to 1.01)
Induced	37 (12.2)	39 (12.7)		
Planned caesarean section	18 (5.9)	15 (4.9)		
Missing	4	2		
Mode of delivery, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 303; fresh-embryo transfer, effective *N* = 307)				
Normal vaginal delivery	28 (9.2)	38 (12.4)	0.75 (0.41 to 1.37)	0.75 (0.54 to 1.05)
Instrumental vaginal delivery	20 (6.6)	30 (9.8)	0.68 (0.33 to 1.38)	0.69 (0.39 to 1.21)
Caesarean section	35 (11.6)	36 (11.7)	0.99 (0.55 to 1.75)	0.99 (0.67 to 1.47)
Missing	4	2		
Preterm delivery (< 37 completed weeks of gestation), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 307; fresh-embryo transfer, effective *N* = 308)	9 (2.9)	12 (3.9)	0.75 (0.25 to 2.30)	–
Missing	0	1		
Very preterm delivery (< 32 completed weeks of gestation), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 307; fresh-embryo transfer, effective *N* = 308)	2 (0.7)	5 (1.6)	0.40 (0.05 to 3.43)	–
Missing	0	1		
Low birthweight (< 2500 g at birth), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 309)	7 (2.3)	13 (4.2)	0.54 (0.17 to 1.79)	–
Missing	1	0		
Very low birthweight (< 1500 g at birth), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 309)	1 (0.3)	8 (2.6)	0.13 (0.01 to 1.92)	–
Missing	1	0		
High birthweight (> 4000 g at birth), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 309)	10 (3.3)	10 (3.2)	1.01 (0.33 to 3.14)	–
Missing	1	0		
Customised birthweight centile (in live births), mean (SD) (mean is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 308)	53.1 (27.9)	45.3 (27.9)	–	–
Missing, *n*	1	1		

continued

TABLE 14 Complications of pregnancy and delivery: ITT analysis (*continued*)

Complication	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	RR (99% CI)	
			Unadjusted	Adjusted[a]
High weight for gestational age (> 90th centile), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 308)	9 (2.9)	10 (3.2)	0.91 (0.28 to 2.90)	–
Missing	1	1		
Low weight for gestational age (< 10th centile), *n* (%) (percentage is of effective *N*: frozen, effective *N* = 306; fresh-embryo transfer, effective *N* = 308)	8 (2.6)	12 (3.9)	0.67 (0.21 to 2.13)	–
Missing	1	1		
Congenital anomaly/birth defect, *n* (%) (percentage is of effective *N*: frozen, effective *N* = 305; fresh-embryo transfer, effective *N* = 308)	6 (2.0)	7 (2.3)	0.87 (0.21 to 3.57)	–
Tongue tie	1 (0.3)	2 (0.6)		
Cleft palate	1 (0.3)	2 (0.6)		
Other	3 (1.0)	1 (0.3)		
Missing	2	1		
Perinatal mortality up to 28 days after birth, *n* (%)	1 (0.3)	0 (0.0)	–	–
Stillbirth	0 (0.0)	0 (0.0)		
Neonatal death up to 28 days after birth	1 (0.3)	0 (0.0)		

a Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).

TABLE 15 Complications of pregnancy and delivery: clinically relevant populations

Complication	Freeze-all arm, *n* (%)	Fresh-embryo transfer arm, *n* (%)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Women with a positive pregnancy test at 2 weeks ± 3 days after embryo transfer				
Sample size	139	154		
Miscarriage	44 (31.7)	40 (26.0)	1.22 (0.76 to 1.96)	1.18 (0.76 to 1.84)
Early (< 12 weeks' gestation)	34/43 (79.1)	34/40 (85.0)		
Late (12 to < 24 weeks' gestation)	9/43 (20.9)	6/40 (15.0)		
Gestation unknown	1	0		
Multiple pregnancy	8 (5.8)	5 (3.2)	1.77 (0.42 to 7.46)	–

TABLE 15 Complications of pregnancy and delivery: clinically relevant populations (*continued*)

Complication	Freeze-all arm, *n* (%)	Fresh-embryo transfer arm, *n* (%)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Pregnant women with an ongoing pregnancy resulting in delivery				
Sample size	87	106		
GDM (percentage is of effective *N*: frozen, effective *N* = 85; fresh-embryo transfer, effective *N* = 103)	4 (4.7)	4 (3.9)	1.21 (0.20 to 7.20)	–
Missing	2	3		
Multiple pregnancy	4 (4.6)	4 (3.8)	1.22 (0.20 to 7.25)	–
Hypertensive disorder (percentage is of effective *N*: frozen, effective *N* = 85; fresh-embryo transfer, effective *N* = 103)	8 (9.4)	7 (6.8)	1.38 (0.39 to 4.97)	–
Chronic hypertension	0	1 (1.0)		
Pregnancy-induced hypertension	4 (4.7)	5 (4.9)		
Pre-eclampsia	5 (5.9)	1 (1.0)		
Eclampsia	0	0		
Missing	2	3		
Most severe hypertensive disorder experienced (percentage is of effective *N*: frozen, effective *N* = 85; fresh-embryo transfer, effective *N* = 103)				
Chronic hypertension	0	1 (1.0)		
Pregnancy induced hypertension	3 (3.5)	5 (4.9)		
Pre-eclampsia	5 (5.9)	1 (1.0)		
Eclampsia	0	0		
Missing	2	3		
Antepartum haemorrhage (percentage is of effective *N*: frozen, effective *N* = 84; fresh-embryo transfer, effective *N* = 103)	11 (13.1)	12 (11.7)	1.12 (0.41 to 3.07)	–
Placenta praevia	1 (1.2)	4 (3.9)		
Placental abruption	2 (2.4)	1 (1.0)		
Other	4 (4.8)	6 (5.8)		
Unexplained	5 (6.0)	3 (2.9)		
Missing	3	3		
Preterm delivery (< 37 completed weeks of gestation) (percentage is of effective *N*: frozen, effective *N* = 87; fresh-embryo transfer, effective *N* = 105)	9 (10.3)	12 (11.4)	0.91 (0.31 to 2.65)	–
Missing	0	1		
Very preterm delivery (< 32 completed weeks of gestation) (percentage is of effective *N*: frozen, effective *N* = 87; fresh-embryo transfer, effective *N* = 105)	2 (2.3)	5 (4.8)	0.48 (0.06 to 4.03)	–
Missing	0	1		

continued

TABLE 15 Complications of pregnancy and delivery: clinically relevant populations (*continued*)

Complication	Freeze-all arm, *n* (%)	Fresh-embryo transfer arm, *n* (%)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Onset of labour (percentage is of effective *N*: frozen, effective *N* = 83; fresh-embryo transfer, effective *N* = 104)				
Spontaneous	28 (33.7)	50 (48.1)	0.70 (0.44 to 1.13)	0.69 (0.43 to 1.11)
Induced	37 (44.6)	39 (37.5)		
Planned caesarean section	18 (21.7)	15 (14.4)		
Missing	4	2		
Babies born				
Sample size	89	107		
Mode of delivery for each baby (percentage is of effective *N*: frozen, effective *N* = 85; fresh-embryo transfer, effective *N* = 105)				
Normal vaginal delivery	28 (32.9)	38 (36.2)	0.91 (0.54 to 1.53)	0.92 (0.63 to 1.33)
Instrumental vaginal delivery	20 (23.5)	30 (28.6)	0.82 (0.43 to 1.56)	0.84 (0.56 to 1.27)
Caesarean section	37 (43.5)	37 (35.2)	1.24 (0.77 to 1.97)	1.21 (0.98 to 1.51)
Missing	4	2		
Low birthweight (< 2500 g at birth) (percentage is of effective *N*: frozen, effective *N* = 88; fresh-embryo transfer, effective *N* = 105)	8 (9.1)	14 (13.1)	0.69 (0.24 to 2.05)	–
Missing	1	0		
Very low birthweight (< 1500 g at birth) (percentage is of effective *N*: frozen, effective *N* = 88; fresh-embryo transfer, effective *N* = 85)	1 (1.1)	8 (7.5)	0.15 (0.01 to 2.28)	–
Missing	1	0		
High birthweight (> 4000 g at birth) (percentage is of effective *N*: frozen, effective *N* = 88; fresh-embryo transfer, effective *N* = 85)	10 (11.4)	10 (9.3)	1.22 (0.41 to 3.62)	–
Missing	1	0		
High weight for gestational age (> 90th centile) (percentage is of effective *N*: frozen, effective *N* = 88; fresh-embryo transfer, effective *N* = 106)	9 (10.2)	10 (9.4)	1.08 (0.35 to 3.33)	–
Missing	1	1		
Low weight for gestational age (< 10th centile) (percentage is of effective *N*: frozen, effective *N* = 88; fresh-embryo transfer, effective *N* = 106)	9 (10.2)	12 (11.3)	0.90 (0.31 to 2.64)	–
Missing	1	1		
Congenital anomaly/birth defect (percentage is of effective *N*: frozen, effective *N* = 87; fresh-embryo transfer, effective *N* = 106)	5 (5.7)	5 (4.7)	1.22 (0.25 to 5.95)	–
Tongue tie	1 (1.1)	2 (1.9)		
Cleft palate	1 (1.1)	2 (1.9)		

TABLE 15 Complications of pregnancy and delivery: clinically relevant populations (*continued*)

Complication	Freeze-all arm, *n* (%)	Fresh-embryo transfer arm, *n* (%)	RR (99% CI)	
			Unadjusted	Adjusted[a]
Other	3 (3.4)	1 (0.9)		
Missing	2	1		
Perinatal mortality up to 28 days after birth	1 (1.1)	0		
Stillbirth	0	0		
Neonatal death up to 28 days after birth	1 (1.1)	0		

a Adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect); clustered by mother to account for correlation between multiple births (in neonatal outcomes).

Early-pregnancy loss

There were three ectopic pregnancies in the freeze-all arm and six in the fresh-embryo transfer arm (RR 0.50, 99% CI 0.08 to 3.07) (see *Table 14*). Two participants underwent a termination in each arm.

There was no statistically significant difference in the risk of miscarriage in pregnancies as a result of frozen-embryo transfer compared with that of fresh-embryo transfer (31.7% vs. 26.0%, respectively) (adjusted RR 1.18, 99% CI 0.76 to 1.84) (see *Table 15*).

Multiple pregnancies

There were four cases of vanishing twins in each arm. There were eight cases of multiple pregnancy in the freeze-all arm and five in the fresh-embryo transfer arm (see *Table 14*). For births, only two couples had multiple births in the freeze-all arm and one couple had a multiple birth in the fresh-embryo transfer arm.

Obstetric complications:

There was no difference in the risk of GDM in pregnancies as a result of frozen-embryo transfer and pregnancies as a result of fresh-embryo transfer (4.7% vs. 3.9%, respectively; RR 1.21, 99% CI 0.20 to 7.20).

There was no difference in the risk of hypertensive disorder in pregnancies as a result of frozen-embryo transfer and pregnancies as a result of fresh-embryo transfer (9.4% vs. 6.8%, respectively) (RR 1.38, 99% CI 0.39 to 4.97). There were no cases of eclampsia in the trial. There were five cases of pre-eclampsia (5.9%) in women who were pregnant as a result of frozen-embryo transfer and one (1%) in a woman pregnant as a result of fresh-embryo transfer.

The risk of antepartum haemorrhage was 13.1% in the freeze-all arm and 11.7% in the fresh-embryo transfer arm (RR 1.12, 99% CI 0.41 to 3.07) (see *Table 15*).

The risk of preterm delivery was 10.3% in deliveries in the freeze-all arm and 11.4% in those in the fresh-embryo transfer arm (RR 0.91, 99% CI 0.31 to 2.65). There was no difference in the risk of very preterm delivery between the freeze-all arm (2.3%) and the fresh-embryo transfer arm (4.8%) (RR 0.48, 99% CI 0.06 to 4.03).

There were no statistical differences between groups (adjusted RR 0.69, 99% CI 0.43 to 1.11) in the proportion of women undergoing spontaneous labour (frozen-embryo transfer arm, 33.7%,

vs. fresh-embryo transfer arm, 48.1%), induced labour (44.6% vs. 37.5%, respectively) or planned caesarean section (21.7% vs. 14.4%, respectively). Data on onset of labour were missing for six couples (four in the frozen-embryo arm and two in the fresh-embryo arm).

A total of 196 babies (89 in the freeze-all arm and 107 in the fresh-embryo transfer arm) were born. In both arms, one-third of babies (freeze-all arm, 32.9%, vs. fresh-embryo transfer arm, 36.2%) were born by normal vaginal delivery (adjusted RR 0.92, 99% CI 0.63 to 1.33). The corresponding figures for instrumental vaginal delivery were 23.5% and 28.6%, respectively (adjusted RR 0.84, 99% CI 0.56 to 1.27), and for caesarean section were 43.5% and 35.2%, respectively (adjusted RR 1.21, 99% CI 0.98 to 1.51). Six couples (four in the freeze-all arm and two in the fresh-embryo transfer arm) had missing outcome data for mode of delivery.

The details of obstetric complications, with clinically relevant denominators, are reported in *Table 15*.

Neonatal outcomes

The risk of having a baby with a low birthweight was not statistically significantly different in the freeze-all arm and the fresh-embryo transfer arm (9.1% vs. 13.1%, respectively; RR 0.69, 99% CI 0.24 to 2.05). Similarly, the risk of delivering a low-birthweight baby was not significantly different between arms (1.1% vs. 7.5%, respectively; RR 0.15, 99% CI 0.01 to 2.28).

There was no statistically significant difference between arms in the proportion of babies born with a high birthweight (freeze-all arm, 11.4%, vs. fresh-embryo transfer arm, 9.3%; RR 1.22, 99% CI 0.41 to 3.62).

There was no statistically significant difference between arms in the risk of having a baby with a high birthweight for gestational age (freeze-all arm, 10.2%, vs. fresh-embryo transfer arm, 9.4%; RR 1.08, 99% CI 0.35 to 3.33).

There was no statistically significant difference between arms in the risk of having a baby with a low birthweight for gestational age (freeze-all arm, 10.2%, vs. fresh-embryo transfer arm, 11.3%; RR 0.90, 99% CI 0.31 to 2.64).

There was no difference between arms in the rate of congenital anomalies (freeze-all arm, 5.7%, vs. fresh-embryo transfer arm, 4.7%; RR 1.22, 99% CI 0.25 to 5.95). There was one neonatal death in the freeze-all arm and no neonatal deaths in the fresh-embryo transfer arm.

The details of neonatal outcomes, with clinically relevant denominator, are reported in *Table 15*.

Measures of effectiveness of the process of freezing embryos

The following measures were used to determine the effectiveness of the freezing process:

- the total number of embryos frozen, thawed and transferred for all randomised couples
- the proportion of thawed embryos that were then transferred for all randomised couples
- no embryos surviving after thawing, leading to no embryo transfer.

To transfer 248 embryos, 280 embryos had to be thawed (i.e. 88.6% of embryos were suitable for transfer after being thawed) (*Table 16*).

Three couples in the freeze-all arm did not have any embryos to transfer because their embryos did not survive the freezing–thawing process (*Table 17*).

TABLE 16 Measures of effectiveness of the process of freezing embryos

Measure	Couples (*N* = 616)
Total number of embryos	
Frozen	967
Thawed	280
Transferred	248
Percentage of thawed embryos that were then transferred	88.6

TABLE 17 Embryos not surviving freezing and thawing

	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
No embryos survived thawing, leading to no embryo transfer, *n* (%)	3 (1.0)	0 (0.0)

Evaluation of emotional status

The couples' emotional state was assessed using the STAI questionnaire.[16] Both partners completed the questionnaire at two time points (at consent and at embryo transfer).

Table 18 reports the data from the STAI questionnaire.

TABLE 18 Evaluation of emotional state

Parameters	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	MD (99% CI)	
			Unadjusted[a]	Adjusted[b]
Consent				
Emotional state score				
Female partner complete responses, *n*	295	295		
STAI score, mean (SD)	35.8 (10.2)	35.0 (10.5)		
Male partner complete responses, *n*	294	295		
STAI score, mean (SD)	30.6 (8.8)	29.9 (8.1)		
Overall satisfaction with the IVF treatment process at consent, n/N *(%)*				
Female partner				
Very satisfied	179/296 (60.5)	174/294 (59.2)		
Satisfied	96/296 (32.4)	102/294 (34.7)		
Neither satisfied nor dissatisfied	19/296 (6.4)	17/294 (5.8)		
Dissatisfied	1/296 (0.3)	1/294 (0.3)		
Very dissatisfied	1/296 (0.3)	0/294		
Missing	11	15		

continued

TABLE 18 Evaluation of emotional state (*continued*)

Parameters	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	MD (99% CI)	
			Unadjusted[a]	Adjusted[b]
Male partner				
Very satisfied	190/295 (64.4)	181/294 (61.6)		
Satisfied	87/295 (29.5)	102/294 (34.7)		
Neither satisfied nor dissatisfied	17/295 (5.8)	11/294 (3.7)		
Dissatisfied	1/295 (0.3)	0/294		
Very dissatisfied	0/295	0/294		
Missing	12	15		
At embryo transfer *Emotional state scores*				
Female partner complete responses, *n*[c]	218	227		
STAI score, mean (SD)	38.2 (11.4)	37.4 (10.8)	0.0 (−2.4 to 2.3)	0.0 (−2.2 to 2.2)
Male partner complete responses, *n*[c]	203	218		
STAI score, mean (SD)	33.5 (11.0)	32.4 (9.1)	0.1 (−1.9 to 2.2)	0.1 (−2.4 to 2.6)
Overall satisfaction with the IVF treatment process at embryo transfer, n/N *(%)*				
Female partner				
Very satisfied	119/217 (54.8)	151/231 (65.4)		
Satisfied	78/217 (35.9)	68/231 (29.4)		
Neither satisfied nor dissatisfied	8/217 (3.7)	9/231 (3.9)		
Dissatisfied	3/217 (1.4)	2/231 (0.9)		
Very dissatisfied	9/217 (4.1)	1/231 (0.4)		
Missing	90	78		
Male partner				
Very satisfied	123/203 (60.6)	141/219 (64.4)		
Satisfied	68/203 (33.5)	71/219 (32.4)		
Neither satisfied nor dissatisfied	9/203 (4.4)	3/219 (1.4)		
Dissatisfied	2/203 (1.0)	3/219 (1.4)		
Very dissatisfied	1/203 (0.5)	1/219 (0.5)		
Missing	104	90		

a Adjusted for STAI score at consent.
b Adjusted for STAI score at consent, woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).
c Excludes scores set to missing (i.e. when questionnaire was missing ≥ 3 responses).

Emotional state score

A total of 295 women and 294 men in the freeze-all arm and 295 women and 295 men in the fresh-embryo transfer arm completed the questionnaire at consent. A total of 218 women and 203 men in the freeze-all arm and 227 women and 218 men in the fresh-embryo transfer arm completed the questionnaire at embryo transfer.

At the time of consent, the mean STAI score for female partners was 35.8 (SD 10.2) in the freeze-all arm and 35.0 (SD 10.5) in the fresh-embryo transfer arm. At embryo transfer, the mean STAI score for female partners was 38.2 (SD 11.4) in the freeze-all arm and 37.4 (SD 10.8) in the fresh-embryo transfer arm. There was no statistical difference between the two arms (adjusted MD 0.0, 99% CI −2.2 to 2.2).

At the time of consent, the mean STAI score for male partners was 30.6 (SD 8.8) in the freeze-all arm and 29.9 (SD 8.1) in fresh-embryo transfer arm. At embryo transfer, the mean STAI score for male partners was 33.5 (SD 11.0) in the freeze-all arm and 32.4 (SD 9.1) in the fresh-embryo transfer arm. There was no statistical difference between the two arms (adjusted MD 0.1, 99% CI −2.4 to 2.6).

Satisfaction with process at consent and embryo transfer

Most female partners who responded (92.9% in the freeze-all arm and 93.9% in the fresh-embryo transfer arm) were either satisfied or very satisfied at the time of consent.

Most female partners (90.8% in the freeze-all arm and 94.8% in the fresh-embryo transfer arm) were either satisfied or very satisfied at the time of embryo transfer.

Most male partners who responded (93.9% in the freeze-all arm and 96.3% in the fresh-embryo transfer arm) were either satisfied or very satisfied at the time of consent.

Most male partners (94.1% in the freeze-all arm and 96.8% in the fresh-embryo transfer arm) were either satisfied or very satisfied at the time of embryo transfer.

Serious adverse events

There were 30 AEs reported, as per the SAE reporting described in *Chapter 2*. None was directly related to the intervention. Two cases of ectopic pregnancies were assessed by the PI as related; however, the chief investigator and the sponsor's assessment found that they were unrelated. Details of all SAEs are given in *Appendix 4*.

Chapter 4 Economic analysis

This chapter reports the economic evaluation of freezing all embryos, followed by frozen-embryo transfer, compared with fresh-embryo transfer, including a within-trial analysis of post-randomisation costs and outcomes up to and including delivery, and a model-based extrapolation of costs and outcomes over a complete cycle (including the subsequent transfer of the remaining frozen embryos in both arms). In addition, a within-trial cost–consequences summary is reported.

Objectives

The primary objective of the economic evaluation was to assess the incremental cost per additional healthy baby born of freezing all embryos, followed by frozen-embryo transfer, compared with fresh-embryo transfer in IVF. Two secondary economic objectives were to compare the cost and consequences between these embryo transfer strategies and to model the longer-term cost-effectiveness of frozen-embryo transfer compared with fresh-embryo transfer.

Methods

Study design and participants

Details of the trial design are provided in the published protocol[1] and in *Chapter 2*. The economic analysis was based on all women randomised, except for three post-randomisation exclusions, and follows the same ITT principle as the statistical analysis in *Chapter 3*.

Cost and outcome assessment

Costs and outcomes were assessed from post randomisation up to and including delivery, using the trial eCRFs completed by the research staff post embryo transfer, during early pregnancy (i.e. 6–8 weeks' gestation), at the 12- and 28-week follow-ups and 6 weeks post delivery, and the paper-based economic questionnaire completed by couples at embryo transfer. Health-care utilisation data collected post embryo transfer, during early pregnancy, at 28 weeks' gestation and at 6 weeks post delivery were used in the economic analysis. Questions related to participant time and travel costs incurred during treatment were included in the embryo transfer economic questionnaire (see *Report Supplementary Material 2*). All costs are reported in 2018/19 Great British pounds. Adjustments for inflation were applied to unit costs, where necessary, using the NHS Cost Inflation Index (NHSCII).[25]

Assessment of health service costs

Given that the economic evaluation seeks to inform the efficient allocation of scarce health-care resources, the base-case analysis adopted the NHS and Personal Social Services perspective. The effect on patient time and travel costs was considered separately as a secondary analysis.

Cost of the primary intervention

The cost of the embryo transfer procedure was estimated based on the health service resource use observed for each arm. The additional cost of freezing all embryos, followed by frozen-embryo transfer, was estimated from resource use data recorded in the eCRF post embryo transfer for each participant who received frozen-embryo transfer. The eCRF captured the number of monitoring visits, blood tests and ultrasound scans prior to embryo transfer, and the method of endometrial preparation. The cost of preparing frozen embryos was also included for the participants who received frozen-embryo transfer. The cost of embryo freezing was applied to all participants who received frozen-embryo transfer, as well as to the participants who had their remaining embryos frozen following a fresh-embryo transfer. The unit costs that were used to value the resource use associated with the intervention are reported in *Appendix 5*.

The costing approach assigned costs to each component of resource use to capture patient-level variation in costs. Each resource use item was mapped to an appropriate Healthcare Resource Group (HRG), where available, and costed using the relevant NHS reference cost.[26] The monitoring visit prior to transfer was assumed to be a 30-minute session led by a nurse.[25] The reported methods of endometrial preparation were valued based on routine regimens obtained from clinical advice and unit costs from the *British National Formulary* (BNF).[27] For embryo freezing and the preparation of frozen embryos, the time spent by an embryologist for each procedure was assumed to be 1 hour based on clinical advice.[25]

Costs of ovarian hyperstimulation syndrome

The clinical management costs associated with OHSS and pregnancy were valued using the *NHS Reference Costs 2018/19*.[26] The resource use for managing OHSS was obtained from the eCRFs post embryo transfer and during early pregnancy. The non-elective inpatient stay cost for a 1-day stay was valued using the inpatient short stay cost, whereas inpatient stays of > 1 day were valued using the inpatient long stay cost, adjusted for length of stay using the excess bed-day cost if the stay was longer than the average length of stay. As some of the relevant data needed for the adjustment of inpatient long-stay costs were not available in the *NHS Reference Costs 2018/19*, the average length of stay for non-elective long stays and the non-elective excess bed-day cost were obtained from the *NHS Reference Costs 2017/18*[28] and inflated. This approach was undertaken for all costs associated with inpatient stays in the analysis.

Costs of pregnancy outcomes

Data on pregnancy outcomes (e.g. miscarriage, biochemical pregnancy, ectopic pregnancy, pregnancy of unknown location and termination) were obtained from the eCRF during early pregnancy, at the 12- and 28-week follow-ups. Miscarriage and ectopic pregnancy were costed by applying the average reference cost per case, whereas termination cost varied by gestation. It was assumed that, on average, a minimum of one ultrasound scan and three beta-human chorionic gonadotropin (βHCG) blood tests would be required for biochemical pregnancy and pregnancy of unknown location.[29]

Costs of antenatal care

The antenatal care (ANC) costs were based on the *NHS Reference Costs 2018/19*[26] and varied according to the maternal complications reported. Primary and secondary care contacts during pregnancy and any complications were captured in the 28-week follow-up CRF and post-delivery eCRF. It was assumed that participants had a community midwife visit following an early pregnancy scan (EPS). The complications were grouped using the *Code to Group: HRG4+ 2019/20 Local Payment Grouper*[30] workbook to determine the corresponding HRG. Episodes of care were costed by applying either the day-case reference cost for an inpatient day care visit or the non-elective inpatient cost (stay of ≥ 1 day), adjusted for length of stay using the excess bed-day cost.

For antenatal ultrasound scans, the resource use was obtained from the eCRFs during early pregnancy, at the 28-week follow-up and post delivery. The costs of ultrasound were determined using the NHS reference cost[26] and were varied in accordance with the standard recommendation for antenatal ultrasound scanning of one scan throughout the pregnancy. Any additional ultrasound scans were costed as non-routine.

Costs of delivery

The delivery method was obtained from the post-delivery eCRF and valued based on the NHS reference cost.[26] The costs varied according to the delivery mode, onset method (with or without induction) and length of inpatient stay for delivery.

Participant travel and time costs

Participant costs associated with travelling to and from appointments and the time spent for a clinic visit during treatment were estimated from post randomisation to embryo transfer. Travel costs were

estimated based on the number of visits to the clinic and travel expenses per visit or distance travelled by car, obtained from the economic questionnaire. Travel costs were estimated based on the expenses reported for participants who travelled using public transport and taxis, whereas the costs for travel by car were calculated using the mileage reported and the private car rate per mile of 45p per mile published by Her Majesty's Revenue and Customs (HMRC).[31] Time costs, which account for time lost from productive activities, were estimated from the economic questionnaire based on the time taken to visit the clinic. Time taken away from normal productive activities was estimated in hours, and appropriate unit costs were used to estimate the opportunity cost of time. Gross age- and sex-specific wage rates obtained from the *Annual Survey of Hours and Earnings* (ASHE),[32] published by the Office for National Statistics, were used to cost the time lost from paid employment. To estimate the cost associated with time lost for the accompanying male partner, the partner's age was assumed to be the same as that of the participant. The cost of time lost from unpaid work was estimated using the value of unpaid work published by the Office for National Statistics.[33] Forgone leisure time was valued using the current value of non-working time, available from the Department for Transport.[34] The unit costs that were used to value the time lost are reported in *Appendix 5*.

Outcome measures

Effectiveness for the economic evaluation was measured in terms of the number of healthy babies born and the secondary clinical outcomes of the trial. Secondary outcomes included live births, maternal safety outcomes (i.e. OHSS), pregnancy outcomes, complications of pregnancy and delivery and adverse birth outcomes.

Statistical analysis of trial economic data

Aggregating costs and effects

Resource use, costs and health outcome data were summarised by trial arm, based on the participants who had the event of interest and by ITT. The IVF costs were broken down into the following categories: freezing of embryo, endometrial preparation, embryo transfer, monitoring visits prior to frozen-embryo transfer, blood tests prior to frozen-embryo transfer, transvaginal ultrasound scans prior to frozen-embryo transfer and preparation of frozen embryos. All cost elements were summed over the follow-up period (up to and including the cost of delivery) to estimate a total NHS cost per patient.

Cost data were fully present with respect to resource use associated with embryo transfers and OHSS; however, given that no further resource use data were collected for 15 participants who did not undergo embryo transfer, these participants were conservatively assigned no further treatment costs other than embryo freezing and thawing, where applicable. This assumption favours the freeze-all approach because three patients in the freeze-all arm may have incurred further work-up costs prior to cancellation of their embryo transfer owing to the embryos failing to survive the thawing process. Therefore, we also conducted a sensitivity analysis in which multiple imputation was used to impute the pre-embryo-transfer monitoring visit, blood test and scan costs for these three participants.

Elements of resource use data were also missing for a small number ($n = 13$) of resultant pregnancies. Two of these participants who had uncomplicated pregnancies were missing entries for the number of antenatal midwifery, outpatient and inpatient attendances between 12 and 28 weeks' gestation only. These two participants were included in the complete-case analysis by assigning a zero cost to these elements; based on a comparison with similar participants with no missing data, it was considered plausible that these elements were missing because the costs were zero and they were not missing at random. Thus, for the complete-case analysis, we retained 616 participants for the cost-effectiveness analysis using treatment plus OHSS costs, and 605 participants for the analysis of total NHS costs (inclusive of ANC and delivery care).

Recognising the uncertainty in the above approach, we also conducted a sensitivity analysis using multiple imputation to impute plausible values for all 13 participants with missing ANC and delivery care cost elements, and the work-up costs for the three cancelled frozen-embryo transfer cycles where missingness could not be ascertained. We did not, however, impute missing values for the primary clinical effectiveness outcome, allowing 614 participants to be included in the cost-per-healthy-live birth multiple-imputation analysis and 616 participants to be included in the cost-per-live birth multiple-imputation analysis.

Within-trial cost-effectiveness and cost-consequence analysis

The within-trial economic analysis was performed on an ITT basis using individual participant-level data from the trial. The cost differences were summarised by ITT against the primary and secondary clinical outcomes using a cost–consequence balance sheet. All analyses were performed using Stata®, version 15 (StataCorp LLC, College Station, TX, USA).

For the within-trial cost-effectiveness analysis, two cost categories were used: treatment costs (including post-randomisation preparation and embryo transfer costs); and OHSS costs and full NHS costs, which, in addition to treatment and OHSS costs, included pregnancy and delivery costs. Cost-effectiveness was expressed in terms of the incremental cost per healthy baby and per live birth of freezing all embryos, followed by frozen-embryo transfer, compared with fresh-embryo transfer. The incremental treatment cost (inclusive of OHSS costs) per additional healthy baby born was estimated as the primary measure of cost-effectiveness, as the management and incidence rate of complications per pregnancy were similar between arms, with no statistically significant differences. Generalised linear models (GLMs), with adjustment for minimisation factors, were used to estimate MDs in costs and effects between the trial arms. For cost outcomes, a gamma family with log-link was selected using the modified Park test, Pearson's correlation, Pregibon link and modified Hosmer–Lemeshow tests.[35] For the effectiveness outcomes (i.e. healthy babies and live births), a Poisson family with log-link was used, as per the statistical analysis. Recycled predictions were used to recover adjusted mean values by trial arm, as well as the incremental differences between trial arms.[35] The incremental cost-effectiveness ratio (ICER) for frozen-embryo transfer compared with fresh-embryo transfer was calculated as the difference in mean cost divided by the difference in mean effect. The variance surrounding the joint incremental costs and effects was characterised using non-parametric bootstrapping (i.e. 1000 iterations), with simulated output summarised graphically using cost-effectiveness plane and cost-effectiveness acceptability curves. For the sensitivity analysis using multiple imputation, the imputation model used chained equations with predictive mean matching ($k = 5$) to generate five imputed data sets ($m = 5$) nested within each bootstrapped resample ($n = 1000$). The imputation model included all of the missing cost elements, treatment allocation, women's age and indicators for pregnancy and live birth as auxiliary variables.

Sensitivity analysis

The sensitivity analysis focused on the costing methodology for the initial interventions and missing data. A sensitivity analysis using multiple imputation chained equation was performed to assess the impact of missing data (including participants with partial missing data) on the robustness of the cost-effectiveness findings of the incremental NHS cost per baby born. The trial-based cost-effectiveness analysis was also conducted using pre-defined subgroups for women's age at ovarian stimulation (< 35 years vs. ≥ 35 years).

Modelling of subsequent frozen-embryo transfers

Although the within-trial analysis is useful for informing cost-effectiveness in the short term, a longer time horizon is required to determine the relative cost-effectiveness of the alternative embryo transfer strategies in the context of routine IVF practice, whereby the subsequent transfer of the remaining frozen embryos can take place if the initial fresh-embryo transfer or frozen-embryo transfer fails to achieve a live birth. Therefore, a Markov model was developed to simulate progression through the

subsequent transfer of the remaining frozen embryos for those failing to achieve live birth in both trial arms. This compares the policy of offering a full cycle of IVF using the freeze-all approach and a full cycle of IVF using the routine approach, in which a fresh embryo is used for the index transfer and the remaining frozen embryos are replaced in subsequent associated transfers. Although NICE[3,36] recommends up to three full cycles of IVF treatment, with remaining good-quality embryos frozen and, subsequently, transferred as part of the same cycle, implementation of this guidance is low in England.[37] Furthermore, the most efficient approach to the first full IVF cycle is also likely to offer the best value for money if repeated full IVF cycles are permitted. Therefore, the economic model considered one full IVF cycle. The index transfer in the model was parametrised using event rates and costs derived from the ITT analysis of the E-Freeze trial data, including post-randomisation costs for the initial embryo transfer, OHSS costs and ongoing costs associated with pregnancies. The costs and outcomes associated with subsequent frozen-embryo transfers were extrapolated using several assumptions (see *Figure 11* for details). The state transition diagram for the model is provided in *Figure 11*. The details of the derived model parameter inputs are provided in *Results*.

The model structure is replicated for the fresh-embryo transfer and freeze-all arms of the E-Freeze trial and runs on a fixed 4-week Markov cycle. Couples start the model in the 'index fresh embryo transfer' or the 'index frozen-embryo transfer' state based on the observed distribution in the respective arms of the E-Freeze trial. Following this, couples proceed to embryo transfer and either achieve a positive pregnancy test result or fail to become pregnant. A small proportion also receive no transfer, as observed in both arms of the trial. Those who fail to become pregnant move to either the

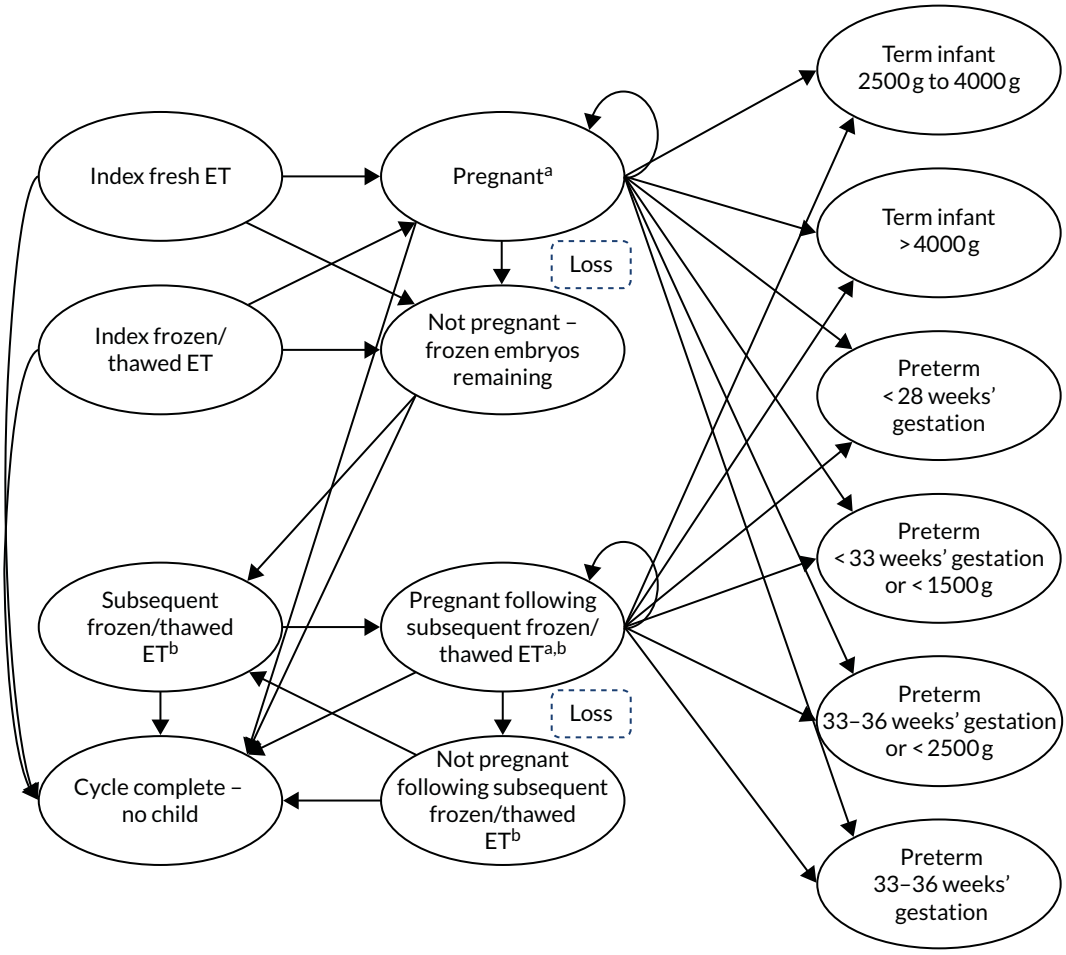


FIGURE 11 State transition diagram for the Markov model. a, Tunnel states consisting of nine 4-week temporary states to capture progression through pregnancy. b, States were multiplied by 6 to allow for up to six subsequent frozen-embryo transfers.

'not pregnant – frozen embryos remaining' or the 'cycle complete – no child' state, depending on the availability of remaining frozen embryos. Those who become pregnant move to the 'pregnant' state, which is a tunnel state consisting of nine temporary states that can be occupied for one 4-week cycle only. This captures progression and outcomes through the stages of pregnancy. During pregnancy, women incur ANC costs relevant to their stage of pregnancy, as observed by trial arm in the E-Freeze trial. Women can also lose their pregnancy; in these situations, they incur the cost of this event and transition to the 'not pregnant – frozen embryos remaining' or 'cycle complete – no child' state.

For those who carry their pregnancy to ≥ 24 weeks' gestation, birth outcomes are modelled as observed by trial arm in the E-Freeze trial, and the relevant costs of delivery care are applied. To fit with the model structure and cycle length, preterm deliveries were categorised into three mutually exclusive categories as follows: < 28 weeks', 28–32 weeks' and 33–36 weeks' gestation. For those transitioning to the 'not pregnant – frozen embryos remaining' state, the observed numbers of remaining embryos by treatment allocation arm in E-Freeze were used, in conjunction with several assumptions informed by external data,[38] to inform transitions through subsequent frozen transfers of remaining embryos (see *Figure 11*). The model states representing subsequent embryo transfers, pregnancy following subsequent transfer, and failure to achieve pregnancy following subsequent transfer (see *Figure 11*), are multiplied by six to allow for up to six frozen transfers for those failing to achieve a live birth. Once a live birth has been achieved, no further transfers are modelled.

For the key outcomes that drive differences in the live birth rate and healthy baby rate between the trial arms, the model utilises relative risks (and 95% CIs) for frozen-embryo transfer and fresh-embryo transfer (ITT) applied to the baseline probabilities of events observed in the fresh-embryo transfer arm of E-Freeze [positive pregnancy following embryo transfer, RR 0.91 (95% CI 0.77 to 1.08); any pregnancy loss following a positive pregnancy test, RR 1.18 (95% CI 0.76 to 1.84); delivery prior to 33 weeks' gestation for ongoing pregnancies at 24 weeks' gestation, RR 0.60 (95% CI 0.15 to 2.34); and delivery between 33 and < 37 weeks' gestation for ongoing pregnancies at end of week 32 of gestation, RR 1.17 (95% CI 0.39 to 3.52)]. The relative risk for OHSS is also applied (0.44 95% CI, 0.15 to 1.3). For other parameters, trial arm-specific event counts and costs are derived from the observed E-Freeze outcome and cost data. The details of these derived model parameter inputs are provided in *Results*.

Following internal validation of the model output for the index embryo transfer against the trial-based cost-effectiveness findings, the model was used to extrapolate the costs and consequences of transferring the remaining frozen embryos. For this, the distribution of remaining embryos by trial arm in the E-Freeze trial for those not achieving live birth was used to estimate the proportion of women expected to have remaining embryos available for a second, third, fourth, fifth, sixth and seventh embryo transfer attempt. This required two key assumptions:

1. The remaining frozen embryos are thawed and replaced one at a time.
2. The transfer of each remaining frozen embryo has an equal chance of resulting in pregnancy and live birth, regardless of the approach to the first transfer and the total number of embryos remaining frozen.

For all subsequent frozen-embryo transfers, the event rates and costs were based on those observed for the index transfer in the frozen arm of the E-Freeze trial. The following adjustments were also made:

1. It was assumed that not all couples with remaining frozen embryos available after each failed transfer would return to use them (i.e. a discontinuation rate was applied after each failed transfer).
2. The survival rate for thawed embryos was set to 88%, in line with data from the E-Freeze trial.
3. The chance of pregnancy with subsequent frozen-embryo transfers was assumed to be lower, relative to the chance of pregnancy in the index transfer in the freeze-all arm of the E-Freeze trial.
4. A duration of three model cycles (i.e. 12 weeks) was assumed between each embryo transfer attempt.

The adjustments described in 1 and 3 above were based on an Australian population-based study reporting on the cumulative live birth rate (CLBR) following a freeze-all strategy compared with a fresh-embryo transfer strategy,[38] including a good-prognosis group with a similar number of embryos available and a similar live birth rate as those of the E-Freeze cohort. Following each failed embryo transfer and using the reported data, a discontinuation rate was calculated as the proportion of women with remaining frozen embryos who did not return for a further transfer. This was taken as the average across the fresh-embryo transfer and freeze-all groups in the best prognosis subgroup of the Australian study. The relative adjustment to the pregnancy rate in subsequent frozen-embryo transfers compared with index frozen-embryo transfer cycles was derived using data reported for the freeze-all group of the best-prognosis subgroup of the Australian study. No more than six subsequent frozen-embryo transfers were incorporated in the model, as < 5% of the E-Freeze cohort had more than six embryos remaining frozen following failure of the index transfer, and the increase in the expected live birth rate from allowing a sixth transfer was < 0.1% compared with that from allowing up to five subsequent frozen-embryo transfers.

The model also included final birth outcome states, as it was originally intended to extrapolate longer-term costs and health outcomes per child born following treatment. This was in anticipation of a potential trade-off between maximising the live birth rate and maximising the health baby rate. However, the E-Freeze trial data indicated that, as a proportion of live births, the healthy baby rate was the same (71%) in both arms. Therefore, a decision was made not to include these in the current model. Although there were differences in the percentages of live births falling into the categories of preterm delivery and abnormal birthweight, these differences were based on very small numbers and, therefore, are highly uncertain. This would consequently translate into a high degree of uncertainty around any modelled difference in expected child health service costs or health outcomes.

Model-based analysis

The model was run probabilistically over a time horizon of 5 years, using 1000 random draws from distributions assigned to each clinical and cost input parameter. The results of the model were assessed in terms of the incremental cost per healthy baby and the incremental cost per live birth. Costs incurred beyond year 1 in the model were discounted using a rate of 3.5%, in line with the NICE reference case,[39] but birth outcomes were not discounted because there is no guidance on the discount rate to apply to these outcomes in the context of fertility treatment. The probabilistic model output was summarised using cost-effectiveness scatterplots and cost-effectiveness acceptability curves, indicating the probability of each strategy being preferred on grounds of cost-effectiveness by increasing levels of societal willingness to pay per additional healthy baby or additional live birth. A further deterministic sensitivity analysis was undertaken to assess the robustness of the model findings to key structural uncertainties and costing assumptions.

Results

Health service resource use and costs

Table 19 summarises NHS resource use by trial arm and *Table 20* summarises costs by trial arm. A total of 601 participants received an embryo transfer, with 117 participants not receiving their allocated treatment. As a result, 223 participants received frozen-embryo transfer, including 21 who were allocated to fresh-embryo transfer. Prior to frozen-embryo transfer, participants had additional monitoring visits, blood tests and transvaginal ultrasound scans. The crossover participants had slightly fewer monitoring visits and transvaginal scans, but more blood tests. The resource use associated with IVF translated to an average post-randomisation treatment cost of £1538 and £1216 in the freeze-all and fresh-embryo transfer arms, respectively, giving an unadjusted cost difference of £322. Compared with frozen-embryo transfer, a larger number of participants developed OHSS in the fresh-embryo transfer arm (8% vs. 4%, respectively), and participants in the fresh-embryo transfer arm had more outpatient visits and inpatient day case visits and a longer inpatient length of stay than participants in the freeze-all arm. The mean OHSS costs by treatment allocation were £17 for frozen-embryo transfer and £201 for fresh-embryo transfer.

TABLE 19 Health service resource use by treatment allocation

Variable	Number of observations	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Fresh-embryo transfer, *n* (%)	378	96 (31)	282 (91)
Frozen-embryo transfer, *n* (%)	223	202 (66)	21 (7)
No transfer, *n* (%)	15	9 (3)	6 (2)
Care associated with frozen-embryo transfer			
Sample size (*n*)	223	202	21
Monitoring visit prior to frozen-embryo transfer, mean (SD)	223	2.19 (2.08)	1.86 (1.39)
Blood test prior to frozen-embryo transfer, mean (SD)	223	0.35 (0.81)	0.62 (1.07)
Transvaginal ultrasound prior to frozen-embryo transfer, mean (SD)	223	1.80 (1.51)	1.38 (0.97)
Endometrial preparation for frozen-embryo transfer (*n*)[a]	223	202	21
Natural cycle, *n* (%)	12	6 (3)	6 (29)
Natural cycle with HCG, *n* (%)	4	4 (2)	0 (0)
Artificial cycle with oestrogen and progesterone, *n* (%)	137	130 (64)	7 (33)
Artificial cycle with oestrogen, progesterone and GnRH agonist, *n* (%)	53	47 (23)	6 (29)
Artificial cycle with oestrogen, progesterone and antagonist, *n* (%)	16	14 (7)	2 (10)
Other, *n* (%)	1	1 (0)	0 (0)
OHSS			
Participants with OHSS, *n* (%)	36	11 (4)	25 (8)
Outpatient hospital visits, mean (SD)	36	0.27 (0.90)	2.32 (3.02)
Inpatient day case visits, mean (SD)	36	1.27 (2.00)	1.64 (2.06)
Inpatient length of stay, mean (SD)	36	0.09 (0.30)	0.68 (1.75)
Pregnancy outcome[b]			
2 weeks post embryo transfer, *n* (%)	601	298	303
Positive	293	139 (47)	154 (51)
Negative	308	159 (53)	149 (49)
6–8 weeks' gestation, *n* (%)	293	139	154
Ongoing pregnancy	227	104 (75)	123 (80)
Biochemical pregnancy	25	10 (7)	15 (10)
Miscarriage	30	19 (14)	11 (7)
Ectopic pregnancy	8	3 (2)	5 (3)
Pregnancy of unknown location	3	3 (2)	0 (0)
12 weeks' gestation, *n* (%)	227	104	123
Ongoing pregnancy	201	93 (89)	108 (88)
Miscarriage[c]	23	10 (10)	13 (11)
Ectopic pregnancy	1	0 (0)	1 (1)
Termination	2	1 (1)	1 (1)

TABLE 19 Health service resource use by treatment allocation (*continued*)

Variable	Number of observations	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
28 weeks' gestation, *n* (%)	201	93	108
Ongoing pregnancy	189	87 (94)	102 (94)
Miscarriage	6	5 (5)	1 (1)
Termination	2	1 (1)	1 (1)
Live birth	4	0 (0)	4 (4)
ANC			
6 to < 12 weeks' gestation (*n*)	293	139	154
Antenatal ultrasound, mean (SD)	293	0.93 (0.26)	0.90 (0.30)
12 to < 28 weeks' gestation (*n*)	201	93	108
Community midwife visit, mean (SD)	199	2.60 (1.64)	2.61 (1.87)
Outpatient hospital visits, mean (SD)	199	2.13 (1.88)	2.25 (2.12)
Inpatient day case visits, mean (SD)	199	0.18 (0.69)	0.15 (0.53)
Inpatient length of stay, mean (SD)	199	0.44 (3.16)	0.33 (1.20)
Antenatal ultrasound, mean (SD)	199	2.09 (1.68)	2.08 (1.45)
Missing, *n* (%)	2	0 (0)	2 (2)
28 weeks' gestation to delivery (*n*)	189	87	102
Community midwife visit, mean (SD)	181	3.13 (2.29)	3.22 (2.42)
Outpatient hospital visits, mean (SD)	181	2.80 (2.22)	2.80 (2.19)
Inpatient day case visits, mean (SD)	181	0.32 (0.84)	0.41 (1.00)
Inpatient length of stay, mean (SD)	181	0.60 (1.63)	0.43 (2.30)
Antenatal ultrasound, mean (SD)	181	2.30 (1.88)	2.24 (1.71)
Missing, *n* (%)	8	3 (3)	5 (5)
Maternal complication			
12 to < 28 weeks' gestation, *n* (%)	201	93	108
No maternal complications	172	81 (87)	91 (84)
Hypertensive disorder (non-exclusive)	6	3 (3)	3 (3)
GDM (non-exclusive)	7	3 (3)	4 (4)
Antepartum haemorrhage	15	7 (8)	8 (7)
Missing	2	0 (0)	2 (2)
28 weeks' gestation to delivery, *n* (%)	189	87	102
No maternal complications	149	68 (78)	81 (79)
Hypertensive disorder (non-exclusive)	13	7 (8)	6 (6)
GDM (non-exclusive)	7	3 (3)	4 (4)
Antepartum haemorrhage	15	6 (7)	9 (9)
Missing	6	3 (3)	3 (3)
Delivery,			
Sample size (*n*)	193	87	106
Inpatient length of stay, mean (SD)	185	3.15 (2.11)	3.12 (1.97)
Missing, *n* (%)	8	3 (3)	5 (5)

continued

TABLE 19 Health service resource use by treatment allocation (*continued*)

Variable	Number of observations	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Delivery mode, *n* (%)			
Normal vaginal delivery	66	28 (33)	38 (36)
Instrumental vaginal delivery	50	20 (23)	30 (28)
C-section	71	35 (41)	36 (34)
Missing	6	4 (5)	2 (2)
Newborns delivered (live births and stillbirths)*, n *(%)			
Sample size	193	87	106
Still births	0	0 (0)	0 (0)
Neonatal deaths	1	1 (1)	0 (0)
Preterm newborns	21	9 (10)	12 (11)
Term newborns	170	77 (89)	93 (88)
Missing	1	0 (0)	1 (1)

a Collected from participants who received frozen-embryo transfer only.
b Based on the outcome recorded on the CRF at each time point.
c 10 miscarriages reported at the 12-week timepoint occurred after 12 weeks' gestation: in the freeze-all arm there wer five miscarriages between 12.7 and 16.9 weeks' gestation and in the fresh-embryo transfer arm there were five miscarriages between 12.3 and 12.9 weeks' gestation.

TABLE 20 Direct medical costs by treatment allocation (£): ITT analysis

Variable	Number of observations	Mean cost (£) (SD)	
		Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
IVF costs	616	1538.45 (473.67)	1215.51 (221.17)
Freezing of embryo	616	41.16 (15.96)	38.14 (18.75)
Endometrial preparation	616	131.88 (104.18)	78.05 (50.45)
Embryo transfer	616	1063.07 (185.05)	1073.91 (151.37)
Monitoring visit prior to frozen-embryo transfer	616	80.81 (111.32)	7.08 (32.94)
Blood test prior to frozen-embryo transfer	616	0.25 (0.75)	0.05 (0.35)
Transvaginal ultrasound prior to frozen-embryo transfer	616	189.66 (239.42)	15.05 (68.56)
Preparation of frozen embryo	616	31.60 (22.33)	3.22 (11.93)
OHSS management costs	616	16.73 (163.06)	201.04 (1066.54)
Pregnancy loss costs	616	89.03 (227.96)	74.65 (205.10)
ANC costs	607	743.70 (1713.17)	803.21 (1787.25)
Delivery inpatient costs	606	1051.62 (1989.32)	1279.38 (2196.31)
Total NHS cost[a]	605	3431.15 (3507.87)	3573.99 (3807.37)

a Total cost was calculated for those patients with complete cost data only.

Of the 293 participants with a positive pregnancy test result at 2 weeks post embryo transfer, 100 suffered pregnancy loss. The number with pregnancy loss was slightly larger in the freeze-all arm, at 52 (37%), than in the fresh-embryo transfer arm, at 48 (31%). The mean cost of pregnancy loss was £89 and £75 for frozen-embryo transfer and fresh-embryo transfer, respectively. As a result, 193 participants had a live birth delivery, with more babies delivered in the fresh-embryo transfer arm than in the freeze-all arm. No obvious, notable differences were observed in the resource use associated with ANC in participants with ongoing pregnancy or in the delivery costs for those achieving live birth. The mean cost of ANC and delivery was higher in the fresh-embryo transfer arm (see *Table 22*) owing to the higher pregnancy rate and the smaller proportion of participants experiencing pregnancy loss.

The resource use from randomisation to delivery translated to a total, average, unadjusted NHS cost of £3431 in the freeze-all arm and £3574 in the fresh-embryo transfer arm, resulting in an unadjusted difference of £143. A breakdown of direct medical costs per participant experiencing each type of resource use event is presented in *Appendix 6*.

Participant travel and time costs

Table 21 presents the travel and time costs for attending clinic appointments between the time of treatment allocation and embryo transfer. A larger number of participants in the freeze-all arm reported at least one clinic visit (135 vs. 41 in the fresh-embryo transfer arm), and participants in the freeze-all arm also reported a larger average number of clinic visits (1.6 vs. 0.6 in the fresh-embryo transfer arm). This translated to an average travel cost of £30 for the thawed freeze-all arm and £25 for the fresh-embryo transfer arm.

Among the 164 participants who reported at least one clinic visit, women in the freeze-all arm reported spending less time in the clinic per visit than women in the fresh-embryo transfer arm. In total, 145 participants reported taking time off from paid work (see *Appendix 7*). The mean productivity cost associated with time away from usual activities was £50 for the freeze-all arm and £27 for the fresh-embryo transfer arm. When travel and time costs were summed, the average patient's time and travel cost came to £80.09 and £52.05 for the freeze-all arm and the fresh-embryo transfer arm, respectively.

Cost-effectiveness analysis results

The cost-effectiveness analysis was conducted using the complete-cases data set, and the incremental cost per baby born is presented in *Table 22*. The adjusted mean treatment cost (including OHSS) per

TABLE 21 Travel and time costs by treatment allocation (£): ITT analysis

Variable	Number of observations	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Clinic visit(s) between treatment allocation and embryo transfer, *n* (%)			
Yes	176	135 (44)	41 (13)
No	279	86 (28)	193 (62)
Missing	161	86 (28)	75 (24)
Number of clinic visits, mean (SD)	443	1.56 (2.08)	0.55 (1.58)
Missing, *n* (%)	186	104 (34)	82 (27)
Total travel costs,[a] mean (SD)	437	29.83 (73.32)	25.38 (138.96)
Total time costs,[b] mean (SD)	432	50.26 (82.86)	26.54 (101.14)
Total patient costs,[c] mean (SD)	429	80.09 (144.06)	52.05 (236.13)

a Estimated using travel costs per visit and the number of visits reported.
b Estimated using time costs per visit and the number of visits reported.
c Sum of total travel costs and total time costs.

TABLE 22 Trial-based incremental cost per baby born (NHS perspective) using complete cases[a]

	Cost (£), mean (95% CI)		Effect, mean (95% CI)		
Cost	Total	Incremental	Total	Incremental	ICER
***Treatment: healthy baby* (n = *614*)**					
Fresh-embryo transfer	1402.02 (1297.21 to 1516.44)		0.242 (0.197 to 0.294)		
Freeze all	1572.88 (1518.45 to 1641.31)	170.86 (60.77 to 284.18)	0.204 (0.160 to 0.246)	−0.039 (−0.104 to 0.023)	Dominated
***Treatment: live birth* (n = *616*)**					
Fresh-embryo transfer	1401.41 (1297.14 to 1516.62)		0.341 (0.289 to 0.397)		
Freeze all	1571.55 (1516.11 to 1642.32)	170.15 (66.79 to 288.57)	0.285 (0.235 to 0.331)	−0.057 (−0.138 to 0.013)	Dominated
***NHS: healthy baby* (n = *605*)**					
Fresh-embryo transfer	3551.41 (3137.70 to 3960.49)		0.233 (0.189 to 0.281)		
Freeze all	3454.15 (3101.50 to 3869.45)	−97.25 (−622.81 to 460.94)	0.193 (0.151 to 0.237)	−0.040 (−0.101 to 0.027)	2425
***NHS: live birth* (n = *605*)**					
Fresh-embryo transfer	3551.41 (3137.70 to 3960.49)		0.329 (0.278 to 0.377)		
Freeze all	3454.15 (3101.50 to 3869.45)	−97.25 (−622.81 to 460.94)	0.273 (0.225 to 0.324)	−0.056 (−0.127 to 0.020)	1742

a Adjusted for woman's age, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic.

participant was £1402 for the fresh-embryo transfer arm and £1573 for the freeze-all arm, resulting in an adjusted MD of £171. The mean treatment cost was significantly higher in the freeze-all arm than in the fresh-embryo transfer arm. The mean adjusted healthy baby rate was 0.242 in the fresh-embryo transfer arm and 0.204 in the freeze-all arm, producing an adjusted MD of −0.039 (95% CI −0.104 to 0.023) in favour of the fresh-embryo transfer arm. The cost-effectiveness scatterplot, using 1000 bootstrapped iterations, in *Figure 12* shows that frozen-embryo transfer was more costly than fresh-embryo transfer in the majority of iterations (≈ 99%). In addition, the healthy baby rate was lower for frozen-embryo transfer than fresh-embryo transfer in 89% of iterations, in line with the MD, in effect favouring fresh-embryo transfer over frozen-embryo transfer. Thus, frozen-embryo transfer was dominated by fresh-embryo transfer. Based on the cost-effectiveness acceptability curves in *Figure 13*, frozen-embryo transfer had a low chance of being cost-effective at all willingness-to-pay thresholds. Similar findings were noted for the cost-effectiveness analysis using live birth as the measure of effect. (see *Table 24*, and *Figures 12* and *13*).

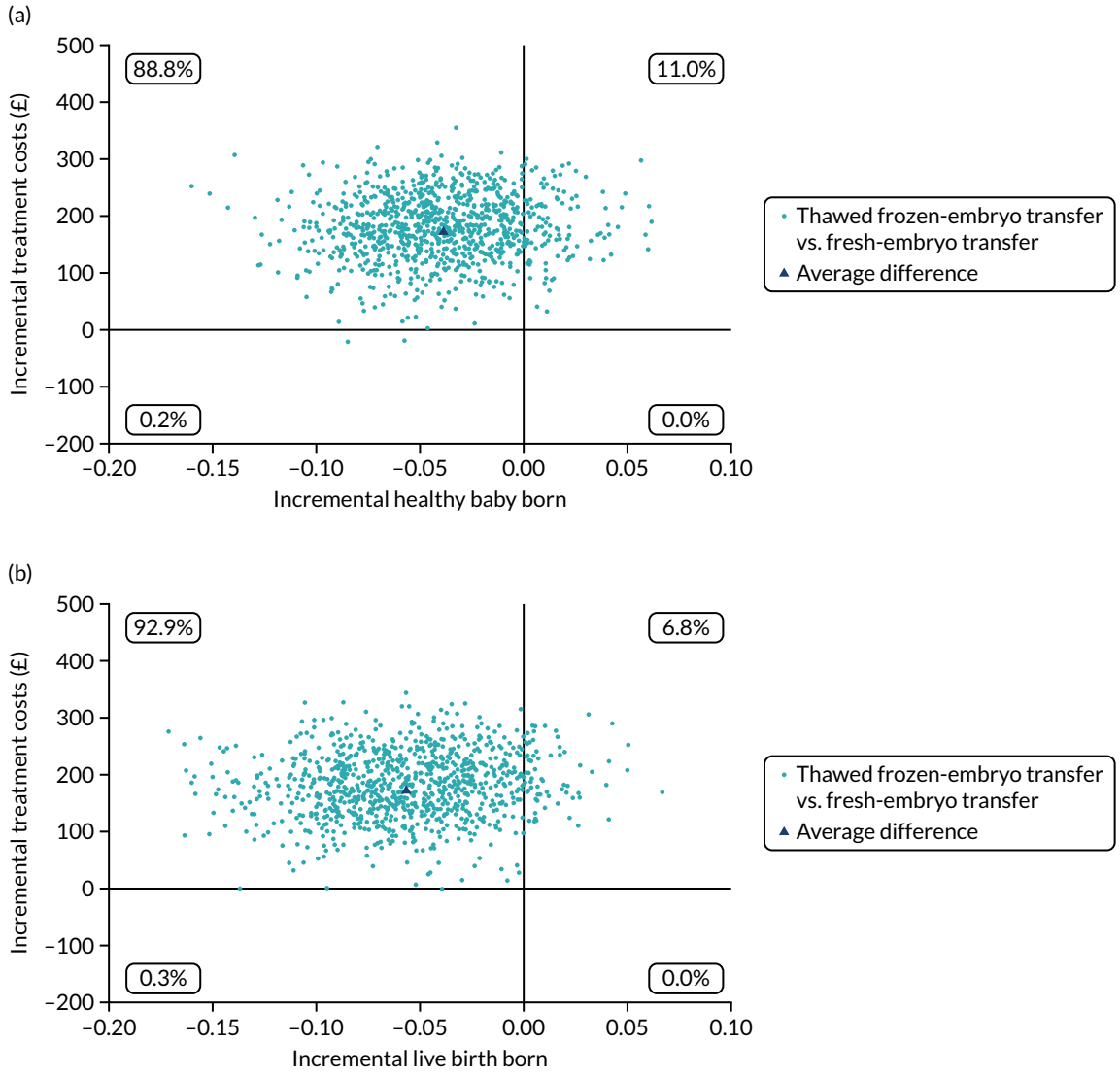


FIGURE 12 Trial-based incremental cost-effectiveness scatterplots for frozen-embryo transfer vs. fresh-embryo transfer. (a) Treatment costs: healthy baby; (b) treatment costs: live birth; (c) NHS costs: healthy baby; and (d) NHS costs: live birth. (*continued*)

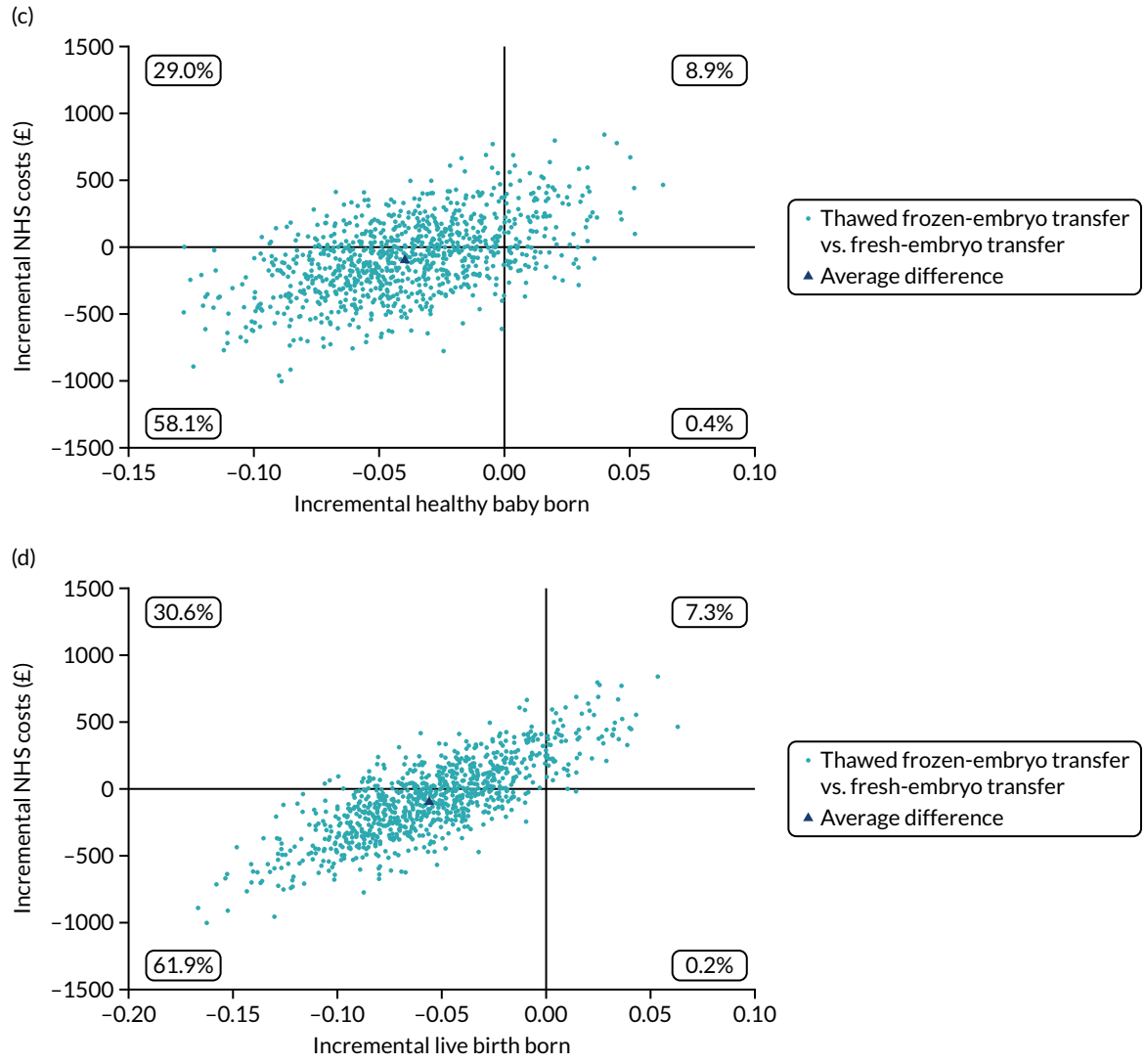


FIGURE 12 Trial-based incremental cost-effectiveness scatterplots for frozen-embryo transfer vs. fresh-embryo transfer. (a) Treatment costs: healthy baby; (b) treatment costs: live birth; (c) NHS costs: healthy baby; and (d) NHS costs: live birth.

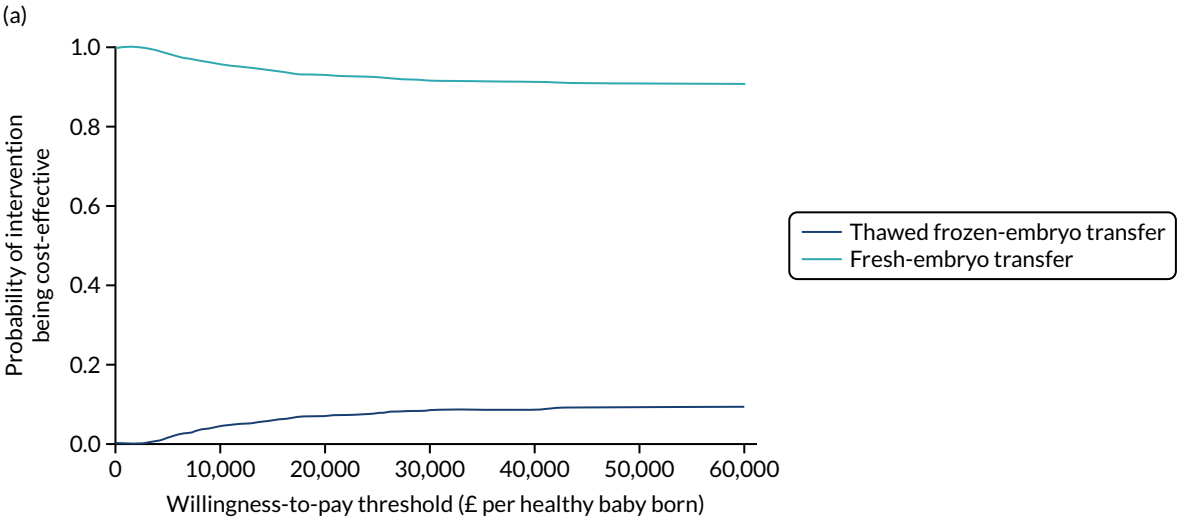


FIGURE 13 Trial-based cost-effectiveness acceptability curves for frozen-embryo transfer vs. fresh-embryo transfer. (a) Treatment costs: healthy baby; (b) treatment costs: live birth; (c) NHS costs: healthy baby; and (d) NHS costs: live birth. (*continued*)

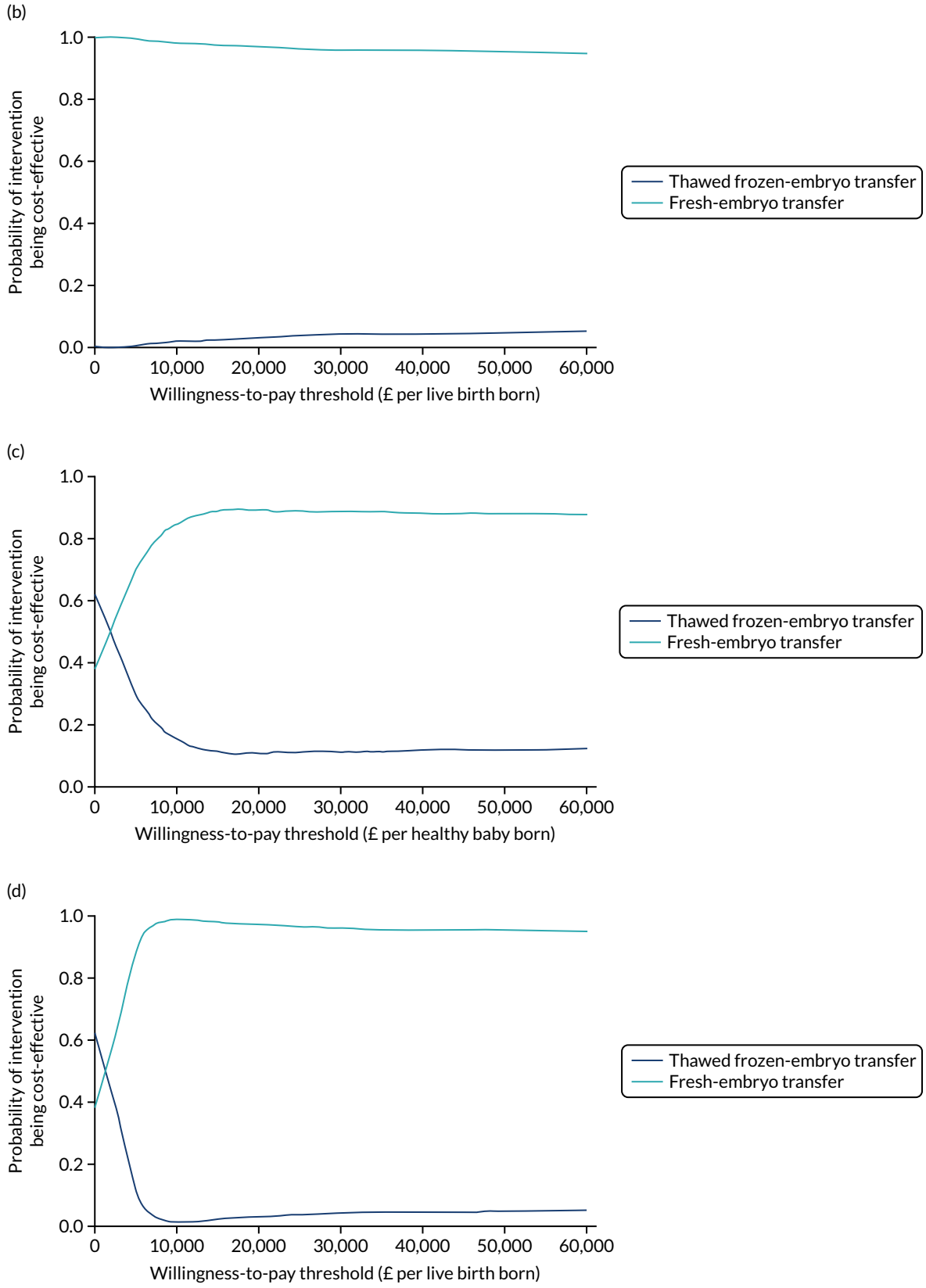


FIGURE 13 Trial-based cost-effectiveness acceptability curves for frozen-embryo transfer vs. fresh-embryo transfer. (a) Treatment costs: healthy baby; (b) treatment costs: live birth; (c) NHS costs: healthy baby; and (d) NHS costs: live birth.

When the total NHS costs were used in the analysis, the adjusted mean NHS cost per participant was £3551 for the fresh-embryo transfer arm and £3454 for the freeze-all arm, resulting in an adjusted MD of £97 (fresh-embryo transfer vs. freeze all). The mean treatment costs for fresh-embryo transfer were slightly higher than those for frozen-embryo transfer because of higher ANC and delivery costs, driven by the higher pregnancy and delivery rates. The ICER for frozen-embryo transfer compared with fresh-embryo transfer, representing cost savings per unit reduction in effect, came to £2425 and £1742 for one less healthy baby and one less live birth, respectively.

Sensitivity and subgroup analyses results

As the cost of transvaginal scans was the main driver of the increased treatment costs for the freeze-all arm compared with the fresh-embryo transfer arm, several sensitivity analyses were conducted using alternative costing methodologies for the scan (*Table 23*). In addition, multiple imputation was conducted to assess the impact of the base-case assumptions around missing cost data (*Table 24*). Prespecified subgroup analyses based on age and the number of previous embryo transfers were also conducted (*Table 25*). The cost-effectiveness scatterplots and cost-effectiveness acceptability curves are shown in *Appendix 8*.

Alternative costing methodology

Table 23 shows the results of the sensitivity analyses. Using alternative, more conservative, assumptions for costing transvaginal ultrasound scans and pre-embryo transfer monitoring, the incremental treatment cost of frozen-embryo transfer was reduced and was no longer significant under the lowest scan-cost scenario. However, both alternative analyses led to similarly low probabilities of frozen-embryo transfer being cost-effective compared with fresh-embryo transfer (see *Appendix 8*).

Multiple imputation

Table 24 presents the results of sensitivity analyses using the multiple imputation approach. The incremental treatment costs were slightly increased (frozen-embryo transfer vs. fresh-embryo transfer) following this approach, and the total NHS cost savings (inclusive of pregnancy delivery costs) were slightly lower (frozen-embryo transfer vs. fresh-embryo transfer). The incremental NHS cost per healthy baby (£2109) and per live birth (£1399) was, consequently, slightly lower for fresh-embryo transfer than for frozen-embryo transfer.

Subgroup analyses

Table 25 reports the results of subgroup analyses by age. In women aged ≥ 35 years, the healthy baby rate was slightly higher in the freeze-all arm, although the difference was not statistically significant, leading to a positive ICER of £24,308 per additional healthy baby. Based on the results of the non-parametric bootstrap, frozen-embryo transfer was found to have a 46.5% chance of being the preferred intervention at the willingness-to-pay threshold of £20,000 per healthy baby (see *Appendix 8*). The cost-effectiveness findings for other subgroups remained less favourable to frozen-embryo transfer than to fresh-embryo transfer.

Costs and consequences summary

The summary of costs and consequences was consistent with the cost-effectiveness findings. Frozen-embryo transfer incurred higher treatment and patient costs than fresh-embryo transfer. There were no significant differences in all primary and secondary outcome measures between the trial arms (*Table 26*), although, directionally, the majority of the outcome measures favoured fresh-embryo transfer over frozen-embryo transfer. The exceptions to this were preterm delivery and low birthweight, which were proportionally higher in the fresh-embryo transfer arm than in the freeze-all arm, although this was based on small numbers of events, with no statistically significant differences found.

TABLE 23 Trial-based sensitivity analysis of incremental treatment costs per healthy baby born

Sensitivity analysis	Cost (£), mean (95% CI)		Effect, mean (95% CI)		ICER
	Total	Incremental	Total	Incremental	
Base-case analysis (NHS reference cost for transvaginal ultrasound scan: £160)					
Fresh-embryo transfer	1402.02 (1297.21 to 1516.44)		0.242 (0.197 to 0.294)		
Freeze all	1572.88 (1518.45 to 1641.31)	170.86 (60.77 to 284.18)	0.204 (0.160 to 0.246)	−0.039 (−0.104 to 0.023)	Dominated
Assuming the transvaginal scan cost was inclusive of a monitoring visit cost					
Fresh-embryo transfer	1397.09 (1292.44 to 1509.98)		0.242 (0.197 to 0.294)		
Freeze all	1508.76 (1461.13 to 1571.11)	111.67 (5.19 to 221.82)	0.204 (0.160 to 0.246)	−0.039 (−0.104 to 0.023)	Dominated
Using an abdominal scan cost (£53) to cost transvaginal scans					
Fresh-embryo transfer	1392.54 (1288.81 to 1503.92)		0.242 (0.197 to 0.294)		
Freeze all	1442.97 (1400.86 to 1498.28)	50.42 (−55.54 to 157.41)	0.204 (0.160 to 0.246)	−0.039 (−0.104 to 0.023)	Dominated

TABLE 24 Trial-based sensitivity analysis of incremental total NHS costs per baby born (using multiple imputation assumptions)

Trial-based sensitivity analysis of incremental costs per baby born (using multiple imputation assumptions)	Cost (£), mean (95% CI)		Effect, mean (95% CI)		
	Total	Incremental	Total	Incremental	ICER
***Treatment costs: healthy baby* (n = 614)[a]**					
Fresh-embryo transfer	1398.56 (1298.96 to 1514.05)		0.242 (0.195 to 0.294)		
Freeze all	1580.80 (1520.49 to 1642.94)	182.24 (63.49 to 290.63)	0.204 (0.159 to 0.251)	−0.039 (−0.108 to 0.025)	Dominated
***Treatment costs: live birth* (n = 616)[a]**					
Fresh-embryo transfer	1398.10 (1299.28 to 1511.60)		0.342 (0.292 to 0.394)		
Freeze all	1580.07 (1519.40 to 1647.80)	181.96 (61.91 to 295.07)	0.284 (0.236 to 0.334)	−0.057 (−0.128 to 0.013)	Dominated
***NHS costs: healthy baby* (n = 614)[a,b]**					
Fresh-embryo transfer	3600.62 (3207.12 to 4024.05)		0.242 (0.195 to 0.294)		
Freeze all	3519.20 (3124.21 to 3946.27)	−81.41 (−652.38 to 492.33)	0.204 (0.159 to 0.251)	−0.039 (−0.108 to 0.025)	2109.12
***NHS costs: live birth* (n = 616)[a,b]**					
Fresh-embryo transfer	3614.84 (3215.32 to 4029.97)		0.342 (0.292 to 0.394)		
Freeze all	3534.61 (3162.81 to 3952.30)	−80.23 (−644.73 to 486.58)	0.284 (0.236 to 0.334)	−0.057 (−0.128 to 0.013)	1398.85

a Pretransfer monitoring visit, blood test and scan costs imputed for three cancelled frozen-embryo transfer cycles (assigned zeros in the base-case analysis).
b Missing ANC or delivery care cost elements imputed for 13 cases.

TABLE 25 Trial-based incremental treatment cost per healthy baby born by predefined subgroups

Subgroup	Cost (£), mean (95% CI)		Effect, mean (95% CI)		ICER
	Total	Incremental	Total	Incremental	
Base-case analysis					
Fresh-embryo transfer	1402.02 (1297.21 to 1516.44)		0.242 (0.197 to 0.294)		
Freeze all	1572.88 (1518.45 to 1641.31)	170.86 (60.77 to 284.18)	0.204 (0.160 to 0.246)	−0.039 (−0.104 to 0.023)	Dominated
Maternal age: < 35 years					
Fresh-embryo transfer	1456.12 (1283.09 to 1630.29)		0.289 (0.215 to 0.364)		
Freeze all	1586.77 (1498.57 to 1709.66)	130.65 (−16.23 to 311.72)	0.190 (0.129 to 0.250)	−0.100 (−0.192 to −0.002)	Dominated
Maternal age: ≥ 35 years					
Fresh-embryo transfer	1328.28 (1251.48 to 1427.94)		0.202 (0.142 to 0.269)		
Freeze all	1577.28 (1500.75 to 1659.19)	249.00 (123.09 to 362.21)	0.212 (0.147 to 0.276)	0.010 (−0.079 to 0.096)	24,308

TABLE 26 Trial-based costs and consequences summary

Outcome	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)	Difference,[a] mean (95% CI)
Costs (£), mean (95% CI)			
Treatment (IVF and OHSS)	1572.88 (1518.45 to 1641.31)	1402.02 (1297.21 to 1516.44)	170.86 (60.77 to 284.18)
NHS	3454.15 (3101.50 to 3869.45)	3551.41 (3137.70 to 3960.49)	−97.25 (−622.81 to 460.94)
Patient	124.75 (101.76 to 190.65)	70.83 (37.45 to 106.44)	53.92 (12.45 to 137.34)
Total	3569.72 (3209.94 to 3986.87)	3626.90 (3217.83 to 4044.10)	−57.18 (−578.94 to 500.62)
Consequences, mean (95% CI)			
Healthy baby born	0.204 (0.160 to 0.246)	0.242 (0.1967 to 0.294)	−0.039 (−0.104 to 0.023)
Live birth	0.285 (0.235 to 0.331)	0.341 (0.289 to 0.397)	−0.057 (−0.138 to 0.013)
Maternal safety outcome*, n *(%)			
OHSS	11 (3.6)	25 (8.1)	0.44 (0.15 to 1.30)[b]
Complications of pregnancy and delivery*, n *(%)			
Miscarriage	44 (14.3)	40 (12.9)	1.09 (0.72 to 1.66)[b]
Ectopic pregnancy	3 (1.0)	6 (1.9)	0.50 (0.08 to 3.07)
Termination	2 (0.7)	2 (0.6)	1.01 (0.08 to 13.12)
GDM	4 (1.3)	4 (1.3)	1.00 (0.16 to 6.13)
Hypertensive disorders of pregnancy	8 (2.6)	7 (2.3)	1.15 (0.31 to 4.28)
Antepartum haemorrhage	12 (3.9)	13 (4.2)	0.93 (0.34 to 2.55)
Preterm delivery	9 (2.9)	12 (3.9)	0.75 (0.25 to 2.30)
Very preterm delivery	2 (0.7)	5 (1.6)	0.40 (0.05 to 3.43)
Low birthweight	7 (2.3)	13 (4.2)	0.54 (0.17 to 1.79)
Very low birthweight	1 (0.3)	8 (2.6)	0.13 (0.01 to 1.92)
High birthweight	10 (3.3)	10 (3.2)	1.01 (0.33 to 3.14)
High weight for gestational age	9 (2.9)	10 (3.2)	0.91 (0.28 to 2.90)
Low weight for gestational age	8 (2.6)	12 (3.9)	0.67 (0.21 to 2.13)
Congenital anomaly	6 (2.0)	7 (2.3)	0.87 (0.21 to 3.57)
Perinatal mortality	1 (0.3)	0 (0.0)	–
Measure of clinical effectiveness outcomes*, n *(%)			
Live birth episode	87 (28.3)	106 (34.3)	0.83 (0.65 to 1.06)[b]
Singleton live birth	85 (27.7)	105 (34.0)	0.82 (0.64 to 1.06)[b]
Singleton live birth at term	78 (25.4)	93 (30.2)	0.85 (0.67 to 1.08)[b]
Singleton baby with appropriate weight for gestation	68 (22.2)	83 (26.9)	0.83 (0.55 to 1.26)[b]
Pregnancy	139 (45.3)	154 (49.8)	0.91 (0.77 to 1.08)[b]
Clinical pregnancy	104 (33.9)	124 (40.1)	0.85 (0.65 to 1.11)[b]

a Effect estimate was reported as unadjusted RR (99% CI) for clinical outcomes, unless stated otherwise.
b RR (99% CI), adjusted for woman's age at ovarian stimulation, primary/secondary fertility, duration of infertility, method of insemination, number of previous egg collections and fertility clinic (as a random effect).

Modelling of subsequent frozen-embryo transfers

All of the derived parameter inputs for the cost-effectiveness model are provided in *Appendix 9*. The results of the modelling exercise, allowing for up to six subsequent frozen-embryo transfers, are provided in *Table 27*, and *Figures 14* and *15*. The results show that, allowing for the transfer of the remaining embryos, the incremental cost associated with frozen-embryo transfer can be expected to increase further, whereas the difference in effect can be expected to narrow slightly. This is driven by the higher initial failure rate in the freeze-all arm than that in the fresh-embryo transfer arm, resulting in a larger proportion of the cohort retuning for further frozen-embryo transfers than fresh-embryo transfers. Allowing for this, fresh-embryo transfer continues to dominate frozen-embryo transfer in

TABLE 27 Model-based incremental cost per baby born (NHS perspective), allowing for use of remaining embryos

	Cost (£), mean		Effect, mean		
Cost	**Total**	**Incremental**	**Total**	**Incremental**	**ICER**
Treatment: healthy baby					
Fresh-embryo transfer	2870		0.381		
Freeze all	3195	325	0.349	−0.031	Dominated
Treatment: live birth					
Fresh-embryo transfer	2870		0.538		
Freeze all	3195	325	0.503	−0.035	Dominated
NHS: healthy baby					
Fresh-embryo transfer	6391		0.381		
Freeze all	6560	169	0.349	−0.031	Dominated
NHS: live birth					
Fresh-embryo transfer	6391		0.538		
Freeze all	6560	169	0.503	−0.035	Dominated

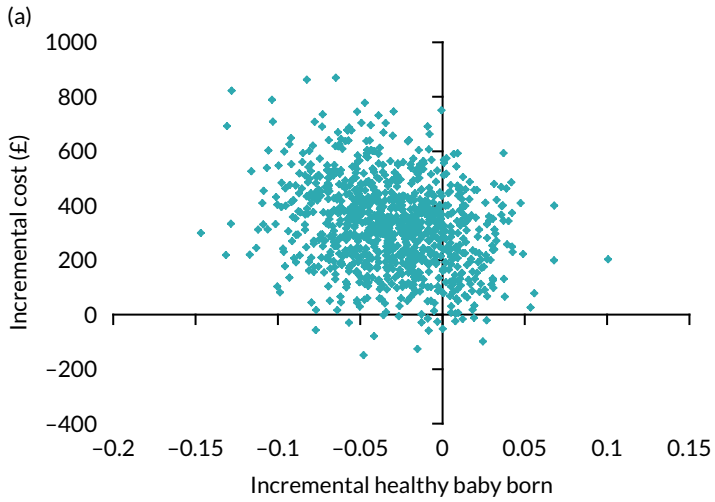


FIGURE 14 Model-based cost-effectiveness scatterplots for frozen-embryo transfer vs. fresh-embryo transfer. (a) Treatment costs (including OHSS): healthy baby; (b) treatment costs (including OHSS): live birth; (c) NHS costs: healthy baby; and (d) NHS costs: live birth. (*continued*)

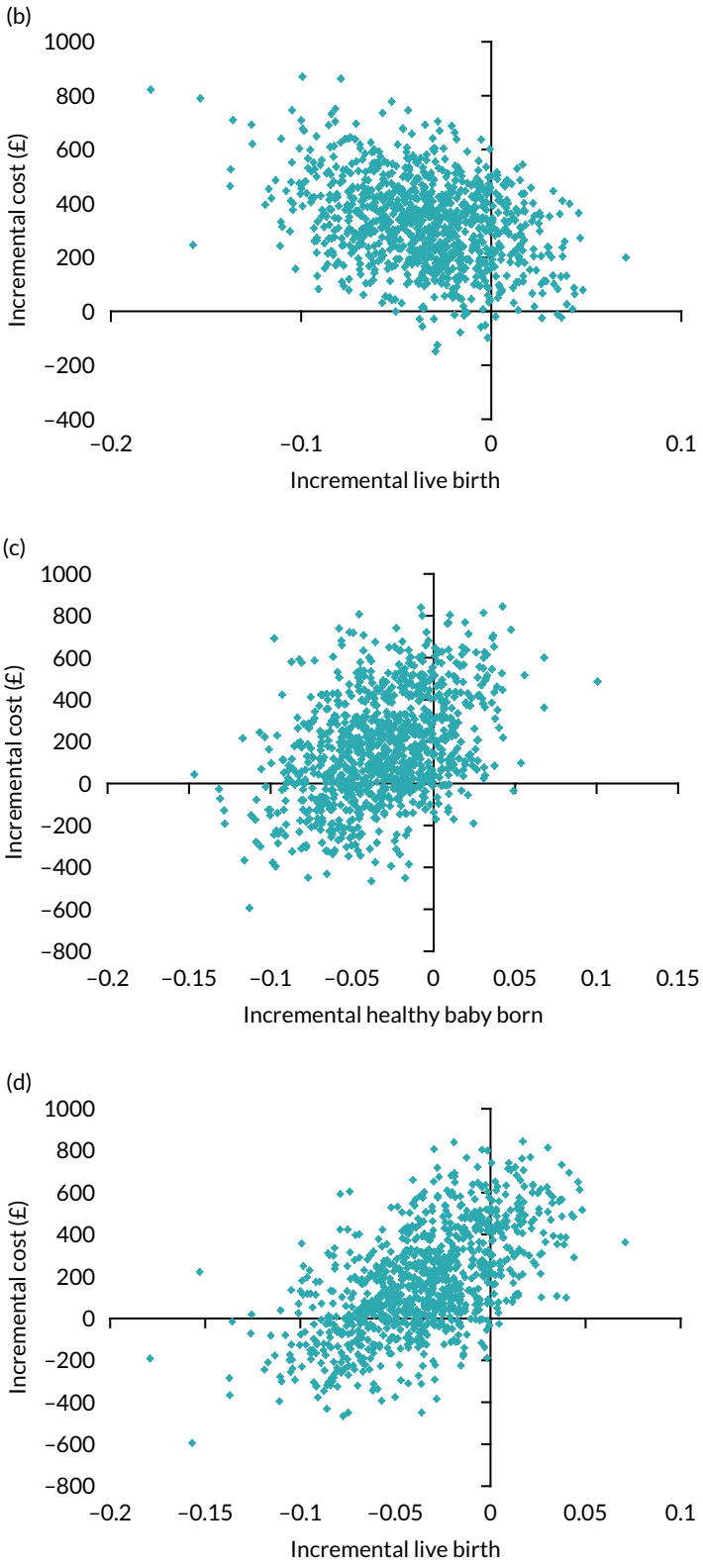


FIGURE 14 Model-based cost-effectiveness scatterplots for frozen-embryo transfer vs. fresh-embryo transfer. (a) Treatment costs (including OHSS): healthy baby; (b) treatment costs (including OHSS): live birth; (c) NHS costs: healthy baby; and (d) NHS costs: live birth.

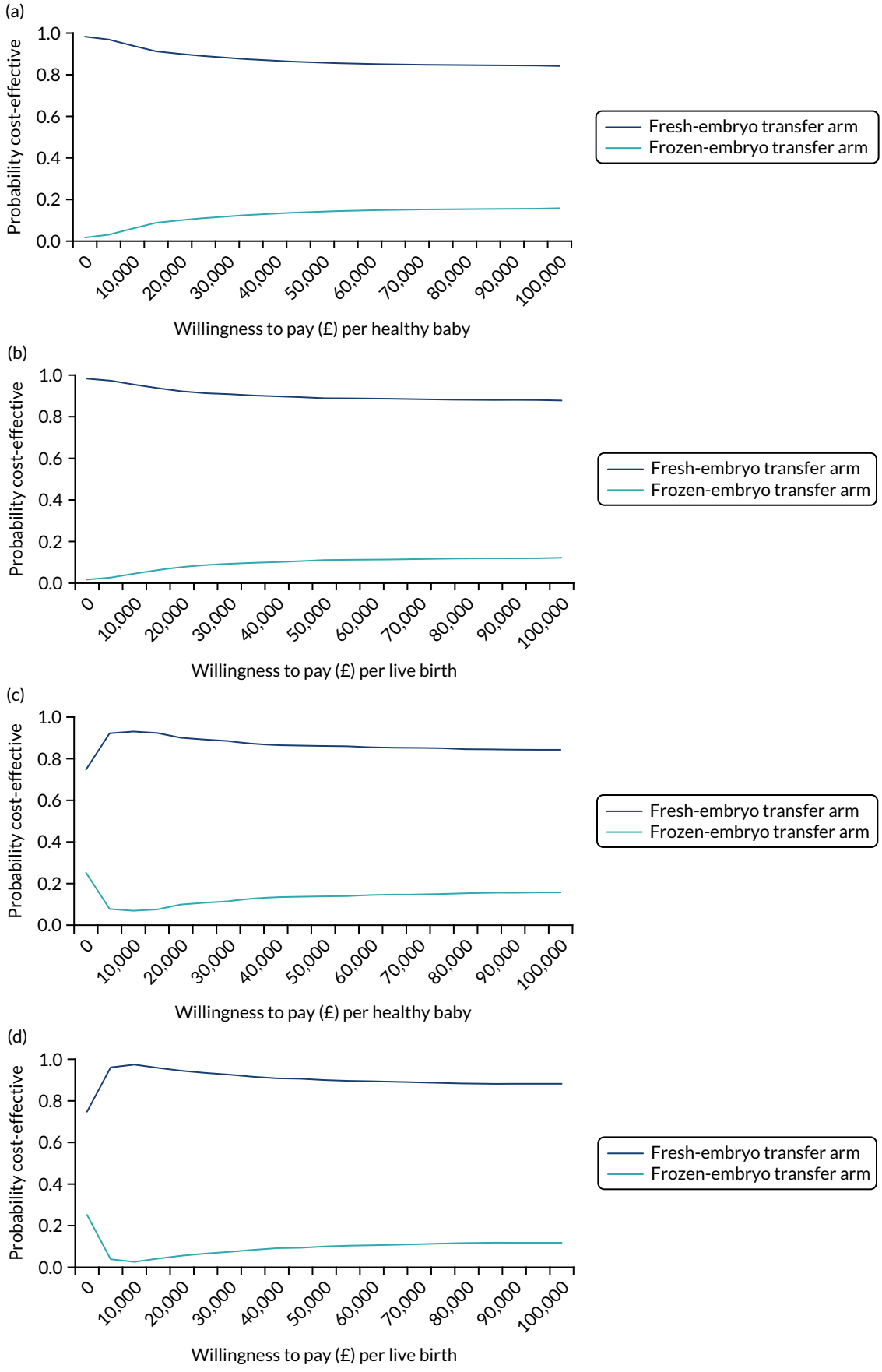


FIGURE 15 Model-based cost-effectiveness scatterplots for frozen-embryo transfer vs. fresh-embryo transfer. (a) Treatment costs (including OHSS): healthy baby; (b) treatment costs (including OHSS): live birth; (c) NHS costs: healthy baby; and (d) NHS costs: live birth.

terms of treatment costs per healthy baby and live birth, and in terms of NHS costs per health baby and live birth. Considering the uncertainty around the joint incremental costs and effect (see *Figure 14*), fresh-embryo transfer retains the higher chance of being preferred on grounds of cost-effectiveness across all values of willingness to pay per health baby or live birth, compared with frozen-embryo transfer (see *Figure 15*).

Model-based sensitivity analysis

Table 28 presents the results of several key sensitivity analyses around the model-based estimates of cost-effectiveness, using incremental treatment cost (including OHSS) per additional healthy baby as the measure of cost-effectiveness. Assuming no discontinuation among those eligible for subsequent frozen-embryo transfers and applying more conservative costs for transvaginal scans and monitoring prior to frozen-embryo transfer, fresh-embryo transfer remains, on average, more effective and less costly than thawed frozen-embryo transfer. Cost-effectiveness acceptability curves for the model-based sensitivity analysis are provided in *Appendix 10*.

TABLE 28 Sensitivity analysis for the model-based incremental cost per healthy baby born, applying NHS treatment plus OHSS costs (excluding ANC and delivery costs)

	Cost (£), mean		Effect, mean		
Sensitivity analysis	**Total**	**Incremental**	**Total**	**Incremental**	**ICER**
Base case					
Fresh-embryo transfer	2870		0.381		
Freeze all	3195	325	0.349	−0.031	Dominated
Assuming no discontinuation among those with embryos remaining for subsequent frozen-embryo transfer cycles					
Fresh-embryo transfer	3124		0.404		
Freeze all	3484	361	0.376	−0.028	Dominated
Using the lower ultrasound scan cost (£53) to cost transvaginal scans					
Fresh-embryo transfer	2693		0.381		
Freeze all	2880	187	0.349	−0.031	−6001

Chapter 5 Discussion and conclusions

Summary of main findings

A total of 1578 couples consented, 619 of whom were randomised (310 to the fresh-embryo transfer arm and 309 to the freeze-all arm). Most non-randomisations ($n = 959$) were owing to the non-availability of three good-quality embryos ($n = 476$). Of those randomised, 117 (19%) couples did not adhere to their allocated intervention: 96 (31.3%) in the freeze-all arm and 21 (6.8%) in the fresh-embryo transfer arm. Non-adherence was higher in the freeze-all arm than in the fresh-embryo transfer arm, with the most common reason being patient choice.

The ITT analysis showed that the healthy baby rate was 20.3% in the freeze-all arm and 24.4% in the fresh-embryo transfer arm (RR 0.84, 95% CI 0.62 to 1.15). Similar results were obtained from CACE analysis (RR 0.77, 95% CI 0.44 to 1.10), per-protocol analysis (RR 0.87, 95% CI 0.59 to 1.26) and as-treated analysis (RR 0.91, 95% CI 0.64 to 1.29). There was no statistical difference in the healthy baby rate across age groups (< 35, 35 to < 40 and > 40 years), the number of previous embryo transfers (0 or ≥ 1), whether it was cleavage or blastocyst transfer, or whether one or two embryos were transferred.

There was no evidence of a difference in live birth rate (28.3% vs. 34.3%; RR 0.83, 99% CI 0.65 to 1.06) or clinical pregnancy rate (33.9% vs. 40.1%; RR 0.85, 99% CI 0.65 to 1.11) between the freeze-all arm and the fresh-embryo transfer arm.

There were no statistical differences between the two arms in any of the obstetrics and perinatal outcomes (i.e. hypertensive disorders of pregnancy, antepartum haemorrhage, preterm delivery, very preterm delivery, onset of labour, mode of delivery, low birthweight, high birthweight, low birthweight for gestational age, high birthweight for gestational age and congenital anomalies).

The risk of ovarian hyperstimulation was 3.6% in the freeze-all arm and 8.1% in the fresh-embryo transfer arm (RR 0.44, 99% CI 0.15 to 1.30). There were 30 reported AEs, but these were not related to the intervention.

A total of 88.6% embryos survived the freezing–thawing process.

There was no statistical difference in STAI scores for male participants (MD 0.1, 99% CI −2.4 to 2.6) and female participants (MD 0.0, 99% CI −2.2 to 2.2) between the arms.

Following adjustment for minimisation criteria, the mean post-randomisation treatment cost (inclusive of OHSS) per woman randomised was £1395 (95% CI £1294 to £1505) in the fresh-embryo transfer arm and £1576 (95% CI 1514 to £1642) in the freeze-all arm. The mean between-group difference was £181 (95% CI £60 to £292). Based on the estimated difference in the healthy live birth rate (−0.039, 95% CI −0.101 to 0.027), fresh-embryo transfer was found to dominate frozen-embryo transfer, being, on average, less costly and more effective. Considering the joint uncertainty surrounding the estimated differences in costs and effects, the probability of fresh-embryo transfer being preferred on the grounds of cost-effectiveness was $> 89\%$ across all willingness-to-pay thresholds per additional healthy live birth.

When ANC and delivery costs were included in the cost-effectiveness analysis, the freeze-all strategy was, on average, less costly, owing to a smaller number of pregnancies and live births (MD −£75, 95% CI −£623 to £461). However, fresh-embryo transfer retained a higher probability of being cost-effective compared with frozen-embryo transfer above a willingness-to-pay threshold of £1921 per additional

healthy live birth. Furthermore, when cumulative costs and outcomes associated with the transfer of the remaining frozen embryos were simulated using a Markov model, fresh-embryo transfer was found to be less costly and more effective than frozen-embryo transfer, even when including the ANC and delivery costs. The same pattern of results was observed when using live births as the measure of effectiveness.

The difference in treatment costs was found to be sensitive to the application of more conservative costs for monitoring ultrasound scans prior to frozen-embryo transfer, but the overall cost-effectiveness findings remained stable, with fresh-embryo transfer retaining a substantially higher probability of being cost-effective than frozen-embryo transfer.

Update and comparison with existing literature

The E-Freeze trial was planned in 2014, awarded funding in 2015 and started recruitment in 2016. Several trials[40–46] across the world were conducted and published during this time (i.e. 2016–20) comparing freezing all embryos, followed by frozen-embryo transfer, with fresh-embryo transfer. Two trials report on hyper-responders (i.e. those who are at high risk of OHSS),[40,41] and five reported on those who were predicted as normal responders (i.e. not at high risk for OHSS).[42–46]

Table 29 summarises the trials reporting on normal responders that were published after the E-Freeze trial began. We present the aggregated meta-analysis on these trials on key clinical outcomes with and without incorporating data from E-Freeze trial. For the comparison of the results and data from the

TABLE 29 Summary of trials published during the conduct of the E-Freeze trial

Trial, country and centre type	Population	Randomisation detail	FET regimes	Conclusions (freeze-all vs. fresh-embryo transfer)
Vuong *et al.*,[42] 2018, Viet Nam, single centre	782 women without PCOS undergoing their first or second cycle of IVF; mean age 32 years; day 3 embryo transfer	Had to have at least one grade 1 embryo on day 3	Most FET by HRT cycle	Similar live birth (31.8% vs. 33.8%) and ongoing pregnancy (34.5% vs. 36.3%) rates
Shi *et al.*,[43] 2018, China, multiple centres	2157 women (non-PCOS); first cycle of IVF; aged 20–35 years with good ovarian reserve; day 3 embryo transfer	Had to have five or more oocytes to be randomised	Natural cycles for most, artificial cycles for some	Similar live birth rate (48.7% vs. 50.2%)
Wei *et al.*,[44] 2019, China, multiple centres	1650 women; first cycle of IVF; aged 20–35 years with regular menstrual cycles; blastocyst transfer only	Randomisation on day 3 after egg collection with four or more high-grade embryos	Natural (62%) or programmed cycles (35%)	Higher singleton live birth (50% vs. 40%) and live birth (53.2% vs. 41.3%) rates
Stromlund *et al.*,[45] 2020, Denmark, multiple centres	453 couples; aged 18–39 years with regular menstrual cycle; AMH > 6.28 pmol/l; normal and high responders	Randomisation at start of stimulation	Modified natural cycle	Similar ongoing pregnancy (27.8% vs. 29.6%) and live birth (27.4% vs. 28.7%) rates
Wong *et al.*,[46] 2021, the Netherlands, single centre	202 couples; aged 18–43 years; any indication of IVF; 205 couples; blastocyst transfer	Randomisation at start of downregulation	Artificial cycle	Similar CLBR (19% vs. 31%)

AMH, anti-Müllerian hormone; FET, frozen-embryo transfer; HRT, hormone replacement therapy; PCOS, polycystic ovary syndrome.

E-Freeze trial with the existing literature, we have included only those trials reporting on normal responders, the populations for which were similar to the population of the E-Freeze trial.

The two trials on hyper-responders[40,41] reported that the freeze-all approach improves the live birth rate and reduces the risk of OHSS in those who are hyper-responders.

The five trials on normal responders reported from Viet Nam,[42] China, [43,44] Denmark[45] and the Netherlands.[46] Our results are consistent with three of these trials,[42,43,45] but are in contrast with the others.[44,46] Wei *et al.*[44] suggest that the singleton live birth rate is higher with freeze-all, followed by frozen-embryo transfer, and Wong *et al.*[46] showed that the live birth rate was significantly lower when freezing all embryos rather than using fresh embryos. There are differences in population, outcome measures and the timing of randomisation in each of the trials (*Table 30*), which may account for these differences.

The outcome healthy baby rate was not reported by any other trial. The closest comparison was singleton live birth, reported by Wei *et al.*[44] Hence, it is not possible to compare the primary outcome measure reported by the E-Freeze trial with any other studies in the literature.

Live birth rate

The live birth rate in our trial was 28.3% in the frozen-embryo transfer arm and 34.3% in the fresh-embryo transfer arm. Although there were no statistically significant differences between the two arms, these figures were similar to the live birth rates reported by the two trials from Europe[45,46] and the trial from Viet Nam.[42] However, the rates are much lower than those of both of the trials reported from China.[43,44] This could be because the trials reporting from China had an upper age limit of 35 years and, therefore, included patients with a better prognosis.

The combined data from these five trials showed no difference in the outcome of live birth between the two arms, which is similar to the results of the E-Freeze trial (*Figure 16*).

TABLE 30 Obstetric and perinatal complications in the E-Freeze trial compared with the population risk

	Risk of complications (%)		
Complication	**General population**	**Freeze-all arm**	**Fresh-embryo transfer arm**
Gestational diabetes	1.5	4.7	3.9
Hypertensive disorder (all)	10–15	9.4	6.8
Pre-eclampsia	4–6	5.9	1.0
Antepartum haemorrhage (all)	6	13.1	11.7
Preterm delivery	5.0	10.3	11.4
Very preterm delivery	0.7	2.3	4.8
Caesarean section	16.2	43.5	35.2
Low birthweight	7.0	9.1	13.1
Very low birthweight	0.5	1.1	7.5
High birthweight	8–10	11.4	9.3
High weight for gestational age	15.9 (using intergrowth chart)	10.2	9.4
Low weight for gestational age	7.6	10.2	11.3
Congenital anomalies	0.2	5.7	4.7
Perinatal mortality	2.6	1.1	0

Risk of general population taken from Corps *et al.*[47] and Hirst *et al.*[48]

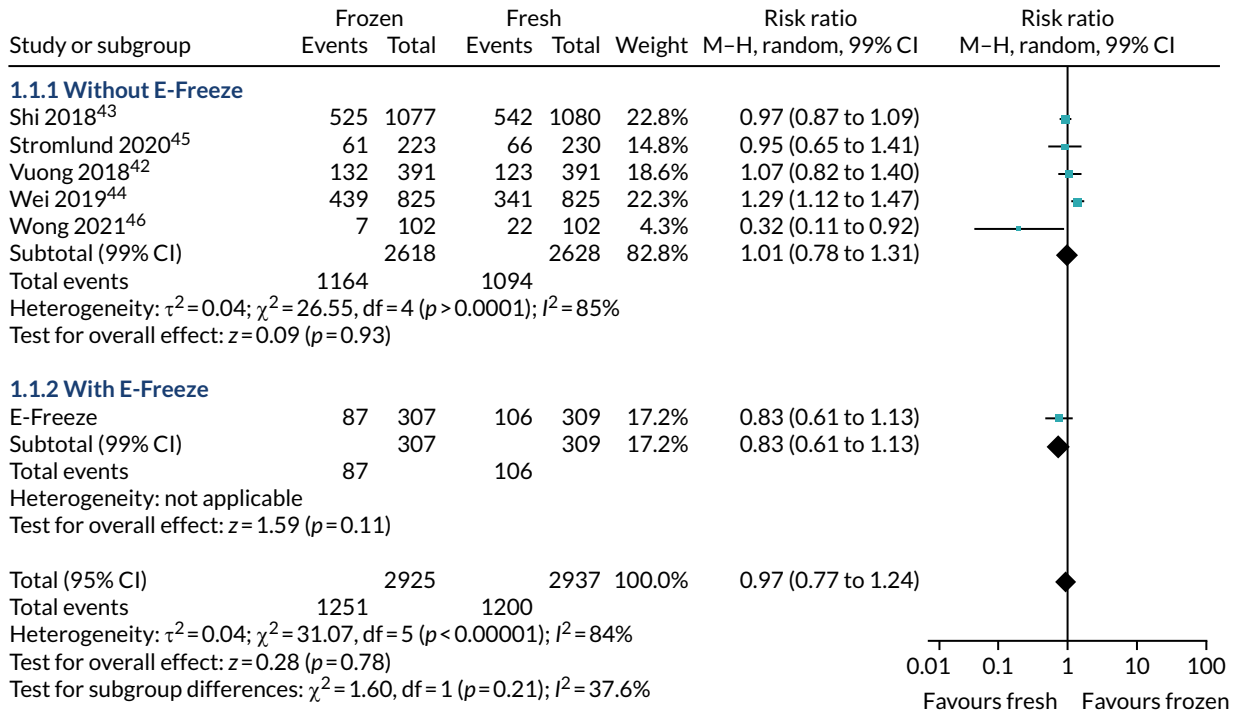


FIGURE 16 Meta-analysis of existing trials,[42–46] with and without the E-Freeze trial, for live birth rate.

Based on nearly 5246 women randomised to fresh-embryo transfer compared with frozen-embryo transfer, an aggregate-data meta-analysis did not seem to favour either fresh-embryo transfer or a strategy of freezeing all embryos, followed by frozen-embryo transfer, with a combined RR of 1.01 (99% CI 0.78 to 1.31). An updated meta-analysis, including randomised data from an additional 616 women from the E-Freeze trial, does not appear to result in a convincing change in the direction, size or precision of the overall effect, with a combined RR of 0.97 (95% CI 0.77 to 1.24).

Ovarian hyperstimulation syndrome

The risk of OHSS reported in the E-Freeze trial was 3.6% in the freeze-all arm and 8.1% in the fresh-embryo transfer arm. Most cases of OHSS were mild, with moderate to severe OHSS in only 1.6% in the freeze-all arm and 5.8% in the fresh-embryo transfer arm. This is higher than the rate quoted for moderate to severe OHSS in national statistics.[6] This difference is because of better ascertainment in the trial setting; it is well known that cases of OHSS are not reported in clinical practice.[49]

The total OHSS figures were higher than those reported by other trials. This could be because we also reported mild OHSS, whereas other trials reported only moderate and severe OHSS. Combined data from the five trials reporting on OHSS[42–46] showed a statistically significant reduction in OHSS when all embryos were frozen compared with fresh-embryo transfer. The addition of data from the E-Freeze trial did not change the direction or magnitude of these figures, but increased the precision (*Figure 17*).

Miscarriage

The risk of miscarriage per couple randomised was 14.3% in the frozen-embryo transfer arm and 12.9% in the fresh-embryo transfer arm. The corresponding figures for risk of miscarriage per pregnancy were 31.7% and 26.0%, respectively. Miscarriage rates were slightly higher in the E-Freeze trial than in other studies (ranging from 9.9% to just over 25% per pregnancy[42–45]). We were unable to explain this higher rate of miscarriage. To explore the higher risk of miscarriage, we undertook a post hoc analysis of the miscarriage rate per centre; there were no significant differences between the five clinics that contributed most data. The combined data from other trials showed no difference in miscarriage rates between trial arms, which is similar to the results reported in the E-Freeze trial.[42–45] Wong *et al.*[46] did not report on miscarriage per pregnancy; hence, their data are not included in the meta-analysis graph. The addition of E-Freeze to existing data does not change the direction, magnitude or precision of effect (*Figure 18*).

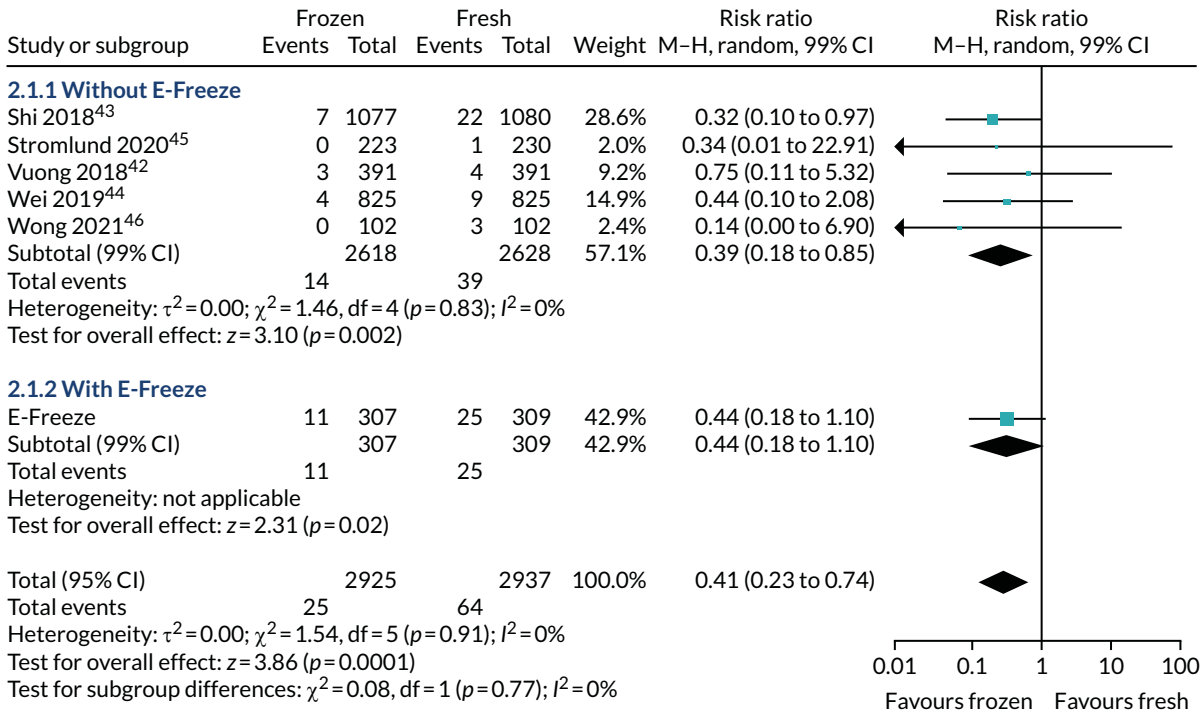


FIGURE 17 Meta-analysis of existing trials,[42–46] with and without the E-Freeze trial, for OHSS.

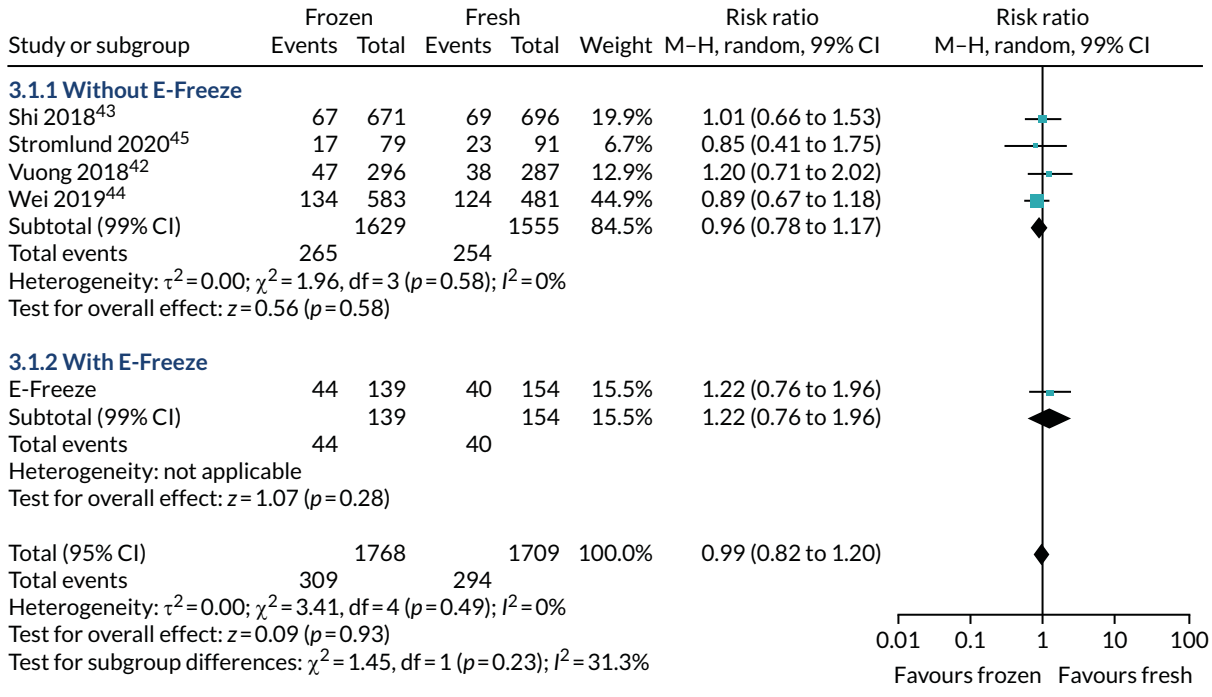


FIGURE 18 Meta-analysis of existing trials,[42–45] with and without the E-Freeze trial, for miscarriage rate.

Obstetric and perinatal complications

There was no statistical difference in obstetric and perinatal complication between arms in the E-Freeze trial. Observational studies and meta-analysis of published data[50–52] suggested that the risk of pre-eclampsia and large for gestational age (LGA) babies is increased in pregnancies that are a result of frozen-embryo transfer. The numbers of each individual complication were too small to draw any

definite conclusions from this trial alone, or from any of the other existing trials individually.[42–46] In comparison with the risk in the general population (see *Table 30*), not all risks were higher in IVF pregnancies, irrespective of whether they were the result of fresh-embryo transfer or frozen-embryo transfer. Although this is reassuring, it is in contrast to the previous findings from systematic review of observational data[7] and could be owing to small numbers of each complication in our trial.

Natural compared with hormone replacement therapy frozen-embryo transfer

Most of the frozen-embryo transfers in the E-Freeze trial were undertaken in hormonally mediated cycles. By contrast, worldwide,[53] 45% of cycles are natural cycles. This can be explained by the fact that participants in the E-Freeze trial were eager to receive treatment and wanted a planned date for their frozen-embryo transfer, after having their treatment delayed by participation in the trial. By contrast, the worldwide data are based on observational, non-randomised data and are more likely to be from patients undergoing transfer of surplus frozen embryos after fresh-embryo transfer has failed, rather than frozen-embryo transfer as their first treatment.

The two Chinese trials[43,44] had a large proportion of participants who underwent endometrial preparation for frozen-embryo transfer using natural cycles. The two European trials[45,46] and the Vietnamese trial[42] had the largest number of patients undergoing hormonally mediated hormone replacement therapy (HRT) cycles.

Hormonally mediated frozen-embryo transfer is more convenient for the clinic and patients, as the date of thaw and transfer can be planned in accordance with the workload of the clinic and at the convenience of the staff and patients. Recently, some concerns have been raised that pregnancies following HRT-mediated frozen-embryo transfer may be at a higher risk of complications than those following a natural cycle.[54]

Non-adherence

Non-adherence in the freeze-all arm was very high in this trial. Other trials have also shown non-adherence to the allocated intervention, but at much lower levels than those seen in the E-Freeze trial. The highest level was reported by Shi *et al.*[43] (freeze-all, 18%; fresh-embryo transfer, 15%). However, non-adherence was reported in both arms, whereas in the E-Freeze trial non-adherence was predominantly seen in the freeze-all arm (31.3%). This level of non-adherence occurred despite the fact that the trial was specifically designed to reduce non-adherence, with consent being reconfirmed just before randomisation and information being provided throughout the process. There could be two reasons for this non-adherence. The funding of IVF treatment is limited across the UK, especially in England, where most of the participating centres were based, and > 60% of treatments in England are funded by the patients themselves. Where funding is available, only one cycle of treatment is funded by most CCGs. Hence, there will be apprehension about freezing all embryos among clinicians, scientists and patients, especially when there are only one or two embryos. There is always a fear that the embryos may not survive the freezing–thawing process, leading to loss of funding for the only funded treatment. Our data showed that, on average, 86% of embryos survived the freezing–thawing process across the participating clinics; hence, the survival rate is far below 100%.

Although there was an intention and acceptance from patients to be randomised to either arm at the time of consent, this did not translate to real practice, with a noticeable preference seen for fresh-embryo transfer. Studies from two different parts of the world[55,56] have shown that patients would accept the intervention of freeze-all, followed by frozen-embryo transfer, if freeze-all reduces the side effects and has at least equal, if not better, success rates. Both conditions must be fulfilled to accept the delay.

Economic analysis

The few published economic evaluations of freeze-all compared with fresh-embryo transfer have produced mixed findings. Roque *et al.*[57] used observational data from a private centre in Brazil to compare the cost per ongoing pregnancy among patients receiving treatment with each strategy.

Although the total cost of treatment was higher per patient undergoing the freeze-all approach, the average cost per pregnancy was lower, given the substantially higher pregnancy rate in the non-randomised cohort (39.7% vs. 31.1%). Thus, Roque *et al.*[57] concluded that a freeze-all strategy was a cost-effective option compared with fresh-embryo transfer.

In an economic evaluation carried out using data from a RCT conducted in Viet Nam, Le *et al.*[58] reported higher mean costs in the freeze-all arm than in the fresh-embryo transfer arm over a full cycle, including the transfer of all embryos obtained from a single, controlled, ovarian hyperstimulation cycle. The live birth rate was also slightly higher in the freeze-all arm than in the fresh-embryo transfer arm (48.6% vs. 47.3%), but the average cost per live birth was higher. In an incremental analysis, the additional cost per additional live birth was estimated to be €30,997 per additional live birth (freeze-all vs. fresh-embryo transfer). The probability of cost-effectiveness for the freeze-all approach remained < 60% irrespective of the willingness to pay per additional live birth. Based on these results, Le *et al.*[58] concluded that the freeze-all approach did not constitute a cost-effective use of resources.

Our findings of increased treatment costs with the freeze-all approach, compared with the fresh-embryo transfer approach, are consistent with those in the published studies.[58] However, directionally, both the health baby rate and the live birth rate favoured fresh-embryo transfer in the E-Freeze trial, leading to a lower probability of the freeze-all approach being considered cost-effective. This pattern remained when the subsequent transfer of the remaining embryos was simulated, both with and without the inclusion of pregnancy and delivery costs.

A further economic analysis was carried out using data from a multinational RCT comparing a personalised embryo transfer strategy, guided by endometrial receptivity, with frozen-embryo transfer and fresh-embryo transfer.[59] The personalised embryo transfer strategy involved the freezing of all viable blastocysts and the use of an array test to predict each individual's optimum window for implantation in a subsequent frozen-embryo transfer with hormonal replacement. Similarly, this study found the cost per embryo transfer to be higher in the freeze-all arm than in the fresh-embryo transfer arm, and reported a slightly lower live birth rate per first frozen-embryo transfer than for single fresh-embryo transfer. The personalised embryo transfer strategy generated the highest live birth rate, but incurred higher treatment costs than both the fresh-embryo transfer and the freeze-all arm. No such treatment arm was included in E-Freeze for comparison.

Strengths

To the best of our knowledge, this is the first and only trial in the UK comparing fresh-embryo transfer with a policy of electively freezing all embryos, followed by subsequent frozen-embryo transfer. In total, 18 clinics participated, of which 13 recruited participants.

The recruited trial population is consistent with what would be expected given the NHS-funded treatment criteria (i.e. age < 40 years, BMI < 30 kg/m^2, non-smoker, no previous children).[3,60] The occurrence rate of aetiological causes of infertility in this trial were similar to those that have been reported in previous population-based studies for other aetiologies of infertility,[61,62] except unexplained infertility, the proportion of which was higher in this trial. The duration of infertility was > 2 years for most participants, which is the minimum duration criterion for unexplained infertility used for accessing NHS-funded IVF, as per national guidance.[3,60]

The E-Freeze trial was a pragmatic trial (i.e. except for randomisation, all other process pre and post randomisation were as per local protocols) involving multiple clinics across the UK. The participants were recruited from both the NHS and private clinics, given that > 60% of IVF in the UK is privately funded by couples themselves. The pragmatic nature of the trial provides a true reflection of what happens in clinical practice.

A healthy baby is a unique outcome chosen for this trial because it encompasses efficacy and safety together. All other trials on this topic have reported on live birth rate or ongoing pregnancy rates.[40–46] As all complications in pregnancy and delivery have an impact on the short- and long-term health of an individual, the E-Freeze trial was unique in taking a holistic view of the infant, rather than just focusing on a live birth.

A detailed economic analysis is presented, based on all costs incurred to the NHS as well as participants, from post randomisation to the delivery of the baby. Cost analysis also included modelling to incorporate the longer-term costs in each of the trial arms of a heathy baby if all remaining embryos were used. Real-time data from clinical record forms and participant questionnaires were used for cost analysis. The response rate for the questionnaires was > 70% from both partners. Of the seven existing trials across the world on this topic,[40–46] only one Vietnamese trial has reported on an economic analysis conducted alongside the trial,[58] stating similar conclusions to ours; however, the Vietnamese trial did not have a societal perspective and was not performed in an NHS setting.

The E-Freeze trial is the only trial on this topic exploring the emotions of both the male and the female partners. It is becoming clear that, along with the clinical outcome, patient perceptions are equally important for any process or procedure to be put in place. This is especially important when one is recommending radical changes to the treatment, such as how IVF treatment is delivered, with delay and uncertainty associated with it. As with the economic questionnaire, the emotions questionnaire had a good return rate of > 70% at both of the time points at which they were administered (i.e. at consent and the actual intervention). Most literature on emotions relates to women only; this trial was unique in exploring the emotions of both the male and the female partner's STAI scores separately. None of the other trials on this topic has evaluated this aspect.

Although a lot of assumptions were made in the sample size calculations because of the unique nature of the primary outcome, the results suggested that most were correct. We anticipated that the healthy baby rate in our trial population would be towards the lower end of the CI, around 25%, taking into account the higher risk of preterm delivery and babies with a low birthweight for their gestational age following IVF. The healthy baby rate was 24.4% in the trial, which was in line with this assumption. We also anticipated that, of those couples who consented, 50% would not obtain three good-quality embryos. In the trial, 49.6% of those consented did not have at least three good-quality embryos and, hence, were not randomised. Therefore, the trial design and sample size calculation were robust, based on the assumptions, which were very close to what was seen in reality.

Limitations

The trial did not reach its predetermined sample size of 1086 and, therefore, lacked the power to provide a definitive answer to the research questions. This was compounded by the bias introduced from non-adherence to the allocated intervention, especially in the freeze-all arm, of up to 31%. The additional analysis by per protocol, as treated and CACE did not change any results. There was no difference in the baseline characteristics (i.e. demographic and clinical, pre and post randomisation) or primary outcome rate between those who adhered to the allocated intervention and those who did not adhere to the allocated intervention. The consistent result across all analysis types indicates that it is likely that non-adherence did not alter the result. However, this cannot be definitively concluded.

There was a significant drop in the number of participants from consent to randomisation, with most participants not reaching three good-quality embryos. This was a result of the broad inclusion criteria, which allowed patients to take part in the study regardless of ovarian reserve, rather than including only those with good ovarian reserve. This was agreed by the co-investigator group at the outset, after much debate, acknowledging that ovarian reserve tests predict only the number of eggs, not their quality. A total of 30 participants had fewer than six eggs; they would not have been included if we had strict criteria based on ovarian reserve tests.

There was a change in practice during the trial, as clinics moved from embryo transfer on day 3 to embryo transfer on day 5. The reason for randomisation at day 3 in this trial was that embryo transfer would be as close to randomisation as possible. When the trial protocol was written, most embryo transfers occurred at day 3. However, as practice changed to transfer on day 5, there was a gap between randomisation and the actual intervention, which provided an opportunity for clinicians and participants to change their mind, contributing to non-adherence.

It has been suggested that freeze-all will benefit those with a large number of eggs, but we did not plan a subgroup analysis based on the number of eggs obtained a priori, as a large number of eggs are at a higher risk of OHSS, which was an exclusion criterion. There are now data available from other trials, published after the E-Freeze trial started recruiting, reporting that the strategy of freeze-all benefits those with a large number of eggs.[40,41] This was revisited by the co-investigator group; however, it was agreed not to undertake a post hoc analysis because the number of patients with more than 15 eggs was small (45/616) and, therefore, it was unlikely to provide a clinically meaningful answer.

Some adverse birth outcomes (e.g. preterm delivery and low birthweight) can have a far-reaching impact on costs and child health outcomes. It was initially planned[1] that modelling would be used to inform cost-effectiveness over an extended time horizon to capture the long-term costs and health outcomes for any infants born as a result of treatment. However, the number of infants with adverse birth outcomes in this trial was too small to inform a robust analysis of any expected differences in long-term outcomes. It was felt that this analysis would be best undertaken as part of an individual patient data (IPD) meta-analysis (IPD-MA), as explained in *Implications for research*.

Meaning of the study

For the strategy of freeze-all to be used as routine policy, it must be better in terms of safety, efficacy and cost, as it involves a delay for couples in getting to pregnancy. There is also extra work involved for clinics. Although there is a biological plausibility that freezing all embryos, followed by frozen-embryo transfer, will be better in terms of success rates, safety and, hence, costs for all couples undergoing IVF/ICSI, this has not been proven when tested in this trial or when the data from other trials were assembled. This is not dissimilar to other interventions in this field (e.g. personalised embryo transfer,[59] endometrial scratch[63] and preimplantation genetic testing[64] for aneuploidy) that had a biological plausibility to improve success rates, but, when put to the stringent test of RCTs, were not proven to be more effective.

The health economic findings from the E-Freeze trial of a low probability of cost-effectiveness for the freeze-all approach compared with fresh-embryo transfer, in terms of NHS treatment costs per healthy baby and per live birth and higher costs incurred by participants, do not currently support the widespread use of the freeze-all approach in the NHS. However, further research to ascertain any differences in child health outcomes and costs between the alternative approaches is required (see *Implications for research*). Although the data did not reach statistical significance, there is a trend towards a reduction in the healthy baby, live birth and clinical pregnancy rates with the freeze-all approach compared with fresh-embryo transfer.

The absolute number of cases with OHSS was small in our trial. Although there is no statistically significant difference in any arm in the E-Freeze trial, the data collated from all trials together show a reduction in OHSS when freezing all embryos compared with fresh-embryo transfer. Hence, from a safety viewpoint, to reduce OHSS there could be a subgroup of participants who may still benefit from freezing all embryos, especially those at high risk of OHSS.

The level of non-adherence in the freeze-all arm suggests that patients still prefer fresh-embryo transfer to the freeze-all approach.

Implications for practice and policy

Based on the fact that the strategy of freezing all embryos, followed by frozen-embryo transfer, did not lead to a higher healthy baby rate or a higher live birth rate, and given it incurred slightly higher treatment costs, its widespread adoption as part of routine NHS practice is not supported by data from the E-Freeze trial. It should be advocated only when there is an indication that the freeze-all approach would be beneficial for the individual patient. There is no indication to recommend a change to current practice in the UK, which is fresh-embryo transfer and the freezing of spare embryos.

The NICE guidance does not specifically mention freeze-all, possibly because the last guidance was published in 2004, when freeze-all was not on the horizon. An update of the guidance was conducted in 2013, but this question was not looked at.[3] It is possible that the next update of the NICE guidance will specifically look at this question, as practice of freeze-all has been increasing.[65] Our results clearly show that freeze all is not a cost-effective strategy from a health-care perspective, despite accounting for the extra costs associated with OHSS in fresh-embryo transfer. In fact, the freeze-all approach is more costly, with no added benefit for normal responders.

The most common reason for non-adherence was patient choice. This indicates that the strategy is not ready to be accepted by patients. This is an equally important finding, as patients' choices must be taken into consideration, with an equal weighting as that of other clinical evidence, when recommending a policy.

Implications for regulators

The Health Fertilisation and Embryology Authority regulates and licenses all clinics providing IVF treatment in the UK. HFEA has a traffic light system for treatment add-ons.[66] Treatment add-ons are optional, additional treatments that patients may be offered on top of their routine fertility treatment, usually at an additional cost. The treatment add-ons claim to improve the chances of a live birth. The traffic light rating system consists of three colours: red, green and amber. Green indicates that there is evidence, in the form of high-quality RCTs, showing that a treatment add-on can safely improve the live birth rate for someone undergoing fertility treatment. The freeze-all approach is currently amber.[67] An amber symbol is given for an add-on where there is 'conflicting evidence' to show that an add-on can improve live birth rates or that the add-on is safe for patients to use. The amber symbol 'means that the evidence is not conclusive and further research is required, and the add-on should not be recommended for routine use' (© HFEA. Reproduced with permission from HFEA[66]). Although there is evidence that the freeze-all approach is suitable for hyper-responders, for whom the risk of OHSS is high, there is no evidence that the chance of a live birth improves for normal responders. The lack of improvement in live birth rate in the freeze-all arm compared with the fresh-embryo transfer arm is clear from this trial, but adding the data from other trials confirms it.[42–46]

Although the E-Freeze trial did not reach an adequate sample size on its own, the sample size is adequate when you combine the data from the other five trials[42–46] that were published during the conduct of this trial. The combined sample size for these trials is much larger than the sample size that was proposed for the E-Freeze trial. The fact that adding the E-Freeze trial data to the data from other trials does not alter the precision, magnitude or direction of the effect means that the evidence is now stable for the live birth rate. There is no need for further RCTs in this area, as they would be unlikely to change the outcome for women undergoing IVF/ICSI. Any trial that has a larger sample size than this combined sample size is unlikely to be conducted in the UK given the recruitment difficulties in the current trial and the fact that it will cost a huge amount of taxpayers' money. With the combined data from the other trials,[42–46] as shown in *Figure 15*, the freeze-all approach could be assigned the red symbol to stop the practice of freezing all embryos (a practice which has been advocated by some clinics[68]) for all patients, including those who are not at a high risk of OHSS.

Implications for funders for NHS in vitro fertilisation/intracytoplasmic sperm injection treatments

Difficulties in recruiting to in vitro fertilisation studies in the UK

Most IVF/ICSI treatment across the UK is funded by patients. Where it is funded by the NHS, the full entitlement reported in the NICE guidance[3] (i.e. three full cycles of IVF/ICSI) is not available for most patients. To randomise patients to a clinical IVF trial in such a set-up is always going to be difficult, especially when the intervention causes a delay and extra costs, and is the only funded treatment that patients may receive. This is, possibly, one of the reasons for the large proportion of patients who were non-compliant. RCTs are the gold standard; for successful recruitment in any future clinical trials in the UK in the field of IVF/ICSI, NHS funding must improve to the level recommended by NICE.[3]

Implications for research

Further analyses of the E-Freeze trial data

Cumulative live birth rates

This trial evaluated the results from the first embryo transfer after randomisation only. However, most participants had any spare embryos frozen. The field of IVF is changing, and providers' and patients' perceptions of the procedure's success are drifting from focusing on the results of the first embryo transfer to the cumulative results of a single ovarian stimulation cycle. We would like to look at the CLBR after all spare embryos are used. This is especially important as it is acknowledged that the CLBR is a more relevant and important outcome for both policy and the individual patient. This has been recognised by regulatory authorities for data reporting, and the most up-to-date data reporting includes the CLBR as the headline.[5,69] There have been concerns raised that the CLBR may be lower if all embryos are frozen.[46,70] Participants were asked to consent to long-term follow-up, to which the majority of participants agreed.

Follow-up of children born

The primary outcome of this study was the healthy baby rate; however, there are long-term implications. We would like to follow up children born from both kinds of embryo transfer to see if there is any impact on long-term outcomes.

Further analysis of State–Trait Anxiety Inventory scores

We plan to perform in-depth analysis of the STAI self-evaluation questionnaire to:

1. investigate if there was an association between baseline demographic and clinical characteristics and anxiety at the start and end of the IVF process
2. examine whether or not anxiety prior to IVF treatment is related to non-adherence to the allocated embryo transfer method.

We will also perform qualitative analysis on the free-text responses for both those participants who complied to their allocated intervention and those participants who did not to elicit the reasons behind non-compliance.

Further research questions raised

Individual patient data meta-analysis

The question of whether or not freezing all embryos, followed by thawed frozen-embryo transfer, is better than fresh-embryo transfer has received a lot of attention. When the E-Freeze trial was planned, several other trials across the world were also planned and conducted. Despite eight RCTs in total (including the E-Freeze trial)[11,12,42–46] and multiple aggregated meta-analyses on this topic, there is still a lack of clarity around the effectiveness and cost-effectiveness of a strategy of elective embryo

freezing or freeze-all in IVF. What is becoming clear from the published trial data and the data from the E-Freeze trial is that freeze-all is not an effective approach in all women undergoing IVF, can reduce the chances of pregnancy in some women and carries potential risks. The current meta-analyses of aggregated data[50,51] have indicated that more data are needed to resolve the current uncertainty as to the groups of patients for whom the strategy of freeze-all would be beneficial.

As the randomised trials[42–46] have a degree of clinical heterogeneity that could mask the potential benefits of frozen-embryo transfer in specific groups of women, rather than investing additional time and resources into further randomised trials, we believe that a patient IPD-MA offers a more efficient and cost-effective way of identifying these subgroups and providing a definitive answer to this important clinical question. The number of published IPD-MAs has increased considerably over the past decade in other areas of medicine. Evidence synthesis involving the collection and analysis of individual patient data (IPD) are considered the best method for assessing participants' characteristics and provide more detailed and robust meta-analysis results.[71] Such an approach could also provide more power to detect any differences in the categories of adverse birth outcomes to better inform any expected differences in child health outcomes and costs.

An IPD-MA approach has both statistical and clinical advantages. Data from existing trials[42–46] suggest that the freeze-all strategy is not effective for all patients but could improve the efficacy and safety of IVF in some women. Therefore, it is very important to identify subgroups of participants from the existing trials in whom a freeze-all strategy could be adopted. For example, the effectiveness of a freeze-all policy may vary by maternal age, number of available eggs and embryos, stage of development of an embryo prior to transfer and the laboratory method used to freeze embryos (i.e. slow vs. fast freezing). No individual trial is large enough to answer this question and conventional meta-analysis of aggregated data does not lend itself easily to the extraction of sufficient compatible data for meaningful subgroup analyses. By contrast, IPD will allow the effective categorisation of participants for subgroup analyses defined by single or multiple factors and, therefore, offers valuable clinical insights that are particularly relevant to our clinical question.

An IPD-MA will allow us to estimate the treatment effects adjusted for baseline factors where, previously, only unadjusted estimates were available. This has the advantage of increasing the statistical power and allowing an adjustment for potential confounding factors. Consistent inclusion and exclusion criteria could be applied across studies in a way that cannot be undertaken using published aggregated data. It is possible to verify the results of the original trials and request additional data from the triallists that are not available from the published reports.

The statistical analysis can be standardised across studies [e.g. the analysis method, how continuous variables (e.g. maternal age) are analysed] and we can combine data that have been recorded in different formats. Moreover, model assumptions can be assessed and more advanced methods can be applied when necessary.

One can estimate the incidence rate of clinically important, but less common, pregnancy and neonatal complications with greater precision in a randomised cohort of children born following either fresh-embryo transfer or frozen-embryo transfer. This will enable precise projections of any expected differences in child health outcomes and costs. An IPD approach will also help to inform future studies that develop prediction models to predict a couple's success rate with fresh-embryo transfer compared with frozen-embryo transfer, which would not be possible with standard published data.

Conclusions

The results of this pragmatic, multicentre, two-arm, parallel-group, non-blinded RCT show no evidence of a difference in the healthy baby rate from freezing all embryos, followed by thawed frozen-embryo

transfer, compared with the rate from fresh-embryo transfer. There was no statistical difference in OHSS, obstetrics or perinatal complications, or in stress and anxiety scores, between the groups.

The health economic analysis shows that freezing all embryos is not a cost-effective strategy; in fact, it is more costly in both the short and the longer terms and is, therefore, unsuitable for use in routine practice currently.

The decision to offer the freeze-all strategy should be balanced against potential benefit and harm for the mother and child. Rather than investing resources in further trials, we need to join our efforts to undertake an IPD-MA to reach definite answers and identify the subgroups who will benefit most from the freeze-all approach.

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Nick Macklon (https://orcid.org/0000-0003-2436-2316) (Co-investigator and Principal Investigator) was responsible for the study design; provided intellectual input during the conduct of the study, modification of the protocol, delivery of the study, interpretation of the findings, recommendations and implications for policy and practice, and dissemination; and approved the final draft of the manuscript.

Raj Mathur (https://orcid.org/0000-0002-7550-1817) (Principal Investigator) provided intellectual input during the conduct of the study, modification of the protocol, delivery of the study, interpretation of the findings, recommendations and implications for policy and practice, and dissemination; and approved the final draft of the manuscript.

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Madhurima Rajkohwa (Co-investigator and Principal Investigator) was responsible for the study design; provided intellectual input during the conduct of the study, modification of the protocol, delivery of the study, interpretation of the findings, recommendations and implications for policy and practice, and dissemination; and approved the final draft of the manuscript.

Lynne Robinson (https://orcid.org/0000-0002-3309-554X) (Principal Investigator) provided intellectual input during the conduct of the study, modification of the protocol, delivery of the study, interpretation of the findings, recommendations and implications for policy and practice, and dissemination; and approved the final draft of the manuscript.

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Publication

Maheshwari A, Bell JL, Bhide P, Brison D, Child T, Chong HY, *et al.* Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze). *Human Reprod* 2022:deab279.

Data-sharing statement

Data will be shared in accordance with the NPEU Data Sharing policy. Requests for access to the data will be considered by the NPEU Data Sharing committee. Access to anonymised data can be requested from general@npeu.ox.ac.uk.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Amendments

E-Freeze

Amendments with Chronology

Amendment	Date of REC Favourable Opinion	Document	Description
Amend 1: AM01	17/11/2015	Consent Form V1.2	• Amendment to reference Couples Information Leaflet Version 2.0 (12/11/2015)
Amend 2: AM02	29/01/2016	Consent Form V1.3 E-Freeze Posters V2.0	• The terminology in the Consent Form was refined to ensure relevance for Scottish participants. The ISRCTN number has also been added and the explanation for longer term follow-up was condensed to avoid repetition. • E-Freeze Poster Version 1.0 (09/09/2015) was given ethical approval as an undesigned version. The poster has now been designed and the wording has been amended slightly to include eligibility criteria and the interventions. The poster has been designed as both a white and green version.
Amend 3: AM03	20/07/2016	GP Letter V1.1 Economic Questionnaire V1.2 Emotions Questionnaire V2.0 Couples Flowchart V1.0 E-Freeze Postcard V1.0 E-Freeze Banner V1.0	• Three new documents; the Couples Flowchart, E-Freeze Postcard and E-Freeze Banner were approved as part of substantial amendment AM03. • The REC Reference was added to the GP Letter. • A data logging box was added to the E-Freeze Economic Questionnaire. • Minor amends have been made to the E-Freeze Emotions Questionnaire including typographical corrections and a tick box for 'first and second questionnaire' and a logging box on the front page to assist with data entry at the Co-ordinating Centre.
Amend 4: AM04	15/09/2016	Invitation email v1.0 CV for new PI	• Use of already approved Invitation Letter in email format • Change of PI at St Bartholomew's Hospital
Amend 5: AM05	19/12/2016	Joint Endometrial Scratch & E-Freeze Patient Invitation Letter V1.0 Joint Endometrial Scratch & E-Freeze Patient Invitation Letter V1.0 E-Freeze and Endometrial Scratch patient summaries V1.0	• In several of the E-Freeze recruiting sites a competing NIHR funded trial called Endometrial Scratch is also taking place. This trial is recruiting a similar patient population. The E-Freeze and the Endometrial Scratch teams have created three new joint documents for use with couples in these centres.

Amendment	Date of REC Favourable Opinion	Document	Description
Amend 6: AM06	03/03/2017	E-Freeze Protocol V2.0 Couples Information Leaflet V3.0 E-Freeze Consent Form V2.0 E-Freeze Poster (Green and White) V3.0 E-Freeze Banner V2.0 Couples Flowchart V2.0 E-Freeze Postcard V2.0 E-Freeze Invitation Letter V2.0 E-Freeze Invitation Email V2.0 E-Freeze CCG Letter V2.0 E-Freeze GP Letter V2.0 E-Freeze Pregnancy Card V1.0 Notification of New PIC Site (Leighton)	• The eligibility criteria for the E-Freeze trial have been amended, couples going through their second and third egg collection will now also be able to take part. The E-Freeze Protocol and several of the supporting documents for the trial have been updated to reflect the new eligibility criteria. • A new document called the Pregnancy Card has been created, this is to be provided to couples that have a positive pregnancy test to inform them of the dates when they will be contacted for follow-up data collection. • Leighton Hospital will be acting as a Participant Identification Centre.
Amend 7: AM07	06/04/2017	N/A	• Change to PI at Liverpool Women's Hospital • Addition of new centre, Queen's Hospital Romford
Amend 8: AM08	04/09/2017	N/A	• Change of PI at Princess Anne, Southampton
Amend 9: AM09	05/12/2017	N/A	• Addition of new centre, Countess of Chester
Amend 10: AM10	06/12/2017	N/A	• Extension of recruitment end date
Amend 11: AM11	09/01/2018	E-Freeze Couples Podcast Interview Guide V1.0 Podcast Invitation Email V1.0 Podcast Card V1.0 Podcast Return Slip V1.0	• Documents inviting couples that have completed E-Freeze and had a baby, to take part in a podcast about what it is like participating in the study.
Amend 12 AM 12	19/03/2018	N/A	• Change of PI at Birmingham Women's and Children's Hospital
Amend 13 AM13	27/07/2018	E-Freeze Couples Podcast V1.0	• Approval of E-Freeze Couples Podcast, for use on the E-Freeze trial website.
Amend 14 AM14	02/10/2018	N/A	• Addition of new centre, ULCH.
Amend 15: AM15	N/A	N/A	• Change of Trial Manager from Christina Cole to Fiona Goodgame Minor amendments do not require REC approval
Amend 16: AM16	N/A	N/A	• Notification of HTA approval for contract variation for a 12 month funded follow up. E-Freeze end date extended from **31/07/2019** to **31/07/2020** Minor amendments do not require REC approval

Amendment	Date of REC Favourable Opinion	Document	Description
Amend 17: AM17	N/A	N/A	• Change of Trial Manager from Fiona Goodgame to Vasha Bari Minor amendments do not require REC approval
Amend 18 AM18	N/A	N/A	• Notification of 6 month extension to grant end date from **31/07/2020** to **31/01/2021**. Minor amendments do not require REC approval

Appendix 2 Participating sites, principal investigators and research staff

Recruiting site for E-Freeze	PI(s)	Research staff
Aberdeen Fertility Centre, Aberdeen	Professor Abha Maheshwari	Avril Kidd and Val Peddie
Birmingham Women's Hospital, Birmingham	Dr Lynne Robinson and Dr Madhurima Rajkhowa	Faye Andrews, Nikkita Carden and Shanteela McCooty
Countess of Chester/IVI Cheshire	Mr Simon Wood	Nichola Kearsley
Glasgow Centre For Reproductive Medicine Clinic, Glasgow	Dr Marco Gaudoin	Laura McLuskey and Claire Wentworth
Guy's Hospital, London	Professor Yacoub Khalaf	Oluyemisi Adegbile, Jean Bvumbe and Charlotte Yearwood-Martin
Hammersmith Hospital, London	Dr Stuart Lavery	Sara Barnett, Anna Bosanquet and Floria Cheng
Homerton Hospital, London	Dr Priya Bhide	Zameen Brar, Merve Digil, Monica James and Elizabeth Timlick
IVI Midland, Midlands	Dr Rhada Venkatakrishnan	Sue Lowbridge and Karen Mayne
Jessop Wing, Sheffield	Dr Rachel Cutting and Dr Helen Clarke	Elizabeth Taylor
King's College Hospital, London	Dr Haitham Hamoda	Yusuf Beebeejaun, Nick Dalton-Brewer and Sarah Lensen
Liverpool Women's Hospital, London	Miss Rebecca Lunt and Dr Stephen Troup	Sarah Hockenhull, Deborah Stephenson and Julie Wray
Nurture Fertility, Nottingham	Associate Professor Nick Raine-Fenning	Kathryn Cocking, Lynne Fogg, Michelle Parris-Larkin and Katie Smith
Oxford Fertility, Oxford	Professor Tim Child	Ginny Mounce
Princess Anne Hospital, Southampton	Professor Nick Macklon and Dr Ying Cheong	Jane Forbes, Teresa Gubbins and Susan Wellstead
Queen's Hospital, Romford	Dr Sesh Sunkara	Annemarie McGregor
St Bartholomew's Hospital, London	Dr Jyotsna Pundir	Alice Rossi, Amy Thomas and Zoi Vardavaki
St Mary's Hospital, Manchester	Dr Raj Mathur	Katie Swindells, Clare Waters and Claudette Wright
University College Hospital, London	Dr Ephia Yasmin	Sarah Ekladios

Appendix 3 Oversight committees

Data Monitoring Committee

- Mr Anthony Rutherford, chairperson, independent member, consultant in reproductive medicine, The Leeds Centre for Reproductive Medicine, Leeds, UK.
- Dr Paul Knaggs, independent member, consultant embryologist, Wales Fertility Institute, University Hospital of Wales, Cardiff, UK.
- Dr Gillian Lockwood, independent member, director, Midland Fertility, Tamworth, UK.
- Dr Elizabeth Allen, independent member, statistician, senior lecturer, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK.

Trial Steering Committee

- Professor Richard Anderson, chairperson, independent member, professor of reproductive medicine, Medical Research Council University of Edinburgh Centre for Reproductive Health, the Queen's Medical Research Institute, Edinburgh, UK.
- Ms Kate Brian, independent member, London representative, Fertility Network, London, UK.
- Ms Gwenda Burns, independent member, chief executive, Fertility Network, London, UK.
- Ms Susan Seenan, independent member, chief executive, Infertility Network, Irvine, UK.
- Ms Aileen Feeney, independent member, head of charity operations, Fertility Network, London, UK.
- Ms Helen Kendrew, independent member, matron, Bath Fertility Centre, Bath, UK.
- Dr Umesh Acharya, independent member, consultant in reproductive medicine, South West Centre for Reproductive Medicine, Plymouth, UK.
- Mr Lee Middleton, independent member, senior statistician, Birmingham CTU, University of Birmingham, Birmingham, UK.
- Professor Abha Maheshwari, non-independent member, consultant and honorary senior lecturer, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen, UK.
- Associate Professor Edmund Juszczak, non-independent member, director, NPEU CTU, University of Oxford, Oxford, UK.
- Professor Siladitya Bhattacharya, observer, professor of reproductive medicine and fertility, Aberdeen Maternity Hospital, Aberdeen, UK.
- Ms Sue Avery, observer, director, Birmingham Women's Fertility Centre, Assisted Conception Unit, Birmingham Women's Hospital, Birmingham, UK.
- Ms Kayleigh Stanbury, observer, senior trials manager, NPEU CTU, University of Oxford, Oxford, UK.
- Ms Christina Cole, observer, E-Freeze trial manager/core trials support, NPEU CTU, University of Oxford, Oxford, UK.

Project Management Group

- Professor Jennifer Kurinczuk, professor of perinatal epidemiology, director, NPEU CTU, University of Oxford, Oxford, UK.
- Professor Abha Maheshwari, consultant and honorary senior lecturer, chief investigator, Aberdeen Maternity Hospital, Aberdeen, UK.
- Associate Professor Ed Juszczak, director, NPEU CTU, University of Oxford, Oxford, UK.
- Ms Kayleigh Stanbury, senior trials manager, NPEU CTU, University of Oxford, Oxford, UK.
- Mr Andy King, head of trials programming, NPEU CTU, University of Oxford, Oxford, UK.
- Mr David Murray, senior trials programmer, NPEU CTU, University of Oxford, Oxford, UK.
- Ms Louise Linsell, senior trial statistician, NPEU CTU, University of Oxford, Oxford, UK.

- Ms Jennifer Bell, trial statistician, NPEU CTU, University of Oxford, Oxford, UK.
- Ms Christina Cole, Observer, E-Freeze Trial Manager/Core Trials Support, NPEU CTU, University of Oxford, Oxford, UK.
- Ms Melanie Greenland, Trial Statistician, NPEU CTU, University of Oxford, Oxford, UK.

Appendix 4 Serious adverse events by trial arm

SAE number	Trial arm	Centre ID	Description	Severity	Related	Action taken	Outcome
1	Fresh-embryo transfer	1	Patient unwell with hyperemesis, GP admitted the patient to hospital for IV fluids	Mild	Not related	None	Resolved
2	Fresh-embryo transfer	1	Patient attended clinic feeling unwell. Observations were recorded and bloods taken, and the results showed signs of OHSS. The patient was admitted for IV therapy, analgesia and management of symptoms	Moderate	Not related	None	Resolving
3	Fresh-embryo transfer	3	During the follow-up telephone call 3 months after birth, the mother reported that the baby had tongue tie	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Unknown
4	Fresh-embryo transfer	4	Participant diagnosed with late onset of OHSS. Admitted to local hospital for further tests and treatment	Moderate	Not related	None	Resolved
5	Fresh-embryo transfer	4	Woman reported that her daughter was born with a cleft palate. She said there is no other complication but that she will see a specialist to have it corrected later this year	Mild	Not related	None	Resolving
6	Fresh-embryo transfer	4	Infection post delivery. Patient complained of redness, pain and pus at site of C-section (infection in the uterus). Patient reported being given antibiotics for 10 days	Mild	Not related	None	Resolved
7	Fresh-embryo transfer	4	Patient had 20/40 [20 week] scan at her local hospital. Possible cardiac (fetal) anomaly seen. Referred to [name] hospital for confirmation. Scanned at 30 + 5/40 [weeks of gestation]. Confirmed fetal diagnosis of coarctation of aorta and ventricular septal defect. No other anomalies detected. No intervention for now. IOL at 38/40 [weeks of gestation]. Follow-up report: baby had surgery to correct heart defect as reported earlier, mother and baby home and well. This was reported during post-delivery follow-up call by site and transposed to the SAE follow-up form by the co-ordinating centre	Moderate	Not related	Discontinued	Resolved

SAE number	Trial arm	Centre ID	Description	Severity	Related	Action taken	Outcome
8	Fresh-embryo transfer	4	Patient reported that her baby boy was tongue tied at birth and struggled to breastfeed. This was rectified immediately at 2 weeks post delivery. In addition, she reported that her son has one testicle that has failed to descend. He is booked to see the specialist	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Unknown
9	Fresh-embryo transfer	5	Fetal abnormality detected on antenatal ultrasound. Patient decided to terminate pregnancy	Severe	Not related	None	Resolved
10	Fresh-embryo transfer	6	Cleft soft palate noted on routine examination of the newborn. No other abnormalities. Reviewed by [location] cleft team [hospital name] while an inpatient. To be followed up as an outpatient. Safe to continue oral feeding	Moderate	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
11	Fresh-embryo transfer	8	Patient had a termination, reported at the 12-week follow-up call. A congenital anomaly was noted but site detailed that the patient was unable to provide more information	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
12	Fresh-embryo transfer	10	Patient was 4 weeks post partum when she had complained that she couldn't sleep or eat, had extreme emotions, paranoia, itchy body rash and flashing light before her eyes. Admitted to A&E	Moderate	Not related	None	Resolved
13	Fresh-embryo transfer	11	Ectopic pregnancy – confirmed [date] – admitted to hospital – left sided – home 4 days later	Moderate	Definitely	N/A [intervention(s) stopped prior to the event starting]	Resolved with sequelae
14	Fresh-embryo transfer	11	Postnatal period, approximately 2 weeks after birth, woman had seizure. Then another 2 weeks later. Now diagnosed as epileptic	Moderate	Not related	None	Resolved with sequelae
15	Frozen	1	Baby found to have a thickened nuchal area and abnormal location of heart outside the thorax	Severe	Not related	None	Resolved
16	Frozen	2	Patient reported being admitted to hospital when 11/40 [weeks of gestation] with severe pain from cyst on left ovary and overstimulated ovaries causing fluid in pelvis. Stayed in hospital for one week on painkillers and IV drip to help with nausea. Discharged, no follow-up and settled on its own with no intervention required	Moderate	Possibly		Resolved

SAE number	Trial arm	Centre ID	Description	Severity	Related	Action taken	Outcome
17	Frozen	2	Participant reports being admitted to hospital around 29 weeks' gestation with a urinary tract infection. She was admitted for two nights on oral antibiotics and pain relief. Note: participant not treated within this trust so limited info available. Participant not able to recall exact medication	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
18	Frozen	2	Participant reports being admitted into hospital around 32 weeks' gestation with diarrohea. She was admitted for one night on IV fluids. Note: Participant not treated within this trust so limited info available. Participant not able to recall exact medication	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
19	Frozen	2	Participant had prolonged hospitalisation due to ?Sepsis. Had raised CRP and creatinine and tachycardic. Was admitted to HDU post emergency C-section under GA. Was on IVAbx and IV fluids – was then observed and later discharged. Note: neonatal death also prolonged hospital stay as patient did not feel ready to go home following events	Moderate	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
20	Frozen	2	Neonatal death. Post-mortem results now available. The pathologist's opinion as to the cause of death: 1, hypoxic–ischaemic brain damage, 2, intrauterine infection manifesting in chorioamnionitis and intrauterine pneumonia	Severe	Not related	N/A [intervention(s) stopped prior to the event starting]	Fatal
21	Frozen	3	The baby was born on [date]. The site collected the data by telephone 1 month and 6 days later, when it was reported that the baby had a cleft palate	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Unknown
22	Frozen	4	The participant reported that her daughter was born at 41^{+5} weeks [of gestation]. Her baby had meconium aspiration during the delivery and had to stay in hospital for 10 days post delivery. The mother left hospital 4 days after delivery. Baby has been discharged on oxygen. She been on oxygen 4 weeks now since delivery and they are suggesting she may have another 6–8 weeks of oxygen therapy to come. Spoke to mother again on the [date] and she is happy to report that her baby is feeding well, her oxygen dose has been lowered to	Moderate	Not related	None	Resolving

SAE number	Trial arm	Centre ID	Description	Severity	Related	Action taken	Outcome
			0.05 l and her baby is sleeping well, growing as normal and thriving. She stated that the her baby is now down to a very low level of oxygen and that she is scheduled to see the doctor next week and expects that the oxygen therapy will be stopped				
23	Frozen	4	Woman diagnosed with cholestasis in later stages of pregnancy	Moderate	Not related	None	Resolved
24	Frozen	4	Baby birthweight was 4400 g. During delivery he experienced shoulder dystocia. He also had tongue-tie, which was addressed through surgery to improve his feeding	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
25	Frozen	5	Baby born on [date] with good Apgar score 9/1 + 10/5 min. Stopped breathing 18 minutes after birth. Ventilated for 2 days. Diagnosed with oesophageal atresia, tracheo-oesphageal fistula, small ventricular septal defect, patent foramen ovale and ductus arteriosus. Had repair surgery and closure of fistula on [date]. Tolerating feed well. Routine surgical and cardiology follow-up for heart murmur	Severe	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
26	Frozen	6	After embryo transfer the patient has reported symptoms of OHSS. She has a positive BHCG and went to [place] with her symptoms of OHSS. We have been told she has had a chest draine as a result of OHSS. She has an appointment with us on [date]. We will receive and provide more information when we see her	Severe	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved
27	Frozen	8	Hirschprung: the baby has a temporary stoma	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Unknown
28	Frozen	11	Suspected ectopic pregnancy (Pain, per vagina bleeding, positive pregnancy test) at 6/40 pregnancy prior to pregnancy scan. Ultrasound revealed right sided ectopic. Admitted via ambulance to local hospital. Stable observation (+ surgery salpingectomy to remove)	Moderate	Definitely	N/A [intervention(s) stopped prior to the event starting]	Resolved
29	Frozen	11	Baby born on [date]. Site collected post-delivery data 3 months later. During the phone call, the mother reported that the baby had tongue-tie	Mild	Not related	N/A [intervention(s) stopped prior to the event starting]	Resolved

SAE number	Trial arm	Centre ID	Description	Severity	Related	Action taken	Outcome
30	Frozen	13	Participant had pre-term and prolonged rapture of membranes from 29 weeks and was on erythromycin for that. According to electronic notes, participant had placenta abruption at 30^{+4} weeks [of gestation] and had emergency caesarean section. Baby is currently admitted at neonatal unit with parenteral nutrition. To this date, is diagnosed with prematurity. intrauterine growth restriction, jaundice, newborn feeding problem due to prematurity, respiratory disease syndrome, suspected sepsis and necrotising enterocolitis	Moderate	Not related		Resolving

A&E, accident and emergency; BHCG, beta-human chorionic gonadotropin; C-section, caesarean section; CRP, C-reactive protein; GA, general anaesthesia; GP, general practitioner; HDU, high-dependency unit; ID, identifier; IOL, induction of labour; IV, intravenous; IVAbx, intravenous antibiotics; N/A, not applicable; TOP, termination of pregnancy.

Appendix 5 Unit costs used in economic analysis (£)

Resource	How it is measured	Source of measurement	Unit cost (£)	Source of valuation
IVF	***See* Cost of the primary intervention**	***Post-embryo transfer eCRF***		
Embryo transfer	Number of embryo transfers		1095 per case	*NHS Reference Costs 2018/19*[26] (MC11Z Implantation of Embryo)
Embryo freezing	1 hour spent by an embryologist		47 per freezing	*Unit Costs of Health and Social Care 2019*[25] (Section IV, p. 143: Hospital-based scientific and professional staff)
Monitoring visit	Number of monitoring visits		56 per visit	*Unit Costs of Health and Social Care 2019*[25] (Section IV, p. 147: Hospital-based nurses, Band 6)
Blood test	Number of blood tests		1 per test	*NHS Reference Costs 2018/19*[26] (DAPS04 Clinical Biochemistry)
Transvaginal ultrasound scan	Number of transvaginal ultrasound scans		160 per case	*NHS Reference Costs 2018/19*[26] (MA36Z Transvaginal Ultrasound)
Endometrial preparation	Treatment regimen used		14 per natural cycle 52 per natural cycle with HCG 48 to 64 per artificial cycle with oestrogen and progesterone 114 per artificial cycle with oestrogen and progesterone, GnRH agonist 335 per artificial cycle with oestrogen and progesterone, antagonist 159 per luteal support for positive pregnancy	*British National Formulary (online)*[27]
Preparation of frozen embryo prior to transfer	1 hour by an embryologist		47 per case	*Unit Costs of Health and Social Care 2019*[25] (Section IV, p. 143: Hospital-based scientific and professional staff, band 6)

Resource	How it is measured	Source of measurement	Unit cost (£)	Source of valuation
OHSS	***See* Cost of OHSS**	***eCRFs post embryo transfer, early pregnancy***		
Outpatient attendance	Number of outpatient hospital visits		126 per visit	*NHS Reference Costs 2018/19*[26] (WF01 A 501 Non-Admitted Face-to-Face Attendance, Follow-up, Obstetrics)
Day case	Number of inpatient day care visits		792 per case	*NHS Reference Costs 2018/19*[26] (MB09 Non-Malignant Gynaecological Disorders with Interventions)
Inpatient stay	Number of inpatient nights		1340 per short stay (one night) 861 per night of a long stay 454 per excess bed-day	*NHS Reference Costs 2018/19*[26] (MB09 Non-Malignant Gynaecological Disorders with Interventions)
Pregnancy outcomes	***See* Cost of pregnancy outcomes**	***eCRFs at early pregnancy, 12 weeks' follow-up and 28 weeks' follow-up***		
Miscarriage			619 per case	*NHS Reference Costs 2018/19*[26] (MB08 Threatened or Spontaneous Miscarriage)
Ectopic pregnancy			537 per case	*NHS Reference Costs 2018/19*[26] (MA48Z Medical Treatment of Ectopic Pregnancy)
Pregnancy of unknown location			170 per case	RCOG review,[29] *NHS Reference Costs 2018/19*[26] (MA36Z Transvaginal Ultrasound, DAPS04 Clinical Biochemistry)
Termination			1016 per case from 9 to 14 weeks' gestation 1450 per case from 14 to 20 weeks' gestation	*NHS Reference Costs 2018/19*[26] (MA51Z Surgical, Abortion or Miscarriage Care from 14 to 20 weeks' gestation; MA52 Surgical, Abortion or Miscarriage Care < 14 week' gestation; MA54Z Medical, Abortion or Miscarriage Care from 14 to 20 weeks' gestation; MA55 Medical, Abortion or Miscarriage Care from 9 to < 14 weeks' gestation)
Biochemical pregnancy			128 per case	Clinical advice, *NHS Reference Costs 2018/19*[26] (NZ22Z Ante-Natal Specialised Non-Routine Ultrasound Scan, DAPS04 Clinical Biochemistry)

Resource	How it is measured	Source of measurement	Unit cost (£)	Source of valuation
ANC	***See* Cost of ANC**	***eCRFs at early pregnancy, 28 weeks' follow-up and post delivery***		
Community midwife visit	Number of community midwife visits		58 per visit	*NHS Reference Costs 2018/19*[26] (HVM N01 A Community Midwife, Ante Natal Visit)
Outpatient attendance	Number of outpatient hospital visits		126 per visit	*NHS Reference Costs 2018/19*[26] (WF01 A 501 Non-Admitted Face-to-Face Attendance, Follow-up, Obstetrics)
Day case	Number of inpatient day care visits		NZ16: 331 per visit NZ18: 390 per visit NZ19: 641 per visit	*NHS Reference Costs 2018/19*[26] (NZ16 Ante-Natal Routine Observation, NZ18 Ante-Natal Complex Disorders, NZ19 Ante-Natal Major Disorders)
Inpatient stay	Number of inpatient nights		NZ16: 386 per short stay, 1220 per night of a long stay, 501 per excess bed-day NZ18: 602 per short stay, 853 per night of a long stay, 506 per excess bed-day NZ19: 417 per short stay, 801 per night of a long stay, 519 per excess bed-day	*NHS Reference Costs 2018/19*[26] (NZ16 Ante-Natal Routine Observation, NZ18 Ante-Natal Complex Disorders, NZ19 Ante-Natal Major Disorders)
Antenatal ultrasound scan	Number of ultrasound scans		NZ21Z: 118 per scan NZ22Z: 124 per scan	*NHS Reference Costs 2018/19*[26] (NZ21Z Ante-Natal Standard Routine Ultrasound Scan, NZ22Z Ante-Natal Specialised Non-Routine Ultrasound Scan)
Delivery	***See* Cost of delivery**	***Post-delivery eCRF***		
Normal delivery	Number of inpatient nights		NZ30 (Spontaneous): 1640 per short stay, 1224 per night of a long stay, 577 per excess bed-day NZ32-NZ34 (Induced): 1930 per short stay, 1202 per night of a long stay, 557 per excess bed-day (weighted average)	*NHS Reference Costs 2018/19*[26] (NZ30 Normal Delivery, NZ31 Normal Delivery, with Epidural or Induction, NZ32 Normal Delivery, with Epiducal and Induction, or with Post-Partum Surgical Intervention, NZ33 Normal Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, NZ34 Normal Delivery, with Epidural, Induction and Post-Partum Surgical Intervention)
Instrumental delivery	Number of inpatient nights		NZ40 (Spontaneous): 1727 per short stay, 1077 per night of a long stay, 511 per excess day	*NHS Reference Costs 2018/19*[26] (NZ40 Assisted Delivery, NZ41 Assisted Delivery, with Epidural or Induction, NZ42 Assisted Delivery, with Epidural and Induction, or with

Resource	How it is measured	Source of measurement	Unit cost (£)	Source of valuation
			NZ42-NZ44 (Induced): 2255 per short stay, 1229 per night of a long stay, 577 per excess day (weighted average)	Post-Partum Surgical Intervention, NZ43 Assisted Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, NZ44 Assisted Delivery, with Epidural, Induction and Post-Partum Surgical Intervention)
Caesarean	Number of inpatient nights		NZ50: 2913 per short stay, 1681 per night of a long stay, 1519 per excess bed-day, NZ51: 2862 per short stay, 1337 per night of a long stay, 563 per excess day	*NHS Reference Costs 2018/19*[26] (NZ50 Planned Caesarean Section, NZ51 Emergency Caesarean Section)
Paid work	***Amount of time spent per visit***	***Economic questionnaire***		***ASHE***[32]
Age (years): female				
22–29			11.43 per hour	
30–39			13.65 per hour	
40–49			13.54 per hour	
Age (years): male				
22–29			12.27 per hour	
30–39			15.67 per hour	
40–49			17.54 per hour	
Unpaid work	***Amount of time spent per visit***	***Economic questionnaire***		***ASHE***[32]
Voluntary work			14.43 per hour	
At home looking after family or dependants			14.92 per hour	Weighted average of childcare and adult care
In education			10.37 per hour	Weighted average of unpaid work done by a full-time student[72]
Other			10.17 per hour	Weighted average across seveb unpaid work activities from ASHE[32]
Leisure			5.03 per hour	*Transport Analysis Guidance (TAG) Data Book*[34]

Appendix 6 Direct medical costs by treatment allocation

Variable	Number of observations	Freeze-all arm ($N = 307$)	Fresh-embryo transfer arm ($N = 309$)
IVF costs (£), mean (SD)	616	1538.45 (473.67)	1215.51 (221.17)
Freezing of embryo	616	41.16 (15.96)	38.14 (18.75)
Endometrial preparation costs	616	131.88 (104.18)	78.05 (50.45)
Embryo transfer costs	616	1063.07 (185.05)	1073.91 (151.37)
Monitoring visit costs prior to frozen-embryo transfer	223	122.82 (116.97)	104.24 (77.95)
Blood test costs prior to embryo transfer	223	0.39 (0.89)	0.68 (1.18)
Transvaginal ultrasound costs prior to embryo transfer	223	288.24 (242.30)	221.50 (156.14)
Preparation of frozen embryo	223	47.33 (0)	47.33 (0)
OHSS management costs (£), mean (SD)	36	467.02 (763.05)	2484.84 (2947.32)
Pregnancy loss costs (£), mean (SD)	100	525.61 (278.99)	480.57 (276.47)
Miscarriage costs	59	618.68 (0)	618.68 (0)
Ectopic pregnancy costs	9	536.95 (0)	536.95 (0)
Pregnancy of unknown location costs	3	169.93 (0)	0 (0)
Termination costs	4	1450.37 (0)	1232.99 (307.42)
Biochemical pregnancy costs	25	127.50 (0)	127.50 (0)
ANC costs			
6 to < 12 weeks' gestation (*n*)	293	139	154
ANC costs (£), mean (SD)	293	169.10 (47.25)	164.46 (54.20)
12 to < 28 weeks' gestation (*n*)	201	93	108
ANC costs (£), mean (SD)	199	999.46 (1927.34)	963.46 (1029.86)
No maternal complications, mean (SD)	172	801.05 (744.31)	786.17 (665.34)
Hypertensive disorder, mean (SD)	5	1379.14 (1373.08)	1155.42 (513.30)
GDM, mean (SD)	6	976.98 (614.77)	808.86 (313.08)
Antepartum haemorrhage, mean (SD)	14	3598.54 (7065.07)	2985.43 (2233.78)
> 1 complication, mean (SD)	1	1761.13 (0)	0 (0)
Missing, *n* (%)	2	0 (0)	2 (2)
28 weeks' gestation to delivery, *n*	189	87	102
ANC costs (£), mean (SD)	181	1343.35 (1324.50)	1254.90 (1752.03)
No maternal complications, mean (SD)	148	1110.82 (1017.13)	955.87 (676.20)
Hypertensive disorder, mean (SD)	11	2361.85 (2201.93)	1293.45 (326.47)
GDM, mean (SD)	6	1300.58 (596.87)	2536.77 (1478.13)
Antepartum haemorrhage, mean (SD)	15	2811.74 (2126.38)	3390.75 (5002.93)
> 1 complication, mean (SD)	1	0 (0)	1954.46 (0)
Missing, *n* (%)	8	3 (3)	5 (5)

Variable	Number of observations	Freeze-all arm ($N = 307$)	Fresh-embryo transfer arm ($N = 309$)
Delivery inpatient costs (*n*)	193	87	106
Delivery costs (£), mean (SD)	183	3873.02 (1908.82)	3850.80 (2148.27)
Normal vaginal delivery costs, mean (SD)	66	3180.55 (1336.91)	2648.41 (1158.45)
Instrumental vaginal delivery costs, mean (SD)	48	3105.21 (1610.56)	3575.44 (1489.73)
C-section costs, mean (SD)	69	4894.95 (2036.53)	5376.53 (2505.25)
Missing, *n* (%)	10	5 (6)	5 (5)
Total NHS cost, mean (SD)	605	3431.15 (3507.87)	3573.99 (3807.37)

C-section, caesarean section.

Appendix 7 Resource use and costs related to travelling and time, by treatment allocation

Variable	Number of observations	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Participant			
Visited clinic (*n*)	176	135	41
Transport mode, *n* (%)			
Train	45	37 (27)	8 (20)
Bus/tram	5	5 (4)	0 (0)
Car	105	77 (57)	28 (68)
Taxi	5	4 (3)	1 (2)
Hospital transport/ambulance	0	0 (0)	0 (0)
Walk/cycle	5	5 (4)	0 (0)
Other	10	7 (5)	3 (7)
Missing	1	0 (0)	1 (2)
Transport costs per visit (£), mean (SD)	168	17.63 (23.33)	29.16 (30.52)
Train costs	41	11.25 (8.11)	42.38 (41.72)
Bus/tram costs	5	8.76 (5.19)	0 (0)
Car costs	103	20.50 (27.08)	25.06 (28.15)
Taxi costs	5	19.78 (10.71)	30 (0)
Hospital transport/ambulance costs (£), mean (SD)	0	0 (0)	0 (0)
Walk/cycle costs, mean (SD)	5	0 (0)	0 (0)
Other transport costs, mean (SD)	9	36.56 (34.27)	29.13 (17.96)
Missing, *n* (%)	8	5 (4)	3 (7)
Other costs per visit (£), mean (SD)	168	0.38 (4.39)	2.84 (12.26)
Missing, *n* (%)	8	5 (4)	3 (7)
Travel costs per visit (£), mean (SD)	168	18.02 (25.04)	32.00 (38.92)
Missing, *n* (%)	8	5 (4)	3 (7)
Time spent to visit the clinic per visit (hours), mean (SD)	164	2.80 (2.98)	4.20 (3.92)
Time off paid work, mean (SD)	145	2.84 (3.11)	4.45 (4.29)
Time off unpaid work, mean (SD)	9	2.50 (1.05)	3.88 (1.18)
Time off leisure/social activities, mean (SD)	10	2.36 (0.94)	2.17 (1.61)
Missing, *n* (%)	12	7 (5)	5 (12)
Time cost per visit (£), mean (SD)	164	33.07 (22.68)	47.25 (27.00)
Cost of time lost from paid work, mean (SD)	145	34.36 (23.11)	50.38 (26.28)
Cost of time lost from unpaid work, mean (SD)	9	32.79 (9.99)	51.58 (24.09)
Cost of time lost from leisure activities, mean (SD)	10	11.86 (4.75)	10.90 (8.08)
Missing, *n* (%)	12	7 (5)	5 (12)

Variable	Number of observations	Freeze-all arm (*N* = 307)	Fresh-embryo transfer arm (*N* = 309)
Accompanying partner			
Clinic visit(s) between the time from treatment allocation and the time to embryo transfer, *n* (%)			
Yes	132	95 (31)	37 (12)
No	298	115 (37)	183 (59)
Missing	186	97 (32)	89 (29)
Number of visits to clinic, mean (SD)	419	1.03 (1.68)	0.45 (1.35)
Missing, *n* (%)	197	104 (34)	93 (30)
Transport mode, *n* (%)			
Train	29	23 (24)	6 (16)
Bus/tram	4	4 (4)	0 (0)
Car	85	59 (62)	26 (70)
Taxi	2	1 (1)	1 (3)
Hospital transport/ambulance	0	0 (0)	0 (0)
Walk/cycle	4	4 (4)	0 (0)
Other	7	4 (4)	3 (8)
Missing	1	0 (0)	1 (3)
Transport cost per visit (£), mean (SD)	127	18.73 (24.63)	29.23 (39.99)
Train, mean (SD)	27	14.85 (17.65)	22.75 (37.92)
Bus/tram, mean (SD)	4	10.20 (4.69)	0 (0)
Car, mean (SD)	83	21.78 (28.25)	27.35 (32.12)
Taxi, mean (SD)	2	18.00 (0)	30.00 (0)
Hospital transport/ambulance, mean (SD)	0	0 (0)	0 (0)
Walk/cycle, mean (SD)	4	0 (0)	0 (0)
Other transport, mean (SD)	7	21.91 (17.44)	21.60 (3.42)
Missing, *n* (%)	5	3 (3)	2 (5)
Other costs per visit (£), mean (SD)	127	0 (0)	3.09 (12.75)
Missing, *n* (%)	5	3 (3)	2 (5)
Travel cost per visit (£), mean (SD)	127	18.73 (24.63)	29.23 (39.99)
Missing, *n* (%)	5	3 (3)	2 (5)
Time spent to visit the clinic (hours), mean (SD)	123	2.61 (1.83)	4.00 (4.08)
Time off paid work, mean (SD)	116	2.64 (1.86)	4.18 (4.22)
Time off unpaid work, mean (SD)	5	1.92 (0.63)	2.75 (1.77)
Time off leisure/social activities, mean (SD)	2	2.50 (0)	1.00 (0)
Missing, *n* (%)	9	5 (5)	4 (11)
Indirect cost per visit (£), mean (SD)	123	39.63 (25.63)	51.14 (33.85)
Cost of time lost from paid work, mean (SD)	116	40.32 (25.93)	55.21 (32.59)
Cost of time lost from unpaid work, mean (SD)	5	28.80 (9.44)	13.16 (18.60)
Cost of time lost from leisure activities, mean (SD)	2	12.58 (0)	5.03 (0)
Missing, *n* (%)	9	5 (5)	4 (11)

Variable	Number of observations	Freeze-all arm ($N = 307$)	Fresh-embryo transfer arm ($N = 309$)
Total travel costs,[a] mean (SD)	415	20.20 (60.19)	19.10 (101.72)
Total time costs,[b] mean (SD)	411	37.66 (77.67)	23.98 (92.86)
Total patient costs,[c] mean (SD)	409	57.89 (120.38)	42.40 (190.04)

a Estimated using travel costs per visit and the number of visits reported.
b Estimated using time costs per visit and the number of visits reported.
c Sum of total travel costs and total time costs.

Appendix 8 Trial-based cost-effectiveness scatterplots and cost-effectiveness acceptability curves

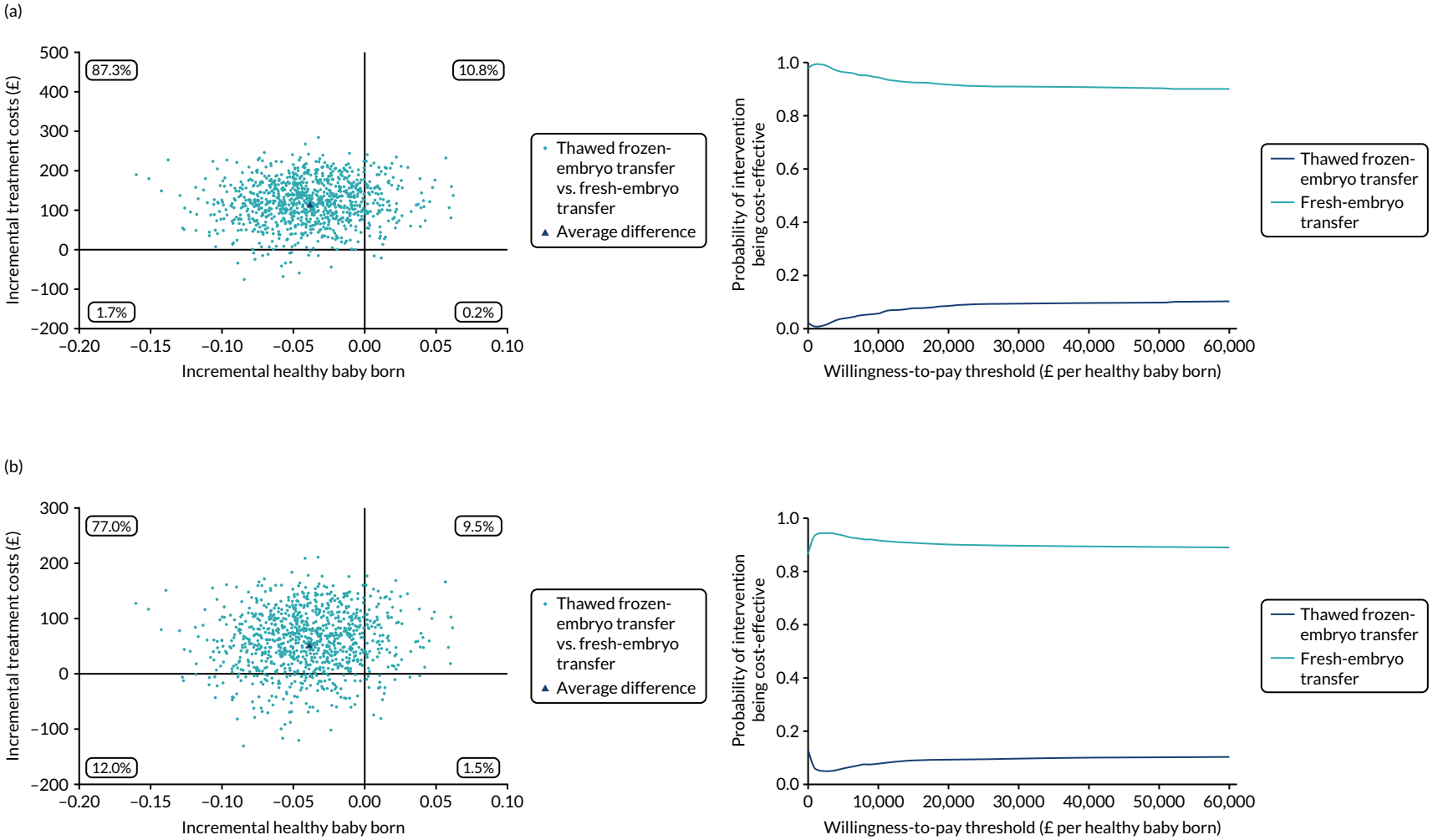
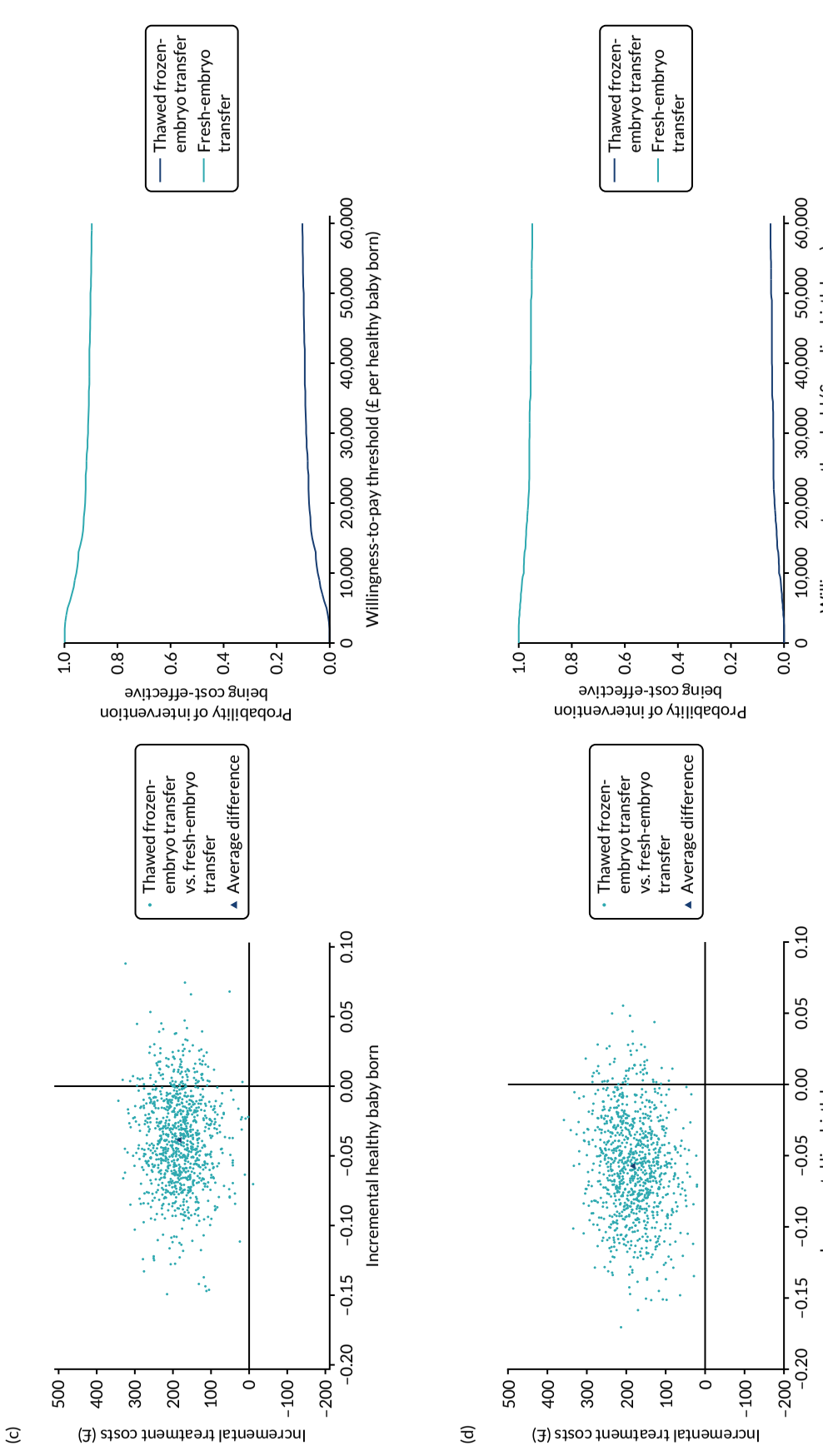


FIGURE 19 Trial-based cost-effectiveness scatterplots and cost-effectiveness acceptability curves generated from sensitivity and subgroup analyses. (a) Sensitivity analysis: assuming that the transvaginal scan cost was inclusive of a monitoring visit; (b) sensitivity analysis: using standard ultrasound scan cost (£53) to cost transvaginal scans; (c) sensitivity analysis: multiple imputation (treatment costs, health baby); (d) sensitivity analysis: multiple imputation (treatment costs, live birth); (e) sensitivity analysis: multiple imputation (NHS costs, healthy baby); (f) sensitivity analysis: multiple imputation (NHS costs, live birth); (g) subgroup analysis: maternal age < 35 years; and (h) subgroup analysis: maternal age ≥ 35 years. Reproduced from Maheshwari *et al.*,[23] Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze), *Human Reproduction*, 2022, deab279, by permission of European Society of Human Reproduction and Embryology. (*continued*)



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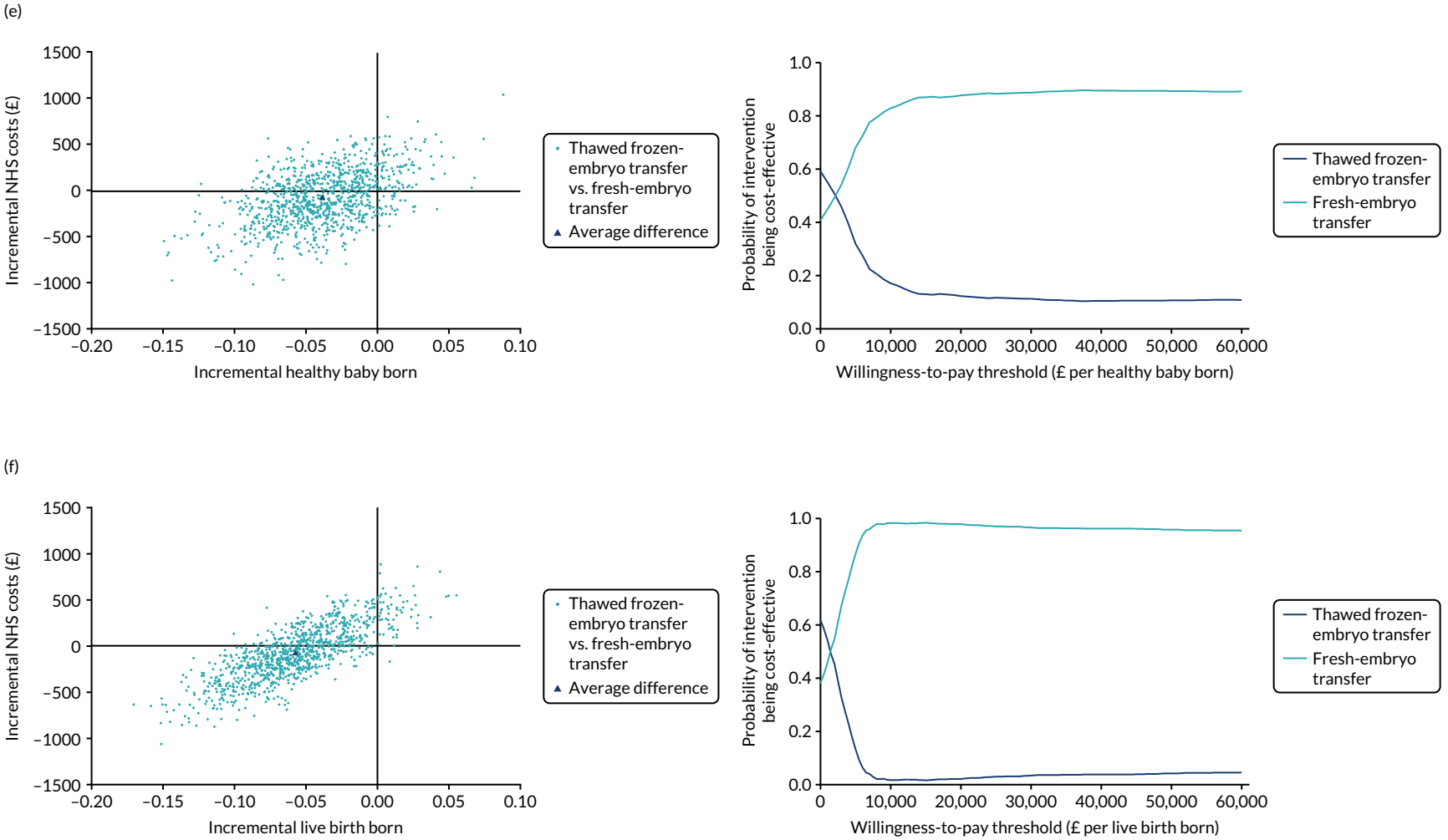

FIGURE 19 Trial-based cost-effectiveness scatterplots and cost-effectiveness acceptability curves generated from sensitivity and subgroup analyses. (a) Sensitivity analysis: assuming that the transvaginal scan cost was inclusive of a monitoring visit; (b) sensitivity analysis: using standard ultrasound scan cost (£53) to cost transvaginal scans; (c) sensitivity analysis: multiple imputation (treatment costs, health baby); (d) sensitivity analysis: multiple imputation (treatment costs, live birth); (e) sensitivity analysis: multiple imputation (NHS costs, healthy baby); (f) sensitivity analysis: multiple imputation (NHS costs, live birth); (g) subgroup analysis: maternal age < 35 years; and (h) subgroup analysis: maternal age ≥ 35 years. Reproduced from Maheshwari *et al.*,[23] Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze), *Human Reproduction*, 2022, deab279, by permission of European Society of Human Reproduction and Embryology. (*continued*)

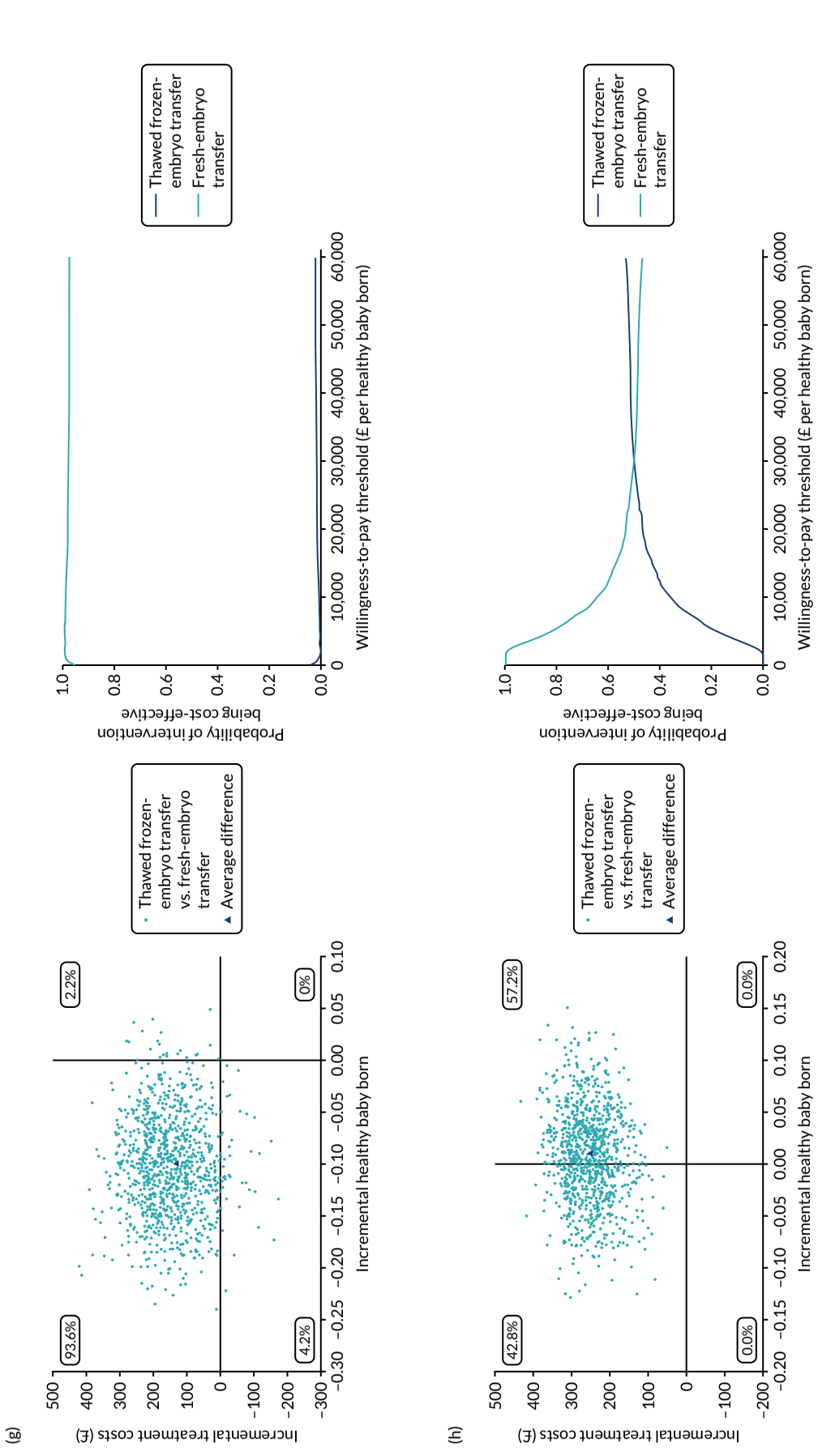

FIGURE 19 Trial-based cost-effectiveness scatterplots and cost-effectiveness acceptability curves generated from sensitivity and subgroup analyses. (a) Sensitivity analysis: assuming that the transvaginal scan cost was inclusive of a monitoring visit; (b) sensitivity analysis: using standard ultrasound scan cost (£53) to cost transvaginal scans; (c) sensitivity analysis: multiple imputation (treatment costs, health baby); (d) sensitivity analysis: multiple imputation (treatment costs, live birth); (e) sensitivity analysis: multiple imputation (NHS costs, healthy baby); (f) sensitivity analysis: multiple imputation (NHS costs, live birth); (g) subgroup analysis: maternal age < 35 years; and (h) subgroup analysis: maternal age ≥ 35 years. Reproduced from Maheshwari *et al.*,[23] Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze), *Human Reproduction*, 2022, deab279, by permission of European Society of Human Reproduction and Embryology.

Appendix 9 Markov model parameter inputs (derived from the analysis of the E-Freeze trial cost and outcome data, unless otherwise noted)

Parameter name	Description	Fresh-embryo transfer arm			Freeze-all arm		
		Expected value	Distribution type	Distribution parameters	Expected value	Distribution type	Distribution parameters
Probabilities (index transfer)							
prop_eFz	Proportion of embryo transfers that are frozen	0.069	Beta	Alpha: 21 Beta: 282	0.678	Beta	Alpha: 202 Beta: 96
prop_Fresh	Proportion of embryo transfers that are fresh	0.931	1 – prop_eFz		0.322	1-prop_eFz	
*p*_transfer	Probability of planned transfer going ahead	0.981	Beta	Alpha: 303 Beta: 6	0.971	Beta	Alpha: 298 Beta: 9
*p*_OHSS	Probability of OHSS	0.081	Beta	Alpha: 25 Beta: 284	= *p*_OHSS × RR_OHSS (see relative risk definition below)		
*p*_test_positive	Probability of a positive pregnancy test following embryo transfer	0.508	Beta	Alpha: 154 Beta: 149	= *p*_test_postive × RR_pos_test (see relative risk definition below)		
*p*_early_loss	Probability of pregnancy loss by 8 weeks following a positive pregnancy test	0.201	Beta	Alpha: 31 Beta: 123	= *p*_early_loss × RR_early_loss (see relative risk definition below)		
*p*_miscarriage	Probability of pregnancy loss by 12 weeks in those ongoing at 8 weeks	0.122	Beta	Alpha: 15 Beta: 108	= *p*_miscarriage × RR_miscarriage (see relative risk definition below)		
*p*_late_miscarriage	Probability of pregnancy loss by 24 weeks in those ongoing at 12 weeks	0.019	Beta	Alpha: 2 Beta: 105	= *p*_late_miscarriage × RR_late_miscarriage (see relative risk definition below)		
*p*_delivery_25_28	Probability of delivery by 28 weeks for ongoing pregnancies at 24 weeks	0.038	Beta	Alpha: 4 Beta: 102	= *p*_delivery_25_28 × RRePT (see relative risk definition below)		
*p*_delivery_29_32	Probability of delivery by 32 weeks for ongoing pregnancies at 28 weeks	0.020	Beta	Alpha: 2 Beta: 99	= *p*_delivery_29_32 × RR_vPreterm (see relative risk definition below)		
*p*_delivery_33_36	Probability of delivery by 36 weeks for ongoing pregnancies at 32 weeks	0.061	Beta	Alpha: 6 Beta: 93	= *p*_delivery_33_36 × RR_Preterm (see relative risk definition below)		

Parameter name	Description	Fresh-embryo transfer arm			Freeze-all arm		
		Expected value	Distribution type	Distribution parameters	Expected value	Distribution type	Distribution parameters
RR (freeze all vs. fresh-embryo transfer)							
RR_OHSS	Relative risk of OHSS by ITT (freeze all vs. fresh-embryo transfer)	Reference group			0.44	Log-normal	umeanoflogs: −0.821 sigmastddevoflogs: 0.551
RR_pos_test	Relative risk for a positive test following embryo transfer (freeze all vs. fresh-embryo transfer)	Reference group			0.913	Log-normal	umeanoflogs: −0.094 sigmastddevoflogs: 0.086
RR_early_loss	Relative risk of any miscarriage conditional on a positive pregnancy test (freeze all vs. fresh-embryo transfer)	Reference group			1.18	Log-normal	umeanoflogs: 0.166 sigmastddevoflogs: 0.226
RR_ePT	Relative risk of delivery prior to 33 weeks for those ongoing at 24 weeks (freeze all vs. fresh-embryo transfer)	Reference group			0.767	Log-normal	umeanoflogs: −0.505 sigmastddevoflogs: 0.692
RR_late_miscarriage	Relative risk of any miscarriage conditional on a positive pregnancy test (freeze all vs. fresh-embryo transfer)	Reference group			1.18	Log-normal	umeanoflogs: 0.166 sigmastddevoflogs: 0.226
RR_miscarriage	Relative risk of any miscarriage conditional on a positive pregnancy test (freeze all vs. fresh-embryo transfer)	Reference group			1.18	Log-normal	umeanoflogs: 0.166 sigmastddevoflogs: 0.226
RR_Preterm	Relative risk of delivery prior to 37 weeks for those ongoing at 32 weeks (freeze all vs. fresh-embryo transfer)	Reference group			1.377	Log-normal	umeanoflogs: 0.164 sigmastddevoflogs: 0.558

Parameter name	Description	Fresh-embryo transfer arm			Freeze-all arm		
		Expected value	Distribution type	Distribution parameters	Expected value	Distribution type	Distribution parameters
RR_vPreterm	Relative risk of delivery prior to 33 weeks for those ongoing at 24 weeks (freeze all vs. fresh-embryo transfer)	Reference group			0.767	Log-normal	umeanoflogs: −0.505 sigmastddevoflogs: 0.692
Probabilities for subsequent frozen ETs							
*p*_embryos_remaining	Proportion with frozen embryos remaining after the index ET cycle	0.777	Beta	Alpha: 153 Beta: 44	0.787	Beta	Alpha: 166 Beta: 45
*p*_embryos_remaining_ET1	Proportion with frozen embryos remaining after first subsequent frozen ET	0.745	Beta	Alpha: 114 Beta: 39	0.789	Beta	Alpha: 131 Beta: 35
*p*_embryos_remaining_ET2	Proportion with frozen embryos remaining after second subsequent frozen ET	0.719	Beta	Alpha: 82 Beta: 32	0.679	Beta	Alpha: 89 Beta: 42
*p*_embryos_remaining_ET3	Proportion with frozen embryos remaining after third subsequent frozen ET	0.622	Beta	Alpha: 51 Beta: 31	0.697	Beta	Alpha: 62 Beta: 27
*p*_embryos_remaining_ET4	Proportion with frozen embryos remaining after fourth subsequent frozen ET	0.686	Beta	Alpha: 35 Beta: 16	0.629	Beta	Alpha: 39 Beta: 23
*p*_embryos_remaining_ET5	Proportion with frozen embryos remaining after fifth subsequent frozen ET	0.629	Beta	Alpha: 22 Beta: 13	0.538	Beta	Alpha: 21 Beta: 18
*p*_subsequent_fz1[a]	Probability of proceeding to first subsequent frozen cycle conditional on frozen embryos being available	0.941	Beta	Alpha: 1720 Beta: 108	Same as the fresh-embryo transfer arm		
*p*_subsequent_fz2[a]	Probability of proceeding to second subsequent frozen cycle conditional on frozen embryos being available	0.902	Beta	Alpha: 1591 Beta: 173	Same as the fresh-embryo transfer arm		

Parameter name	Description	Fresh-embryo transfer arm			Freeze-all arm		
		Expected value	Distribution type	Distribution parameters	Expected value	Distribution type	Distribution parameters
*p*_subsequent_fz3[a]	Probability of proceeding to third subsequent frozen cycle conditional on frozen embryos being available	0.902	Beta	Alpha: 1591 Beta: 173	Same as the fresh-embryo transfer arm		
*p*_subsequent_fz4[a]	Probability of proceeding to fourth subsequent frozen cycle conditional on frozen embryos being available	0.902	Beta	Alpha: 1591 Beta: 173	Same as the fresh-embryo transfer arm		
*p*_subsequent_fz5[a]	Probability of proceeding to fifth subsequent frozen cycle conditional on frozen embryos being available	0.902	Beta	Alpha: 1591 Beta: 173	Same as the fresh-embryo transfer arm		
*p*_subsequent_fz6[a]	Probability of proceeding to fifth subsequent frozen cycle conditional on frozen embryos being available	0.902	Beta	Alpha: 1591 Beta: 173	Same as the fresh-embryo transfer arm		
RR (subsequent frozen-embryo transfer versus index)							
RR_preg_subs_vs_index[a]	Relative risk of pregnancy in subsequent frozen cycles versus index frozen cycle	–			0.785	Log-normal	umeanoflogs: −0.245 sigmastddevoflogs: 0.076
Cost parameters							
cOHSS	Cost of managing OHSS in those who get it	2484.84	Gamma	Alpha: $[(2484.84)^2]/[(589.46)^2]$, lambda: $(2484.84)/[(589.46)^2]$	467.02	Gamma	Alpha: $[(467.02)^2]/[(230.68)^2]$ Lambda: $(467.02)/[(230.68)^2]$
cFreezing	Cost of freezing embryos by ITT	37.22	Gamma	Alpha: $[(37.22)^2]/[(1.11)^2]$ Lambda: $(37.22)/[(1.11)^2]$	39.78	Gamma	Alpha: $[(39.78)^2]/[(0.99)^2]$ Lambda: $(39.78)/[(0.99)^2]$

		Fresh-embryo transfer arm			Freeze-all arm		
Parameter name	Description	Expected value	Distribution type	Distribution parameters	Expected value	Distribution type	Distribution parameters
cEndo_prep_luteul_support	Cost of endometrial preparation and luteal support by ITT	78.05	Gamma	Alpha: $[(78.05)^2]/[(2.87)^2]$ Lambda: $(78.05)/[(2.87)^2]$	131.88	Gamma	Alpha: $[(131.88)^2]/[(5.95)^2]$ Lambda: $(131.88)/[(5.95)^2]$
cMonitoring_fz	Expected cost of monitoring prior to ET for those undergoing frozen ET	104.24	Gamma	Alpha: $[(104.24)^2]/[(16.62)^2]$ Lambda: $(104.24)/[(16.62)^2]$	122.82	Gamma	Alpha: $[(122.82)^2]/[(8.23)^2]$ Lambda: $(122.82)/[(8.23)^2]$
c_ultrasound_fz	Expected cost of scans prior to ET for those undergoing frozen ET	221.50	Gamma	Alpha: $[(221.50)^2]/[(33.29)^2]$ Lambda: $(221.50)/[(33.29)^2]$	288.24	Gamma	Alpha: $[(288.24)^2]/[(17.48)^2]$ Lambda: $(288.24)/[(17.48)^2]$
cBlood_tests_fz	Expected cost of blood tests prior to ET for those undergoing frozen ET	0.68	Deterministic		0.39	Deterministic	
c_prep_thawed_embryos	Cost preparing frozen embryos for transfer	47.33	Deterministic		(Same as the fresh-embryo transfer arm)	Deterministic	
cET	Cost of the ET procedure itself	1095.18	Deterministic		(Same as the fresh-embryo transfer arm)	Deterministic	
cEarly_preg	Cost of early pregnancy, including confirmatory scan at 3–8 weeks, up to 12 weeks	164.46	Gamma	Alpha: $[(164.46)^2]/[(4.37)^2]$ Lambda: $(164.46)/[(4.37)^2]$	169.10	Gamma	Alpha: $[(169.1)^2]/[(4.01)^2]$ Lambda: $(169.1)/[(4.01)^2]$
cEarly_loss	Cost per pregnancy loss occurring by 8 weeks	367.83	Gamma	Alpha: $[(367.83)^2]/[(42.78)^2]$ Lambda: $(367.83)/[(42.78)^2]$	432.87	Gamma	Alpha: $[(432.87)^2]/[(39.20)^2]$ Lambda: $(432.87)/[(39.20)^2]$

Parameter name	Description	Fresh-embryo transfer arm			Freeze-all arm		
		Expected value	Distribution type	Distribution parameters	Expected value	Distribution type	Distribution parameters
c_Miscarriage	Cost per pregnancy loss occurring between 8 and 12 weeks	639.69	Gamma	Alpha: $[(639.69)^2]/[(27.40)^2]$ Lambda: $(639.69)/[(27.40)^2]$	694.29	Gamma	Alpha: $[(694.29)^2]/[(75.61)^2]$ Lambda: $(694.29)/[(75.61)^2]$
c_Late_Miscarriage	Cost per pregnancy loss occurring between 12 and 24 weeks	1034.53	Gamma	Alpha: $[(1034.53)^2]/[(415.84)^2]$ Lambda: $(1034.53)/[(415.84)^2]$	757.30	Gamma	Alpha: $[(757.3)^2]/[(138.62)^2]$ Lambda: $(757.3)/[(138.62)^2]$
cANC_12_28w	Cost of ANC between 12 and 28 weeks (in those ongoing at 12 weeks)	963.46	Gamma	Alpha: $[(963.46)^2]/[(100.03)^2]$ Lambda: $(963.46)/[(100.03)^2]$	999.46	Gamma	Alpha: $[(999.46)^2]/[(199.86)^2]$ Lambda: $(999.46)/[(199.86)^2]$
cANC_post_28w	Cost of ANC after 28 days up to but excluding delivery (in those ongoing at 28 weeks)	1254.90	Gamma	Alpha: $[(1254.90)^2]/[(177.89)^2]$ Lambda: $(1254.90)/[(177.89)^2]$	1343.35	Gamma	Alpha: $[(1343.35)^2]/[(142.00)^2]$ Lambda: $(1343.35)/[(142.00)^2]$
cDelivery	Cost of delivery in those who deliver post 24 weeks	3850.80	Gamma	Alpha: $[(3850.80)^2]/[(208.66)^2]$ Lambda: $(3850.80)/[(208.66)^2]$	3873.02	Gamma	Alpha: $[(3873.02)^2]/[(204.65)^2]$ Lambda: $(3873.02)/[(204.65)^2]$
c_Endo_prep_subs_fz	Cost of endometrial preparation and luteal support in subsequent frozen cycles	–			131.88	Gamma	Alpha: $[(131.88)^2]/[(5.95)^2]$ Lambda: $(131.88)/[(5.95)^2]$

Parameter name	Description	Fresh-embryo transfer arm			Freeze-all arm		
		Expected value	Distribution type	Distribution parameters	Expected value	Distribution type	Distribution parameters
Birth outcomes (term infants)							
prop_Term_lbw	Proportion of term births that are below 10th percentile for gestation	0.097	Dirichlet	Alpha: 9	0.115	Dirichlet	Alpha: 9
prop_Term_nbw	Proportion of term deliveries of normal birthweight (healthy term babies)	0.806	Dirichlet	Alpha: 75	0.795	Dirichlet	Alpha: 62
prop_Term_hbw	Proportion of term deliveries of high birthweight (macrosomia)	0.097	Dirichlet	Alpha: 9	0.090	Dirichlet	Alpha: 7
prop_term_lga_below1500g	Proportion of term low birthweight for gestational age infants < 1500 g	0.111	Dirichlet	Alpha: 1	0.000	Dirichlet	Alpha: 0
prop_term_lga_below2500g	Proportion of term low weight for gestational age infants 1500 g to < 2500 g	0.111	Dirichlet	Alpha: 1	0.143	Dirichlet	Alpha: 1
prop_term_lga_2500g_plus	proportion of term low birthweight for gestational age infants ≥ 2500 g	0.778	Dirichlet	Alpha: 7	0.795	Dirichlet	Alpha: 6

ET, embryo transfer; RR, relative risk.

a Parameters derived from published Australian population based data[38] on CLBRs following a frozen-embryo or fresh-embryo transfer, followed by frozen–thawed embryo-transfer approach (see *Chapter 1, Modelling of subsequent frozen-embryo transfers*, for details).

Appendix 10 Cost-effectiveness acceptability curves for model-based sensitivity analysis

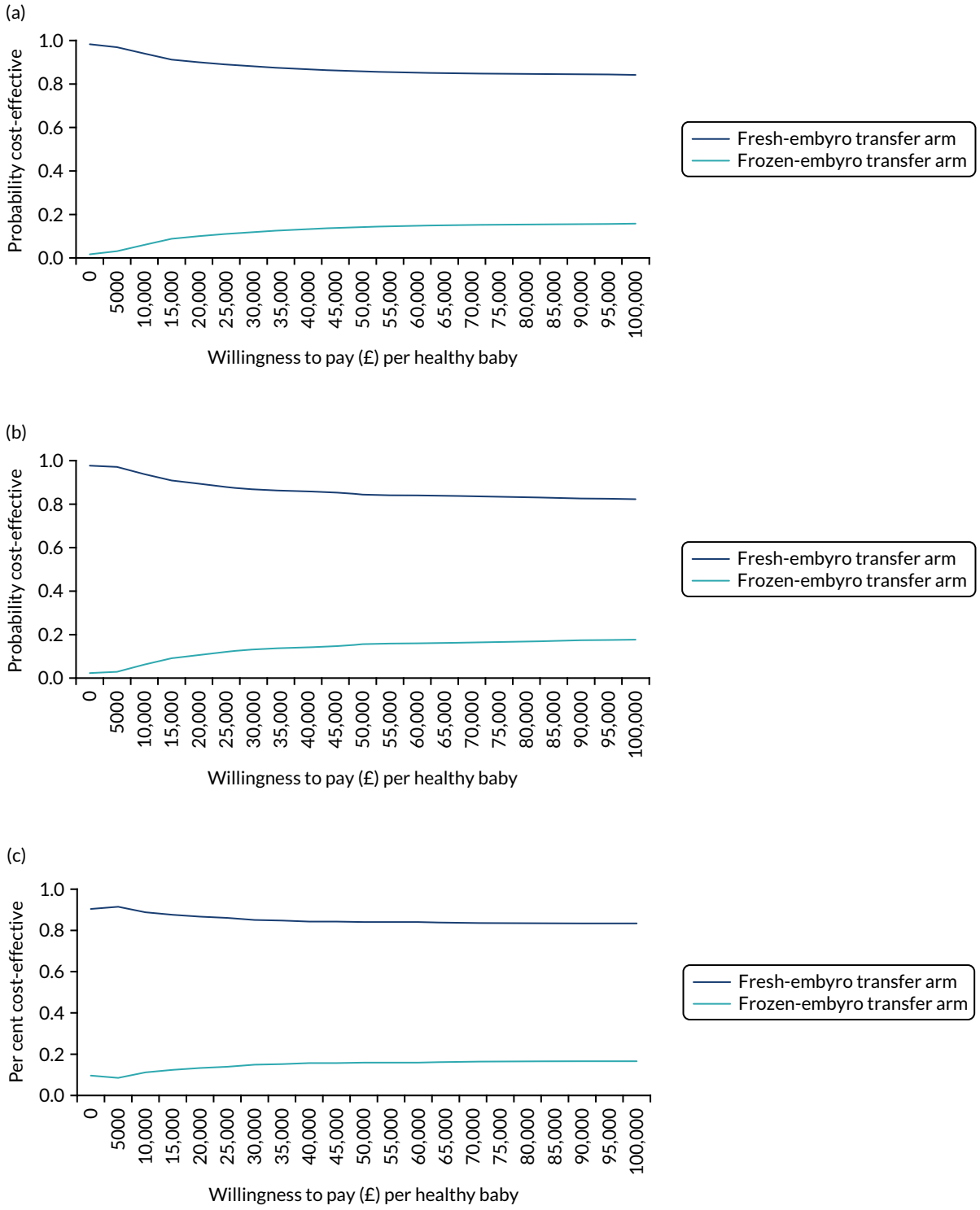

FIGURE 20 Cost-effectiveness acceptability curves for model-based sensitivity analysis. (a) Base case; (b) no discontinuation among those eligible for subsequent embryo transfer; and (c) using the lower ultrasound scan cost (£53) to cost transvaginal scans. Reproduced from Maheshwari *et al.*,[23] Elective freezing of embryos versus fresh embryo transfer in IVF: a multicentre randomized controlled trial in the UK (E-Freeze), *Human Reproduction*, 2022, deab279, by permission of European Society of Human Reproduction and Embryology.

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