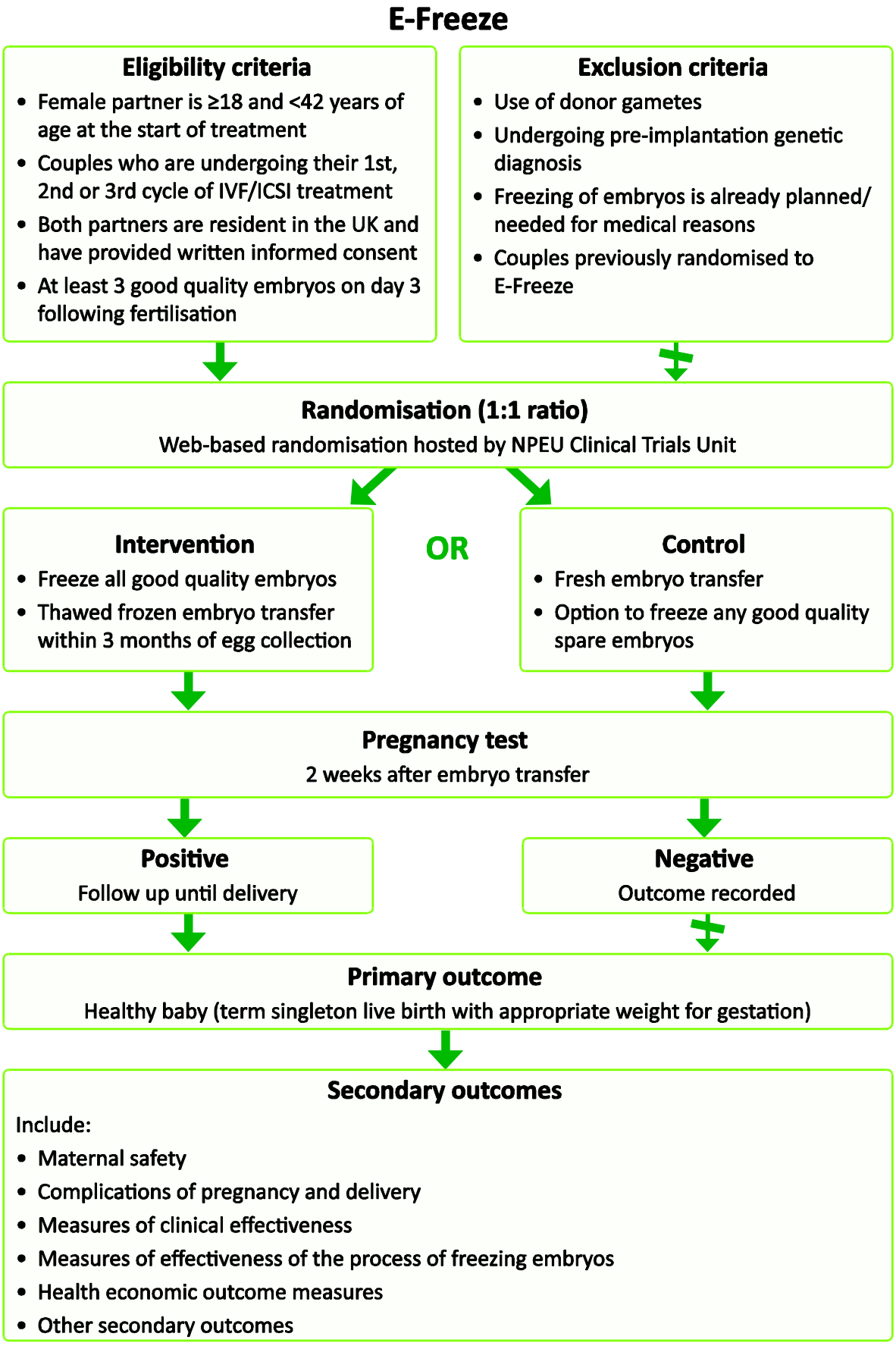
Study Protocol

Full Title:	**Freezing of embryos in assisted conception:** a randomised controlled trial evaluating the clinical and cost-effectiveness of a policy of freezing embryos followed by thawed frozen embryo transfer, compared with a policy of fresh embryo transfer in women undergoing in vitro fertilisation.
Study Acronym:	**E-Freeze**
Sponsor:	**University of Aberdeen & NHS Grampian**
Funder:	NIHR HTA Programme
Chief Investigator:	Dr Abha Maheshwari
REC Reference Number:	15/NS/0114
R&D Reference Number:	180950
ISRCTN / Clinicaltrials.gov No:	ISRCTN61225414


E-Freeze
Eligibility criteria
Female partner is ≥18 and <42 years of age at the start of treatment
Couples who are undergoing their 1st, 2nd or 3rd cycle of IVF/ICSI treatment
Both partners are resident in the UK and have provided written informed consent
At least 3 good quality embryos on day 3 following fertilisation
Exclusion criteria
Use of donor gametes
Undergoing pre-implantation genetic diagnosis
Freezing of embryos is already planned/ needed for medical reasons
Couples previously randomised to E-Freeze
Randomisation (1:1 ratio)
Web-based randomisation hosted by NPEU Clinical Trials Unit
Intervention
Freeze all good quality embryos
Thawed frozen embryo transfer within 3 months of egg collection
OR
Control
Fresh embryo transfer
Option to freeze any good quality spare embryos
Pregnancy test
2 weeks after embryo transfer
Positive
Follow up until delivery
Negative
Outcome recorded
Primary outcome
Healthy baby (term singleton live birth with appropriate weight for gestation)
Secondary outcomes
Include:
Maternal safety
Complications of pregnancy and delivery
Measures of clinical effectiveness
Measures of effectiveness of the process of freezing embryos
Health economic outcome measures
Other secondary outcomes

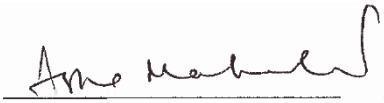
Contents

1 Protocol Approval

Freezing of embryos in assisted conception: a randomised controlled trial evaluating the clinical and cost-effectiveness of a policy of freezing embryos followed by thawed frozen embryo transfer, compared with a policy of fresh embryo transfer in women undergoing in vitro fertilisation.

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

ABHA MAHESHWARI Chief Investigator	 Signature	13/02/2017 Date
Pollyanna Hardy Individual Responsible for Statistical Review	 Signature	13th February 2017 Date

2 Synopsis

Trial Acronym	E-Freeze
Trial Long Title	**Elective Freezing of embryos in assisted conception**: a randomised controlled trial evaluating the clinical and cost-effectiveness of a policy of freezing embryos followed by thawed frozen embryo transfer, compared with a policy of fresh embryo transfer in women undergoing in vitro fertilisation.
Clinical Phase	Phase III
Trial Design	Multi-centre, randomised controlled trial
Trial Participants	Couples undergoing their 1st, 2nd or 3rd cycle of IVF/ICSI treatment at fertility centres in the UK
Inclusion Criteria	• The female partner is ≥ 18 and < 42 years of age at the start of treatment (i.e. start of ovarian stimulation) • Couples who are undergoing their 1st, 2nd or 3rd cycle of in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment • Both partners are resident in the UK • Both partners have provided written informed consent • At least 3 good quality embryos on day 3 following fertilisation
Exclusion Criteria	• Donor gametes are used • Pre-implantation genetic testing is planned • Elective freezing of all embryos is planned for medical reasons (e.g. severe risk of OHSS/fertility preservation) • Couples previously randomised to E-Freeze
Planned Sample Size	1,086 couples
Interventions	• Standard care arm: Women will undergo fresh embryo transfer at the cleavage or blastocyst stage according to local protocols. • Intervention arm: All good quality embryos will be frozen according to local protocols. Women will be contacted by their embryologist/research nurse (or delegate) after randomisation and arrangements will be made for frozen embryo transfer (typically after 4 to 6 weeks and always within 3 months of the egg retrieval process). The couples will attend for a clinic

	visit and additional monitoring visits before thawed frozen embryo transfer is performed.
Primary Objective	The primary objective of the trial is to determine if a policy of freezing embryos, followed by thawed frozen embryo transfer results in a higher healthy baby rate when compared with the current policy of transferring fresh embryos.
Secondary Objectives	The secondary objectives of the trial are 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: 1. Fewer complications associated with IVF/ICSI treatment and pregnancy 2. Greater cost-effectiveness from a health service and broader societal perspective
Primary Outcome	The primary outcome is a healthy baby.
Secondary Outcomes	**Maternal safety outcome** • Ovarian hyperstimulation syndrome (OHSS) **Complications of pregnancy and delivery outcomes** • Vanishing twin or triplet (defined as either: 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 (chronic hypertension, pregnancy induced hypertension, pre-eclampsia and eclampsia) • Most severe hypertensive disorder (from least to worst: chronic hypertension, pregnancy induced hypertension, pre-eclampsia and eclampsia)

	• Antepartum haemorrhage (any bleeding per vaginum after 28 weeks of pregnancy including placenta praevia and placental abruption) • Onset of labour (spontaneous, induced or planned caesarean section) • Mode of delivery for each baby (normal vaginal delivery, instrumental vaginal delivery or caesarean section) • Preterm delivery (defined as delivery at < 37 completed weeks) • Very preterm delivery (defined as delivery at < 32 completed weeks) • Low birth weight (defined as weight < 2,500 g at birth) • Very low birth weight (defined as weight < 1,500 g at birth) • High birth weight (defined as weight > 4,000 g at birth) • Large for gestational age (defined as birth weight > 90th centile for gestational age at delivery, based on standardised charts) • Small for gestational age (defined as birth weight < 10th centile for gestational age at delivery, based on standardised charts) • Congenital anomaly/birth defect (all congenital anomalies/birth defects identified will 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 will count as one) • 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 six and eight weeks gestation; ectopic pregnancy counts as a clinical pregnancy; 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 • Failure of all embryos to survive after 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 male partners)

3 ABBREVIATIONS

ACE	Association of Clinical Embryologists
AE	Adverse Event
AGA	Appropriate for gestational age
CI	Chief Investigator
CIG	Co-Investigator Group
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GDM	Gestational Diabetes Mellitus
GP	General Practitioner
HFEA	Human Fertilisation and Embryology Authority
HTA	Health Technology Assessment
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilisation
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPEU CTU	National Perinatal Epidemiology Unit Clinical Trials Unit
OHSS	Ovarian Hyperstimulation Syndrome
PI	Principal Investigator
PIL	Participant Information Leaflet
PMG	Project Management Group
R&D	NHS Trust Research and Development Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
TSC	Trial Steering Committee

4 SUMMARY

In vitro fertilisation (IVF) involves several steps. Initially, hormones are used to stimulate a woman's ovaries to produce eggs which are harvested surgically. Next, embryos are created in the laboratory by mixing eggs with sperm produced by her partner, in conventional IVF; these are grown in culture for a few days before being replaced within the uterus by a process known as fresh embryo transfer. Spare embryos are usually frozen with a view to transfer at a later point in time – especially if the initial fresh transfer does not result in a pregnancy. Despite improvements in technology, IVF success rates remain low with an overall live birth rate of 25% per treatment. Additionally, there are concerns about health outcomes for mothers and babies conceived through IVF, particularly after fresh embryo transfer, including maternal ovarian hyperstimulation syndrome (OHSS) and perinatal morbidity.

It is believed that high levels of ovarian hormones during ovarian stimulation could create a relatively hostile environment for embryo implantation whilst increasing the risk of OHSS. It has been suggested that electively freezing embryos with the intention of thawing and replacing them within the uterus at a later stage (thawed frozen embryo transfer) instead of fresh embryo transfer, may lead to improved pregnancy rates and fewer complications. However, the existing evidence in support of an elective frozen embryo transfer policy, derived from three small randomised trials is inadequate to justify such a radical change in practice.

A two-arm parallel group randomised controlled trial is proposed across multiple fertility centres in the UK. Women ≥ 18 and < 42 years of age undergoing their first, second or third IVF/ICSI treatment, with at least 3 good quality embryos will be randomised to either fresh embryo transfer (standard treatment arm) or thawed frozen embryo transfer, this typically will take place after 4 to 6 weeks and always within 3 months of egg retrieval (intervention treatment arm).

A single episode of thawed frozen embryo transfer (after elective freezing of embryos) will be compared to a single episode of fresh embryo transfer with a healthy baby (defined as a live singleton baby born at term with an appropriate weight for gestation) – the primary outcome.

With 90% power and a two-sided 5% level of statistical significance, we will need to randomise 1,086 couples (543 in each arm) to show an absolute difference in the primary outcome of at least 9% (e.g. from 25% to 34%), between fresh and thawed frozen embryo transfer respectively.

A full economic evaluation will assess the costs and consequences of the new strategy compared with standard practice. The trial data will be combined with modelling to estimate the long term costs of health and social care using a previously developed decision analytic model.

5 INTRODUCTION

5.1 Background

Infertility is common, affecting 1 in 7 couples in the UK. The National Institute for Health and Care Excellence (NICE) recommends IVF as the definitive treatment for prolonged unresolved infertility[1]. In 2013, over 49,000 women received over 64,600 IVF treatment cycles in the UK, resulting in over 20,000 pregnancies (www.hfea.org.uk).

IVF treatment involves a number of consecutive steps. Initially each woman is treated with hormones to encourage the development of 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 from the male partner and incubated to create embryos. Conventionally, these embryos are allowed to develop in the laboratory for a few days before one or two of them is/are selected for transfer into the uterus (fresh embryo transfer). Additional embryos are frozen and stored for replacement at a later date without the need for ovarian stimulation.

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: IVF success rates remain modest with a mean live birth rate of 25% per treatment involving a fresh embryo transfer. Data from the American and European Registries suggest that there has been no improvement in IVF live birth rates over the last 3 years.
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 IVF treatments, 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 compared to those associated with natural conception. A systematic review[2] has shown that babies conceived following IVF are more likely to die during the perinatal period (risk ratio [RR], 95% confidence interval [CI]: 1.87, 1.48 to 2.37), deliver preterm (RR, 95% CI: 1.54, 1.47 to 1.62), have low birth weight (RR, 95% CI: 1.65, 1.56 to 1.75) and have congenital anomalies (RR, 95% CI: 1.67, 1.33 to 2.09) when compared with babies conceived without IVF treatment. Women who become pregnant as a result of IVF are more likely to develop pre-eclampsia (RR, 95% CI: 1.49, 1.39 to 1.59), bleeding in pregnancy (RR, 95% CI: 2.49, 2.30 to 2.69), diabetes (RR, 95% CI: 1.48, 1.33 to 1.66) and require caesarean section (RR, 95% CI: 1.56, 1.51 to 1.60) when compared to those after natural conception.

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[1] has meant that the NHS burden of dealing with its short and long term complications is a serious and growing problem.

5.2 Rationale

A possible cause for sub-optimal live birth rates as well as adverse maternal and perinatal outcomes following IVF is the impact of 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. It has been suggested that avoiding embryo transfer at a time when the uterus is less receptive could improve success rates. Such a strategy also reduces the risk of OHSS by ensuring that a pregnancy does not occur in the presence of hyper stimulated ovaries.

A systematic review of observational data[3] has shown that babies conceived from frozen embryos have a reduced risk of perinatal morbidity (RR, 95% CI: 0.68, 0.48 to 0.96) and preterm delivery (RR, 95% CI: 0.84, 0.78 to 0.90) and the risk of severe OHSS is greatly reduced, making IVF safer and more effective for women and babies.

Preliminary data from small randomised trials from Iran[4] and the USA[5, 6] suggest that a strategy of not replacing embryos when they are created but freezing them followed by thawed frozen embryo transfer into the uterus at a later date improves pregnancy rates. A meta-analysis of data from these three RCTs[7]

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.
- 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 by intention-to-treat and conduct, since all involved co-interventions which were not accounted for in the analysis.

One of the publications[4] has been retracted on the grounds of serious methodological flaws. Hence, the current evidence base comprising two small trials of suboptimal quality is not sufficiently robust to support a radical change in clinical practice. Additionally, their results cannot be directly applied to a UK setting due to very different regulatory and funding arrangements. There is, therefore, an urgent need to perform a definitive randomised controlled trial in the UK evaluating elective freezing of embryos followed by subsequent thawed frozen embryo transfer in terms of clinical and cost-effectiveness.

6 STUDY OBJECTIVES

6.1 Primary Objective

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

6.2 Secondary Objectives

The secondary objectives of the trial are 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

7 OUTCOMES

7.1 Primary Outcome

The primary outcome is a healthy baby.

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

7.2 Secondary Outcomes

The secondary outcomes are separated by 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 (OHSS) – defined and classified as per the Royal College of Obstetricians and Gynaecologists (RCOG) green top guidelines[8].

Complications of pregnancy and delivery outcomes

- Vanishing twin or triplet (defined as either: 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 still births)
- Hypertensive disorders of pregnancy (chronic hypertension, pregnancy induced hypertension, pre-eclampsia and eclampsia)
- Most severe hypertensive disorder (from least to worst: chronic hypertension, pregnancy induced hypertension, pre-eclampsia and eclampsia)
- Antepartum haemorrhage (any bleeding per vaginum after 28 weeks of pregnancy including placenta praevia and placental abruption)
- Onset of labour (spontaneous, induced or planned caesarean section)

- Mode of delivery for each baby (normal vaginal delivery, instrumental vaginal delivery or caesarean section)
- Preterm delivery (defined as delivery at < 37 completed weeks)
- Very preterm delivery (defined as delivery at < 32 completed weeks)
- Low birth weight (defined as weight < 2,500 g at birth)
- Very low birth weight (defined as weight < 1,500 g at birth)
- High birth weight (defined as weight > 4,000 g at birth)
- Large for gestational age (defined as birth weight > 90th centile for gestational age at delivery, based on standardised charts)
- Small for gestational age (defined as birth weight < 10th centile for gestational age at delivery, based on standardised charts)
- Congenital anomaly/birth defect (all congenital anomalies/birth defects identified will 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 will count as one)
- 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 six and eight weeks gestation; ectopic pregnancy counts as a clinical pregnancy; 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
- Failure of all embryos to survive after 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 male partners)

8 STUDY DESIGN

8.1 Study Description

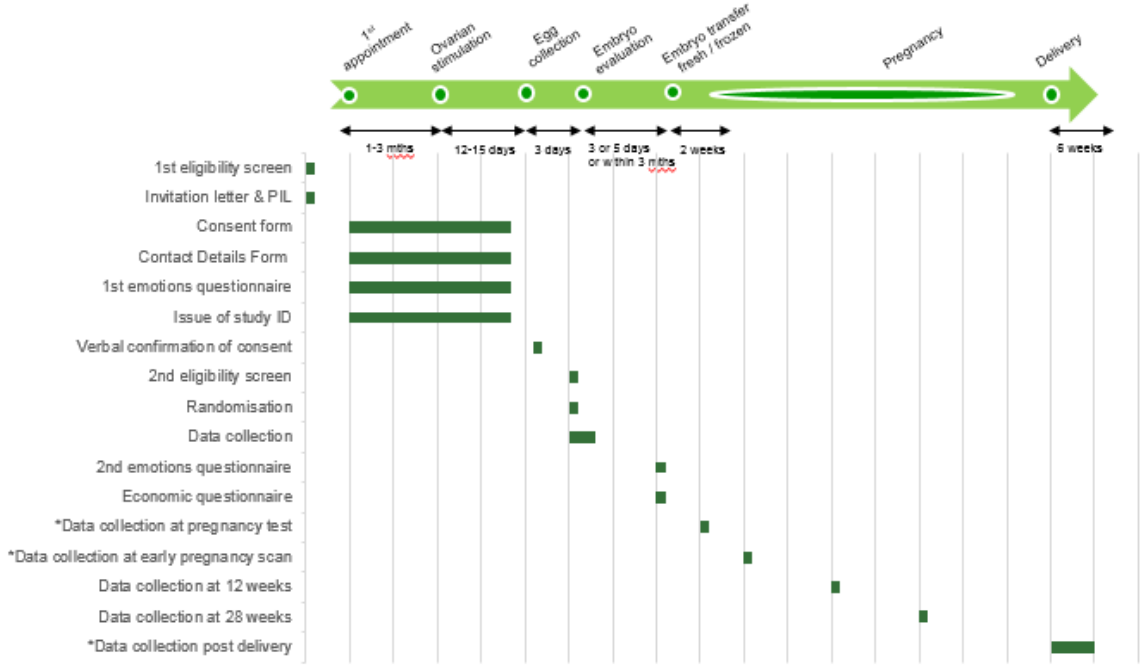
This study is a pragmatic multi-centre two arm parallel group randomised controlled trial to evaluate the effectiveness of the proposed intervention using the most rigorous gold standard experimental methodology in real-life conditions. As with most multi-centre RCTs, there is variability in procedures carried out across centres. All clinical elements of IVF treatment, apart from the randomised interventions, will be carried out according to local protocols.

- All couples embarking on their 1st, 2nd or 3rd cycle of IVF, ICSI or a combination of both will receive a letter of invitation, introducing the trial; plus a copy of the Participant Information Leaflet. This will be sent with their clinic appointment.
- Participant Information Leaflets also will be distributed to couples attending an introductory patient information session which will occur before their first clinic appointment.
- Eligible couples will be invited by a clinician involved in their care to participate in the trial. They will have the opportunity to speak to a research nurse to ask questions.
- Consent forms need to be signed by both partners. This can be done at their clinic appointment or at a subsequent visit up until but prior to the procedure of egg collection.
- After consent, couples will each fill in a short questionnaire on how they are feeling emotionally. Each participant will seal their questionnaire in an envelope after completion and questionnaires will be destroyed unopened if the couple do not proceed to randomisation.
- Data needed for randomisation/minimisation will be recorded by the consent and randomisation program.
- On the 1st day after egg collection the embryologist or research delegate will confirm consent during a routine phone call to the couple to discuss outcome of fertilisation.
- On the 3rd day after egg collection couples with at least 3 good quality embryos will be randomised by the embryologist or research nurse to fresh or frozen embryo transfer.

- Couples who are randomised to delayed transfer will be contacted by the research nurse or research delegate within 3 working days post-randomisation to plan thawed frozen replacement treatment typically 4 to 6 weeks later and always within 3 months of egg collection.
- At embryo transfer (cleavage or blastocyst for fresh, or typically 4 to 6 weeks later for frozen embryo transfer but always within 3 months) couples will be asked to complete a short questionnaire to assess additional costs related to the treatment, and to repeat the emotions questionnaire they filled in at consent.

Women who have a positive pregnancy test 2 weeks (+/- 3 days) after embryo transfer will be contacted by their research nurse (by telephone) to record pregnancy events and outcomes at: 12 and 28 weeks of gestation and again around 6 weeks after delivery. Outcomes presenting themselves > 6 weeks post-delivery will not be 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 to the regulatory body, the Human Fertilisation Embryology Authority (HFEA), including stillbirth, congenital anomalies and perinatal mortality. Usually this information is provided to each IVF clinic by couples themselves. Alternatively, clinic staff contact couples by telephone to collect this information to report it back to the HFEA.

8.2 Study Matrix



*Routinely collected as part of regulatory requirement

9 STUDY POPULATION

9.1 Number of Participants

1,086 couples undergoing their 1st, 2nd of 3rd cycle of IVF/ICSI treatment at fertility centres in the UK.

9.2 Inclusion Criteria

- The female partner is ≥ 18 and < 42 years of age at the start of treatment (i.e. start of ovarian stimulation)
- Couples who are undergoing their 1st, 2nd or 3rd cycle of IVF/ICSI treatment
- Both partners are resident in the UK
- Both partners are able to provide written informed consent
- At least 3 good quality embryos (as defined by the Association of Clinical Embryologists, UK) on day 3 after egg collection (day of egg collection is counted as day 0). Good quality embryos on day 3 are defined as those with 6–8 cells grade 3/3 or above using the agreed national grading scheme.[9]

Couples can be on their 1st, 2nd or 3rd cycle, where a cycle is defined as egg collection following ovarian stimulation.

9.3 Exclusion Criteria

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

10 PARTICIPANT SELECTION AND ENROLMENT

10.1 Identifying Participants

Potentially eligible couples will be identified from IVF clinic case notes. An invitation letter and participant information leaflet will be mailed to eligible couples prior to their clinic appointment. A participant information leaflet will also be given at patient information / open evenings attended by couples preparing for their fertility treatment. This is usually at least 24 hours prior to their clinic appointment. Eligible couples will be approached by a clinician involved in their care and invited to

participate in the trial. Those interested in participating will be able to discuss the study with a research nurse on the same day or at a later date.

10.2 Consenting Participants

Informed consent for the study will be obtained from both partners by an appropriately delegated member of the study team. Contact details and baseline characteristics necessary for randomisation will be recorded by the research nurse immediately after consent is obtained. Consent will be obtained before the procedure of egg collection. Consent will be confirmed by telephone during a routine phone call from the embryologist or research delegate informing the couple of the fertilisation results (the day after egg collection). Couples that may have previously consented to take part in E-Freeze, during their first or second cycle of IVF, will still be eligible to participate in E-Freeze if they were not previously randomised into the trial. For couples that have previously been consented but not randomised to the trial, informed consent will be re-obtained for any participation during future cycles and a new study number will be generated.

10.3 Screening for Eligibility

A final eligibility check will be carried out on day 3 post egg retrieval. Women with a minimum of 3 good quality embryos (as determined by national guidance from the Association of Clinical Embryologists in the UK)[9] will be randomised to receive either fresh embryo transfer (current standard practice-control arm) or elective freezing of all good quality embryos followed by subsequent transfer of thawed embryos within 3 months (intervention arm).

Good quality embryos on day 3 are defined as those with 6–8 cells grade 3/3 or above using the agreed national grading scheme.[9]

10.4 Ineligible and Non-Recruited Participants

Details of all consenting couples will be entered on a dedicated secure online database. It is anticipated that a proportion of those consented may not proceed to randomisation; the reasons for this will be recorded (if available) including non-availability of three good quality embryos on day 3. As part of routine practice, the embryologist contacts the couple by telephone to let them know how many eggs are fertilised (next day after egg collection, day 1) and the quality of their embryos (on day 3 after egg collection). The embryologist or research delegate will confirm consent on day 1 and inform them whether or not they fulfilled the final inclusion criteria (at least 3 good quality embryos on day 3) and

which arm they have been randomised to at the time of their routine phone call on day 3. The research nurse will then contact the couple if they have not fulfilled the inclusion criteria to answer any queries and offer follow-up in the clinic. Couples not proceeding to randomisation will be offered the most appropriate standard treatment. All clinics have access to supportive counselling as a mandatory requirement of the regulatory authority.

10.5 Randomisation and Blinding

10.5.1 Randomisation

Randomisation will be performed after the creation of embryos, 3 days post egg collection. This will minimise the randomisation-to-intervention time interval as embryos are either transferred at the cleavage or blastocyst stage. Once all eligibility criteria are established (including ensuring that three or more good quality embryos are available), women will be randomised (allocation ratio 1:1) to a strategy of either:

Fresh embryo transfer

or

Elective freezing of embryos followed by thawing and replacement at a later date (typically 4 to 6 weeks later and always within 3 months of egg collection)

Randomisation will be undertaken by the research nurse or a delegated member of the research team using a secure web-based centralised system (with 24/7 telephone backup 365 days/year) hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU), University of Oxford (ensuring allocation concealment). The randomisation will employ 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 (cycles).

10.6 Treatment Allocation

Blinding of the allocated intervention is not possible in this trial because of the nature of the treatments and statutory requirements of the regulatory body – the HFEA.

Discussion with the couple about the time and day of embryo transfer is routinely conducted over the telephone on the third day after fertilisation of eggs in the laboratory in all IVF clinics as part of routine

care. A member of the IVF laboratory (embryology) team or research delegate will inform consented eligible couples on day 3 of the outcome of randomisation over the telephone.

The process will be as follows:

- Standard care arm: Women will undergo fresh embryo transfer at the cleavage or blastocyst stage according to local protocols.

- Intervention arm: All good quality embryos will be frozen according to local protocols. Women will be contacted by their research nurse after randomisation and arrangements will be made for thawed frozen embryo transfer (typically this takes place within 4 to 6 weeks and always within 3 months of the egg retrieval process). This will involve a few visits to hospital to prepare the endometrium.

10.6.1 Follow-up

A pregnancy test will be carried out in all randomised women 2 weeks (+/- 3 days) after embryo transfer. All women who have a positive pregnancy test at 2 weeks (+/- 3 days) will undergo 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.

Those who have a positive pregnancy test will be followed up by the research nurse or a delegated member of the research team (by telephone) to record pregnancy outcomes and complications in pregnancy at around 12 and 28 weeks of gestation and again around 6 weeks after delivery. Outcomes presenting themselves > 6 weeks post-delivery will not be recorded.

Those who have a negative pregnancy test will not be followed up any further as part of this trial.

10.6.2 Withdrawal Procedures

Couples will be able to withdraw their consent to take part in the trial at any time without giving a reason. Withdrawal from the intervention/study will not affect their ongoing care. If consent is withdrawn, permission will be sought to use data already collected up to the point of withdrawal and to complete follow-up outcomes data collection.

Non-adherence to the allocated intervention may also occur; this is defined as a difference between the treatment allocation provided at randomisation and the allocation received by the woman at the time of embryo transfer. Non-adherence to the allocated intervention may occur if the clinician feels it is in the couple's best interests, e.g. freezing all created embryos is necessary for medical reasons, or transferring fresh embryos for clinical reasons. In the case of a non-adherence to the allocated intervention, the couple, with their on-going consent, would continue to be part of the trial, with outcome data collected in the routine manner.

11 SAFETY REPORTING

A Data Monitoring Committee (DMC) will be established to ensure the wellbeing of study participants. The DMC will periodically review study progress and outcomes as well as reports of unexpected SAEs. The DMC will, if appropriate, make recommendations regarding continuance of the study or modification of the study protocol.

11.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a participant, which does not necessarily have to have a causal relationship with this intervention. Due to the high incidence of adverse events routinely expected in this patient population (e.g. abnormal laboratory findings, new symptoms, etc.), only those adverse events identified as serious will be recorded for the trial.

11.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

The term 'severe' is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance. This is not the same as 'serious', which is based on participant/event outcome or action criteria usually associated with events that pose 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 if it were more severe. Medical and scientific judgement should be exercised in deciding whether an adverse event is serious in other situations.

11.3 Foreseeable Serious Adverse Events

Foreseeable SAEs are those events which are expected in the patient population or as a result of the routine care/treatment of a patient. The following events are foreseeable in women or couples undergoing IVF treatment and as such do not require reporting as SAEs. Foreseeable SAEs will be collected on the eCRF as part of routine data collection.

Events relating to the female partner, or couple:

- Ovarian hyperstimulation syndrome (OHSS)
- Miscarriage
- Hypertensive disorders of pregnancy
- Antepartum haemorrhage
- Gestational Diabetes Mellitus (GDM)
- Multiple pregnancy
- Failure of any embryos to survive thawing

Events relating to the baby, when born:

- Low birth weight
- Very low birth weight
- Large for gestational age
- Preterm delivery
- Very preterm delivery
- Small for gestational age

11.4 Unforeseeable Serious Adverse Events

An unforeseeable SAE is any event that meets the definition of a SAE and is not detailed in the list above as foreseeable. The following unforeseeable SAEs must be reported:

- Maternal death

- Stillbirth
- Congenital anomaly detected antenatally or postnatally
- Neonatal death

Unforeseeable SAEs will be reported up to 6 weeks post-delivery. They will be reported to the NPEU CTU as soon as possible after staff at the site become aware of the event. SAEs can be reported in one of the following ways:

i) using the Clinical Database OpenClinica, only staff with access to OpenClinica may report SAEs in this way, site staff will be required to print off the OpenClinica SAE form and obtain the information and signature of the Study Clinician carrying out the causality assessment. The completed signed SAE form must be emailed or faxed to NPEU CTU. NPEU CTU staff will automatically be informed via email of any SAEs reported electronically.

ii) by completing an SAE form which is emailed or faxed to NPEU CTU. Paper copies will be available with the trial documentation to enable anyone to report an SAE. Guidance for the research site is provided on the paper SAE reporting form.

iii) if it is not possible to report an SAE as detailed in points (i) and (ii), the unforeseeable SAE may be reported by telephone and the SAE form will be completed by staff at the NPEU CTU.

If any additional information regarding the SAEs becomes available this will be detailed on a new SAE form and also emailed or faxed to NPEU CTU or reported electronically using OpenClinica.

The SAE form will be copied to the Sponsor by NPEU CTU as soon as possible after receipt. The Chief Investigator will assess whether a serious adverse event (SAE) was 'related' (resulted from administration of any of the research procedures) and 'unforeseeable' in relation to those procedures. Any reports of related and unforeseeable SAEs should be submitted to the REC that gave a favourable opinion of the study, the Sponsor and the centre where the SAE occurred, within 15 working days of the Chief Investigator becoming aware of the event.

All recorded SAEs will be reviewed by the DMC at regular intervals. The CI will inform all PIs concerned of relevant information that would adversely affect the safety of the participants.

11.5 Data Collection

Data for both clinical and economic outcomes will be collected using bespoke eCRFs and entered directly into the study's OpenClinica electronic database by the centre's research staff. Data will be single-entered only and at the point of entry the data will undergo a number of validation checks to verify the validity and completeness of the data captured.

After consent and at embryo transfer, the couples will each complete a short paper-based questionnaire asking them how they are feeling.

A short questionnaire will be provided for each partner to record details of time and travel expenses accrued during their treatment as part of the economic evaluation. This is to be completed at the time of embryo transfer.

12 STATISTICS AND DATA ANALYSIS

12.1 Sample Size Calculation

The proposed primary outcome for this trial is novel and is not currently reported by IVF clinics or national regulatory bodies. This means that a number of assumptions have been made in order to determine the expected event rate in the control arm (receiving current standard treatment), which may in turn result in a degree of imprecision in the estimate.

The most recent data from the HFEA[10], which collects data on all IVF cycles from all clinics in the UK, show 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 figures are 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 are similar[11]. No data are available regarding the healthy baby rate (live singletons born between 37 and 42 weeks' with appropriate weight for gestation), the primary outcome for this study. For our trial population we anticipate that the control arm event rate is likely to be less than 25%, possibly as low as 17%.

To provide relevant information regarding the event rate expected in the control arm, we surveyed 10 IVF centres that expressed an interest in the study, collecting data on the number of live births in women under the age of 42 undergoing their first IVF treatment in 2012. The average live birth episode rate from

this survey was 31% with a 95% confidence interval of 25% to 37%. Accurate data on the healthy baby rate in those with at least 3 good quality embryos were not available. Although the live birth rate is expected to be higher in women with at least 3 good quality embryos (likely to have a better prognosis), we anticipate that the **healthy baby rate** in our trial population will be towards the lower end of the confidence interval, around 25%, taking into account the higher risk of preterm delivery and small for gestational age babies following IVF[2].

The following assumptions have been made for the sample size calculation:

We have assumed a healthy baby rate of between 17% and 25% in women eligible for the trial (age under 42 years with 3 good quality embryos) undergoing standard care (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 panel of clinicians across the UK agreed that the strategy of freezing embryos would be considered effective if the percentage of women having a healthy baby is increased by at least 8% in absolute terms. With 90% power and using a two-sided 5% level of statistical significance, we will need to randomise a total of 1,086 couples (543 in each group) in order 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, between fresh embryo transfer and transfer of thawed frozen embryos. The difference detectable differs slightly depending on the event rate in the standard care group, which will be reviewed periodically by the DMC.

It is a regulatory requirement for clinics in the UK to report live birth outcomes (including number, weight and gestation) after all embryo transfers i.e. there will be no loss to follow-up. Therefore, we have not taken into account loss to follow-up for these sample size calculations.

It is anticipated that a proportion of those consented may not reach randomisation (e.g. those not having 3 good quality day 3 embryos or requiring all embryos to be frozen for medical reasons), therefore a higher number will need to be consented. As there are no valid data to support the exact proportion, this will be monitored by the DMC.

12.2 Analysis

A detailed Statistical Analysis Plan (SAP) will be developed in-house and agreed by the Trial Steering Committee (TSC) before the analysis is undertaken. The analysis and presentation of results will follow the most up-to-date recommendations of the CONSORT group.

Baseline demographic factors and clinical characteristics of the woman will be summarised with counts and percentages for categorical variables, means (with standard deviations) for normally distributed continuous variables, or medians (with interquartile ranges) for other continuous variables.

All outcomes will be analysed in the groups to which they are assigned, regardless of deviation from the protocol or treatment received under the intention-to-treat analysis principle.

All comparative analyses will adjust for the minimisation factors wherever possible. Binary outcomes will be analysed using a log binomial regression model, or using a log Poisson regression model with a robust variance estimator if the binomial model fails to converge. Linear regression will be used for normally distributed continuous outcomes and quantile regression for skewed continuous outcomes.

Comparative analyses will entail calculating the adjusted risk ratio (RR) and 95% confidence interval (CI) for the primary outcome, adjusted RRs and 99% CIs for all binary secondary outcomes, adjusted mean differences (with a 99% CI) for normally distributed continuous secondary outcomes, or median differences (99% CI) for skewed continuous secondary outcome variables (unless the data can be transformed to Normality).

For neonatal secondary outcomes (e.g. low birth weight, small for gestational age, congenital anomaly and perinatal mortality) the adjusted analysis will also account for the anticipated correlation in outcomes between multiple births.

12.2.1 Pre-specified subgroup analysis

The consistency of the effect of electively freezing embryos followed by thawed frozen embryo transfer on the primary outcome across specific subgroups will be assessed using the statistical test for interaction. Pre-specified subgroup analyses are (i) woman's age (test for trend), (ii) fertility clinic, (iii) cleavage vs blastocyst embryo transfer, (iv) single vs multiple embryo transfer, (v) number of previous embryo transfers.

12.2.2 Secondary analysis

The primary analysis for all primary and secondary outcomes will be by intention-to-treat. Secondary analyses will be performed to include the clinically relevant denominators such as:

- Miscarriage rate (per total number of women with a positive pregnancy test at 2 weeks +/- 3 days after embryo transfer)
- Gestational diabetes mellitus (per total number of pregnant women with an ongoing pregnancy resulting in delivery)
- Multiple pregnancy (per total number of pregnant women with an ongoing pregnancy resulting in delivery)
- Hypertensive disorders (per total number of pregnant women with an ongoing pregnancy resulting in delivery)
- Antepartum haemorrhage (per total number of pregnant women with an ongoing pregnancy resulting in delivery)
- Preterm delivery (< 37 completed weeks) (per total number of pregnant women with an ongoing pregnancy resulting in delivery)
- Very preterm delivery (< 32 completed weeks) (per total number of pregnant women with an ongoing pregnancy resulting in delivery)
- Low birth weight (< 2,500 g at birth) (per total number of babies born)
- Very low birth weight (< 1,500 g at birth) (per total number of babies born)
- High birth weight (> 4,000 g at birth) (per total number of babies born)
- Large for gestational age (> 90th centile) (per total number of babies born)
- Small for gestational age (< 10th centile) (per total number of babies born)
- Congenital anomaly/birth defect (per total number of babies born)
- Perinatal mortality (per total number of babies born)

Failure of embryos to survive after thawing (per embryo thawed) will be reported for the intervention group.

12.3 Economic Evaluation

A formal economic evaluation will be undertaken to assess the cost-effectiveness of the alternative approaches to treatment used in the trial. Resource use and costs will be estimated primarily from a health and personal social services perspective. However, personal time and travel costs, associated with any additional treatment-related visits which are not part of standard routine practice, will also be estimated via a short questionnaire administered at the time of embryo transfer. This is to be completed

by both partners. In addition, longer-term social costs associated with child health outcomes will be modelled based on existing literature.

Trial data collection instruments (eCRFs) will be 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. Appropriate unit costs[12, 13] will be used to value resource use events recorded in the case report forms. These costs will be summarised by treatment allocation group (by intention-to-treat), and presented in relation to the primary and secondary clinical outcomes. A cost-consequence balance sheet will be constructed to highlight the favoured strategy on cost and each clinical outcome at 12 months. The extra cost per additional healthy baby delivered (in the thawed frozen embryo transfer group versus fresh embryo transfer) will also be estimated using linear regression with adjustment for minimisation variables and baseline covariates as appropriate.

Many couples who fail to conceive following the initial embryo transfer will have access to subsequent frozen/thawed transfers, although the costs and outcomes associated with these will not be captured within the trial follow-up. Additionally, some adverse birth outcomes (e.g. preterm delivery, low birth weight) can have a far reaching impact on costs and child health outcomes. Modelling will therefore be used to inform cost-effectiveness over an extended time horizon. In order to do this, we will adapt an existing decision model[14] to simulate the progression of couples (who do not experience live birth following their initial embryo transfer) to the subsequent transfer of their remaining frozen embryos. The model will also capture the longer-term cost and quality of life outcomes for any infants born as a result of treatment. The outputs of this modelling exercise will also be presented in the form of a cost-consequence balance sheet. Deterministic and probabilistic sensitivity analyses will be undertaken to characterise the uncertainty surrounding the estimated differences in costs and outcomes between approaches, and to assess the impact of changes in key model input parameters and assumptions.

13 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 Trial Steering Committee (TSC)

The role of the TSC is to provide the overall supervision of the study. The TSC should monitor the progress of the study and conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The TSC will consist of an independent chair and at least two other independent members. Committee members will be deemed to be independent if they are not involved in study recruitment and are not employed by any organisation directly involved in the study conduct. Representatives from relevant Patient/Public Involvement groups, the Chief Investigator and other Investigators/Co-applicants will be joined by observers from the NPEU CTU. The NIHR programme manager will be invited to attend all TSC meetings.

A TSC Charter will be prepared before and agreed at the first TSC meeting to document how the committee will operate.

13.2 Data Monitoring Committee (DMC)

A DMC independent of the applicants and the TSC will review the progress of the trial at least annually and provide advice on the conduct of the trial to the TSC who will report to the HTA programme manager. The committee will periodically review study progress and outcomes. The timings and content of the DMC reviews will be detailed in a DMC Charter, which will be agreed at its first meeting.
The DMC will consist of an independent chair and at least two other independent members, who will be experts in their field, such as an embryologist, statistician or an IVF clinician.

13.3 Project Management Group (PMG) and Clinical Investigators' Group (CIG)

The study will be supervised on a day-to-day basis by the Project Management Group (PMG). This group reports to the TSC, which has overall responsibility for the conduct of the study.

The core PMG will consist of the Chief Investigator and NPEU CTU staff which may include:

- Clinical Trials Unit Director
- Senior Trials Manager
- Senior Trials Programmer
- Trial Co-ordinator
- Senior Trial Statistician
- Administrator/Data Manager

The core PMG will meet regularly (at least monthly). The Co-Investigators Group (CIG) will meet at regular intervals through the duration of the trial; this will comprise all co-applicants and the members of the core PMG.

13.4 Trial Management

The trial co-ordinating centre will be at the NPEU CTU University of Oxford where the Trial Co-ordinator will be based. The NPEU CTU will be responsible for trial oversight, IT system/functions such as randomisation, clinical and administrative databases, all programming and statistical analyses, servicing both the DMC and TSC, and, in collaboration with the Chief Investigator and the Local Research Nurse for the general day-to-day running of the study including recruitment of sites and training of staff. A 24/7 (365 days a year) emergency helpline is available for out-of-hours queries relating to the trial. The economic analysis will be conducted at the University of Aberdeen.

13.5 Risk Assessment and Monitoring

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

14 CONFIDENTIALITY, DATA PROTECTION AND DATA MANAGEMENT

Direct access to source data/documents (including hospital records/notes, clinical charts, laboratory reports, pharmacy records and test reports) will be granted to authorised representatives from the NPEU CTU, the Sponsor and host organisations to permit study related monitoring, audits and inspections.

Overall responsibility for ensuring that each participant's information is kept confidential will lie with the study Sponsor who has delegated this responsibility to the NPEU CTU. All paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998). Data entered onto the eCRFs will be automatically transferred for storage in an electronic database hosted by NPEU CTU on behalf of the Sponsors, in which the participant will be identified only by a study specific number. The participant's name and any other identifying details will be stored in a separate database also held by NPEU CTU on behalf of the Sponsors which will be linked to the database containing study data only by the participant's study number. After the study has been completed and the reports published, the data will be archived. Electronic and paper documents will be archived by the NPEU using their secure archiving facilities, as detailed in NPEU Standard Operating Procedures.

Electronic files will be stored on a file server that has restricted access. The server is in a secure location and access is restricted to a few named individuals. Access to the building in which the NPEU CTU is situated is via an electronic tag and individual rooms are kept locked when unoccupied. Authorisation to access restricted areas of the NPEU CTU network is as described in the NPEU CTU security policy. Data will be processed on a workstation by authorised staff. The computer workstations access the network via a login name and password (changed regularly). No data are stored on individual workstations. Backing up is done automatically overnight to an offsite storage area. The location of the backup computer is in a separate department which has electronic tag access. Access to the room in which the backup machine is located is via a key-pad system.

15 STUDY CONDUCT RESPONSIBILITIES

15.1 Declaration of Helsinki

The Chief Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

15.2 Guidelines for Good Clinical Practice

The Chief Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the Guidelines for Good Clinical Practice.

15.3 Approvals

The trial will start after gaining approval from a Research Ethics Committee. NHS Trust Research and Development Office (R&D) will be sought for individual trial sites.

15.4 Protocol Amendments, Deviations and Breaches

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, NIHR HTA, REC and NHS R&D Office(s). Amendments to the protocol or other study documents will not be implemented without these approvals.

Incidents and protocol deviations will be reported as soon as possible to the NPEU CTU and assessed by the PMG. In the event that a serious breach is suspected the Sponsor must be contacted as soon as possible. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if

appropriate, the Sponsor will report it to the REC committee and the NHS host organisation within seven calendar days.

15.5 Insurance and Indemnity

The University of Aberdeen and Grampian Health Board are Co-Sponsoring this study. The University of Aberdeen will obtain and hold insurance policies for legal liabilities arising from the study. Grampian Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which covers the legal liability of Grampian in relation to the study.

The participating sites are all run as NHS units and have indemnity arrangements in place which will cover their liabilities in relation to their participation in the study. In the event that non-NHS sites join the study, the indemnity arrangement for these centres will be assessed to ensure appropriate cover is in place prior to the non-NHS site being approved to participate in the study.

15.6 Study Record Retention

All study documentation will be kept for at least 25 years after publication of the study results.

15.7 End of Study

The end of study is defined as database lock. This will occur when all data have been collected, cleaned and queries have been resolved. The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow-up is arranged for all participants. A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

16 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 Authorship Policy

Primary responsibility for preparing all output for publication will lie with the CI. A writing committee drawn from the co-investigators (trial grant holders), trial co-ordinators and others substantially involved in execution, analysis and interpretation will be named authors on the principal publications arising from the trial provided they meet the authorship criteria used by most high impact peer reviewed journals (see http://www.icmje.org).

Principal Investigators will be named formally as collaborators on the publication; other trial personnel with significant input to the running of the trial will be named in the Acknowledgements in publications. The Chief Investigator will nominate and agree appropriate authorship on all publications prior to commencement of writing.

16.2 Publication

The CI and NPEU CTU will co-ordinate dissemination of the results from this trial. All publications using data from this trial to undertake original analyses will be submitted to the TSC and to the Sponsor for review before release. The research will be submitted for publication in high impact, peer reviewed, scientific journals. More general dissemination of the results will be achieved through publication of summary findings. There are no commercial or intellectual rights issues that would delay publication of results.

16.3 Peer Review

The study has been peer reviewed internally (prior to submitting grant application) and was externally peer reviewed by the funder. After REC approval has been obtained, the intention is that this protocol will be submitted for publication and will be available for download via the NPEU website.

17 References

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