TRIAL PROTOCOL

UNiTY

A randomised controlled trial evaluating the clinical and cost effectiveness of Intra Uterine Insemination versus In-Vitro Fertilisation for **UN**explained **i**nfertili**TY**

Version Number:	***2.0***
Version Date:	***17 Jan 2024***

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

FUNDED BY

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PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version	Type of amendment	Summary of amendment

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Trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results are the responsibility of sponsor and their delegates, though the funder will monitor progress against key milestones via the submission of regular progress reports. The Funder of the trial has had no role in the trial design, data collection, data analysis or data interpretation.

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name	UNiTY: A randomised controlled trial evaluating the clinical and cost effectiveness of IUI versus IVF for UNexplained InfertiliTY
Protocol version number	2.0
Protocol version date	17 Jan 2024
CI name	Jackson C Kirkman-Brown
Signature and date	 01 Mar 2024

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the UNiTY trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the UNiTY trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018, Human Fertilisation and Embryology Act 2008 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name: Protocol version number:	UNiTY: A randomised controlled trial evaluating the clinical and cost effectiveness of IUI versus IVF for UNexplained InfertiliTY Version: 2.0
Protocol version date:	17 / Jan / 2024
PI name:	
Name of Site: Signature and date:	 _____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AMH	Anti Mullerian Hormone
ART	Assisted Reproductive Therapy (see MAR)
BCTU	Birmingham Clinical Trials Unit
BMI	Body Mass Index
BNF	British National Formulary
CACE	Complier Average Causal Effect
CASA	Computer-Aided Sperm Analysis
CCGs	Clinical Commissioning Groups – (older NHS commissioning term see ICB)
CEAC	Cost-Effectiveness Acceptability Curve
CI	Chief Investigator
COS	Controlled Ovarian Stimulation
CPI	Consumer Price Index
CRF	Case Report Form
CSQ-8	Client Satisfaction Questionnaire
DCEA	Distributional Cost-Effectiveness Analysis
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
EIA	Equity Impact Analysis
EQA	External Quality Assurance
GCP	Good Clinical Practice
HDD	Hard Disk Drive
HDU	High Dependency Unit
HFEA	Human Fertilisation & Embryology Authority
HRQoL	Heath-Related Quality of Life

HRA	Health Research Authority
HTA	Health Technology Assessment
ICB	Integrated Care Board (regional commissioning and integrating NHS services)
ICF	Informed Consent Form
ICU	Intensive Care Unit
ISF	Investigator Site File
IUI	Intra Uterine Insemination
IVF	In-Vitro Fertilisation
MAR	Medically Assisted Reproduction (newer term for ART)
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OHSS	Ovarian Hyperstimulation Syndrome
ONS	The Office for National Statistics
PALS	Patient Advice and Liaison Service
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
QPE	Qualitative Process Evaluation
RCT	Randomised Controlled Trial
QPE	Qualitative Process Evaluation
REC	Research Ethics Committee
RGT	University of Birmingham Research Governance Team
RR	Relative Risk
SAE	Serious Adverse Event
TMF	Trial Master File

TMG	Trial Management Group
TSC	Trial Steering Committee
TTP	Time to Pregnancy
UK	United Kingdom
UEI	Unexplained Infertility
UoB	University of Birmingham
WHO	World Health Organisation

TRIAL SUMMARY

Title

UNiTY – A randomised controlled trial evaluating the clinical and cost effectiveness of Intra Uterine Insemination versus In-Vitro Fertilisation for **UN**explained **i**nfertilit**Y**

Aim

To evaluate the clinical and cost-effectiveness of up to three cycles of Intra Uterine Insemination (IUI), compared to one cycle of In-Vitro Fertilisation (IVF) in couples with unexplained infertility.

Trial design

Parallel, open, multicentre, non-inferiority, randomised controlled trial with integrated economic, healthcare science and bioethics evaluations, including an internal pilot with embedded qualitative process evaluation.

Participant population and sample size

Couples with a diagnosis of unexplained infertility *(see eligibility section for full list of inclusion/exclusion criteria).* The trial will recruit 942 couples in total, 471 per group at a 1:1 randomisation ratio.

Setting

Human Fertilisation and Embryology Authority (HFEA) licensed fertility treatment centres in the UK.

Arms

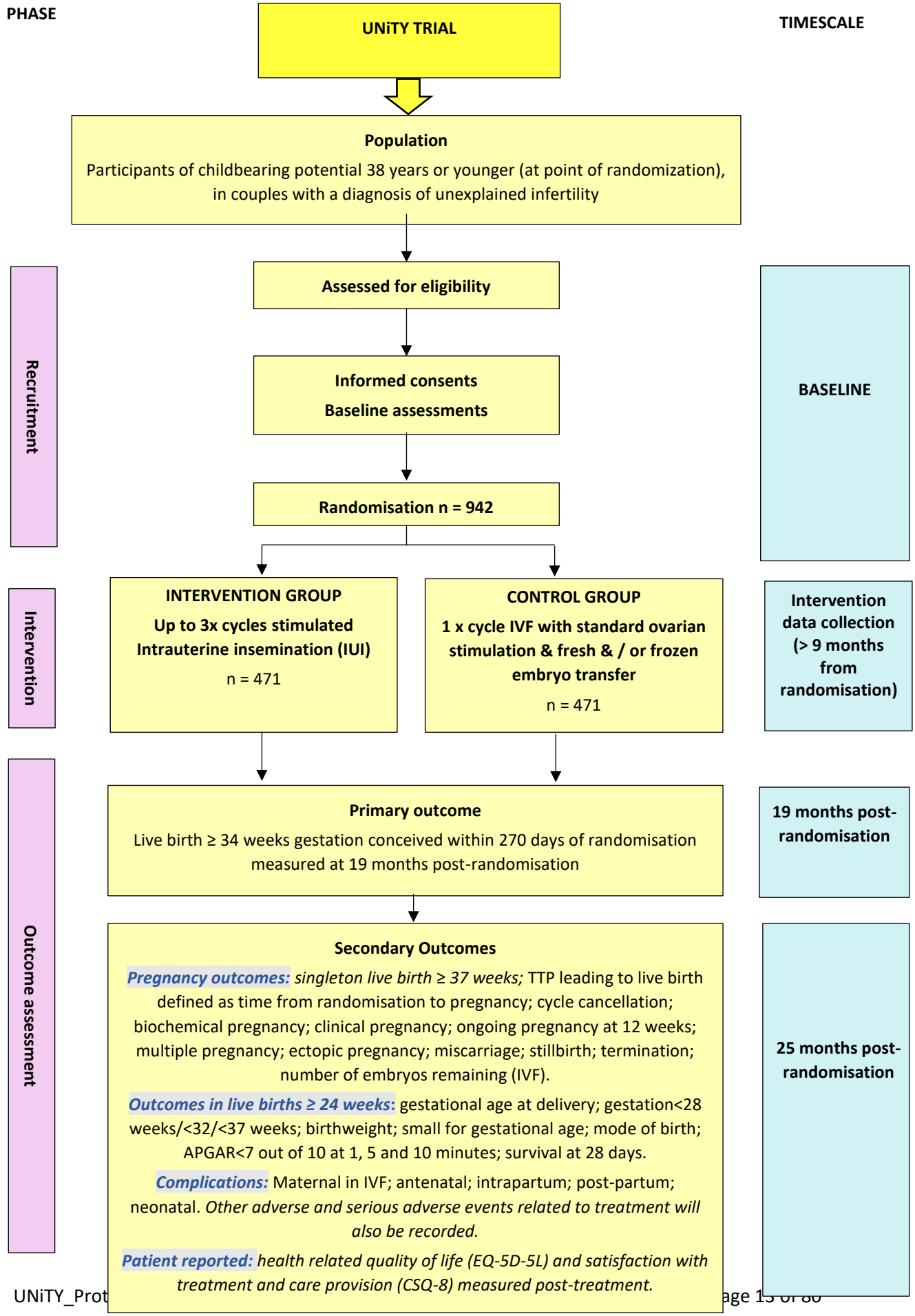
Intervention: Three cycles of letrozole stimulated Intra Uterine Insemination (IUI).

Control: One cycle of In-Vitro Fertilisation (IVF) with standard ovarian stimulation and first fresh or frozen embryo transfer.

Outcomes

The primary outcome is live birth ≥34 weeks gestation conceived within 270 days (approximately 9 months) of randomisation, assessed at 19 months post-randomisation *(see outcomes section for full list of primary and secondary outcomes).*

TRIAL SCHEMA



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1. BACKGROUND AND RATIONALE

1.1 Background

UNiTY is a National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA)-commissioned trial to investigate the clinical and cost-effectiveness of intrauterine insemination (IUI) versus in vitro fertilisation (IVF) for couples with unexplained infertility (UEI).

1.1.1 What is the burden of the treatment?

Couples in the United Kingdom (UK) pursued approximately 28,000 IVF cycles using their own eggs and sperm in 2019 (1). Around 32% (~8900) of those cases are classified as UEI by the Human Fertilisation and Embryology Authority (HFEA). However, the clinics that we have engaged with suggest that this figure may, in practice, be lower. We therefore conservatively estimate that 4000-9000 UK IVF cycles per annum are classified as UEI.

UEI has significant psychological and emotional impacts, one being embarking upon the intense, invasive, and expensive route (if self-funded) of IVF (2). National Institute for Health and Care Excellence (NICE) guidance recommends three cycles of National Health Service (NHS) funded IVF for couples with UEI when the partner providing eggs is under the age of 40 (3). In practice, three cycles of IVF are often not funded by the NHS with significant national and local variation; NHS funding is available: nationally in Scotland (three cycles); Wales (two cycles); and Northern Ireland (one cycle); and decided locally in England by Integrated Care Boards (ICBs) (previously known as Clinical Commissioning Groups (CCGs)) leading to considerable regional variation. Most often only a single IVF attempt is NHS funded in England (4). The alternative, IUI, is practiced and recommended in many countries worldwide (2). However, NICE guidance, based on low quality evidence, recommends that IUI should not be offered for couples with unexplained infertility in the UK (3).

1.1.2 How do the treatment options differ?

The key differences between IVF and IUI include risks, cost, and time to pregnancy (TTP) (2).

Risk

The main risk associated with IVF is ovarian hyperstimulation syndrome (OHSS), which causes ovaries to become enlarged and fluid to leak into the abdomen. When mild this is uncomfortable and interferes with daily activities. However, when severe, patients are at high risk of blood clots and may need to be hospitalised. IVF also involves egg collection, a surgical procedure with the most common risks being bleeding and pelvic infection.

Multiple pregnancy with twins is highly risky for the pregnant partner and the babies, with the HFEA acting via regulation to minimise these occurrences. There are some concerns that the rates of multiple pregnancies may be higher in IUI compared to IVF (single embryo transfer is well-controlled by regulation). However, there is also evidence to say that the numbers are comparable (5).

Cost

IVF is an intensive procedure involving a large multidisciplinary team including advanced embryology laboratory facilities (6). As such the cost is considerable. It is because of this large cost that many ICBs add parameters to access funding beyond the NICE guidelines, meaning many couples in the UK need to personally fund their treatment.

IUI involves much lower costs, as it requires less medication and monitoring. Further, because there is no complex technology, the treatment can be delivered at a local hospital rather than at a specialist IVF laboratory (7).

Time to pregnancy

IVF has a shorter TTP and increased chance of live birth in a single attempt compared to IUI (1).

1.1.3 Review of the published evidence

NICE maintain a recommendation that IUI with or without ovarian stimulation should not be routinely offered for couples with UEI, based on poor quality evidence (3).

Since the 2013 NICE recommendation (3), there has been one UK study with 207 couples randomised from a single centre, limiting generalisability and precision of outcome estimates. This study suggests three cycles of IUI may offer a similar likelihood of successful pregnancy as a single cycle of IVF (25% IUI singletons vs 31% IVF), albeit with some uncertainty (relative risk (RR) 1.3, 95% confidence interval): 0.8-2.0) (8). A Cochrane review suggested that 3 cycles of stimulated IUI significantly increases live birth rates in couples with UEI, but that couples with good prognosis should be offered expectant management for 6 months as IUI with ovarian stimulation does not increase live birth rates in this cohort (9). Following on from this, in 2017, a study showed that ovarian stimulation using clomiphene and IUI significantly increased the live birth rates compared to expectant management in couples with a Hunault score <30%, which predicts chance of pregnancy i.e. low prognosis couples (10).

There are concerns that IUI with controlled ovarian stimulation (COS) may increase the risk of multiple pregnancies and births. However, evidence suggests that the rates are similar, or possibly less, than those following IVF treatment (5, 11). Finally, international studies have suggested that IUI may be more cost effective than IVF (12, 13). The latest ESHRE guideline issued since this study was funded suggests IUI for unexplained infertility (14, 15) but this still lacks the evidence-base this trial is designed to supply.

1.1.4 Research trial proposed

There is a great deal of uncertainty regarding IUI versus IVF. Stimulated IUI, if effective, is potentially an attractive option for many couples and for ICBs because it is lower risk, less invasive and possibly more cost effective.

The UNiTY trial is a multi-disciplinary, multi-centre randomised controlled trial (RCT) designed to answer the question of whether IUI is an effective and cost-effective alternative to IVF for UEI in an ethnically and socially diverse UK population. In line with the new Medical Research Council (MRC) (NIHR) framework for developing and evaluating complex interventions, UNiTY will assess feasibility, value for money, safety and patient acceptability throughout the process. The potentially unreliable result of semen analysis is a significant factor in defining UEI and therefore trial entry. Inter-centre quality assurance of sperm analysis therefore forms a cornerstone of our trial and is a necessity to allow for the diversity of practice across the UK.

The intervention is the policy of offering three cycles of letrozole-stimulated IUI and the comparator is the policy of offering one cycle of IVF with standard ovarian stimulation and the first fresh and / or frozen embryo transfer. We will initially assess outcomes 19 months post-randomisation, when we anticipate couples will have been treated with their first IVF cycle or three cycles of stimulated IUI and subsequent pregnancy outcomes obtained. As we expect all couples unsuccessful after three cycles of IUI will proceed to at least one cycle of IVF, we will also collect and assess this data up to 25 months post-randomisation (treatment with further IVF cycles in either group will be dependent on local policy, if further NHS funding is available in a locality to a couple this will also be recorded). Within all cycles in the IVF pathway, the number of surplus frozen embryos will be documented as this can clearly inform of potential cumulative pregnancy rates – which could later be followed-up in future investigations.

The trial protocol will not alter local practice for IVF, which will be variable across the centres, as this is a pragmatic trial and reflects what would occur in current treatment. As IUI is not a standard / routine current treatment, this will be subject to more standardisation in-line with the findings from the Cochrane review (16) and global recommendations from the World Health Organisation Human Reproduction Programme (the United Nations Development Programme /United Nations Population Fund /World Health Organisation /World Bank Special Programme of Research, Development and Research Training in Human Reproduction) team who studied this question (17) *[MRC/NIHR framework, core element 1: context]*.

Assessing and quantifying male factors is clearly a critical step in defining infertility as 'unexplained' and as such determining suitability for an IUI intervention. However, there is a lack of evidence defining the lower parameters of semen quality which should be used for couples undergoing IUI. Cohlen et al. conducted a RCT comparing stimulated IUI outcomes and found that it significantly increased live birth rates in couples with a total progressively motile sperm concentration >10 m/ml, but not in couples with total motile sperm concentration <10 m/ml (18).

The criteria for offering stimulated IUI vs. IVF to couples will therefore be: UEI of ≥24 months, with the partner providing sperm having a total progressively motile sperm count of >10M (categories A + B), with at least 3% morphological normal forms (17).

Diagnosis of the partner providing sperm underlies suitability for an IUI approach and qualification for the trial, but we know that worldwide (and more-specifically in the UK) that this has great variability (19) so, the need for standardised quality assurance (QA) in assessment of the partner providing sperm is well known. We will therefore run a careful QA system for these observations across the lab teams at participating sites to characterise the variance occurring in assessments (see Section 16.2). This evaluation is fundamental to understanding future application and interpretation of the trial outcome as the single biggest weakness identified in most fertility trials involving male factors (20), it will also enable assessment of emergent technologies highlighted by the World Health Organisation (WHO) as of potential diagnostic value (21, 22) *[MRC/NIHR framework, core element 1: context]*.

1.2 Trial rationale

There is a clear need for a large multicentre trial to provide rigorous evidence evaluating IUI treatment vs IVF for couples with UEI.

1.2.1. The patient perspective

A fertility patient group, engaged throughout the funding application, had three high priority concerns: A) obtaining the best possible chance of a healthy child; B) the TTP; and C) the cost / their financial limitations in achieving the best chance of a healthy child. Potential health risks of IVF related procedures both to the pregnant partner and child were identified as important; however, these were perceived as less so when compared to the outcomes above.

The single consistent patient feeling was that, if IUI was unsuccessful, couples would request an IVF attempt. In developing this study, our survey of clinicians and the local ICB commissioning team in Birmingham supported and understood this patient viewpoint. Indeed, we note that across currently accessible ICB policies, where NHS funding is provided for IVF, self-funded IUI is not a disqualification.

The themes that were interpreted during initial patient discussions included confidentiality, accessibility, ease, and impact of treatment. Most couples who had undergone an IVF journey found it very disruptive to their lives, due to multiple hospital visits particularly during the ovarian stimulation and monitoring phase, as well as days of egg collection and embryo transfer. The reduction in medicalisation, visits and their duration for IUI was felt to be a positive that should be highlighted

to couples considering their options. In terms of confidentiality, couples felt this was linked in part to convenience – with short occasional appointments being a 'medical appointment' they could get time off for, but that a 'day off' around egg collection or embryo transfer was harder to explain/hide from others. In general, couples did not want to share their fertility journey with work colleagues or those around them – this was most strongly felt in the ethnic minority groups where most participants did not even wish to share information with family members. Again, the less involved IUI pathway may be the preference for these couples as it facilitated a more 'hidden' treatment possibility. IUI can be performed in centres which don't perform IVF and therefore can be more accessible, incorporating smaller or satellite units and involving less travelling for patients. We intend to examine these types of responses and thoughts further as part of the trial's qualitative work – as they are separate to prognosis or cost – in being motivators for a certain treatment type that may nevertheless impact on couples' psychological comfort around their fertility issues [MRC/NIHR framework, core element 4: uncertainties].

Patients from our Patient and Public Involvement (PPI) advisory group have also been keen to engage with ethical questions around the trial *[MRC/NIHR framework, core element 3: stakeholders]*. In particular, the complications arising from the design of a trial that encompasses both NHS- and self-funding couples. Through careful discussions, including with our bioethicist Dr Lucy Frith, we have developed a model for recruiting and progressing couples through each arm of the trial that addresses their concerns (see section 6.1 for details).

1.2.2 Justification of target population

The target population for this trial is partners providing eggs aged <39 years in couples with a diagnosis of UEI; so that they can have multiple cycles of treatment in the trial before they are 40, the exclusion criteria is ≥39 years on the date of randomisation. We have adopted broad entry criteria, and will recruit from a large ethnically, socially, and economically diverse population to increase the generalisability of the findings, and to fit with NICE recommendations.

1.2.3 Justification for design and framework

A RCT design has been selected as the gold standard for comparing interventions.

The UNiTY evaluation and intervention design aligns with the 'effectiveness' research perspective of the new 2021 MRC/NIHR framework for developing and evaluating complex interventions (23, 24). The methods include consideration of the framework's six core elements: (i) considering context; (ii) developing programme theory; (iii) engaging stakeholders; (iv) identifying uncertainties; (v) refining the intervention; and (vi) economic considerations.

Inclusion of the framework's six core elements will be identified throughout this protocol using italic square brackets e.g. *[MRC/NIHR framework, core element 1: context].*

1.2.4 Justification for choice of intervention

IUI is a simpler, cheaper, and less invasive alternative treatment to IVF. Studies have shown that IUI can offer a similar likelihood of successful pregnancy as IVF (25, 26) . Further studies have suggested that it requires three cycles of IUI in order to achieve pregnancy rates similar to those of one cycle of IVF (8). Supporting this clinical justification, the patient perspective highlights that there is a strong desire for interventions that are less invasive, less expensive, require fewer hospital visits, and yet retain an acceptable outcome success rate. The choice of IUI is also notable as something offered broadly in an unlimited fashion across Belgian fertility centres on the basis of financial modelling (27). Partners providing eggs in couples randomised to the IUI arm of the study will undergo ovarian

stimulation using letrozole as it is likely that these achieve a slightly higher live birth rate than clomid (28-30).

A subsequent cycle of IVF after three cycles of IUI will be offered to couples. Though this cycle is not part of the trial intervention, information on the outcome of these cycles will be collected. Consideration has been given as to whether it is an appropriate comparison when in one arm the IVF cycle occurs immediately and in the other it will be delayed by many months due to the IUI ovarian stimulation. This will be considered when interpreting the outcomes, but any detectable effect would only occur in the oldest eligible patients, and it was determined not appropriate or acceptable to delay direct IVF entry to those in that trial arm. This is because published HFEA data reflects rapid decreases in IVF success as the partner providing eggs age goes beyond 38 (1) – as such providing these patients a non-treatment trial delay would significantly decrease their chance of a child and be unethical.

1.2.4. Justification for choice of primary outcome

As a healthy live birth is the most important outcome for our couples, we have chosen live birth ≥34 weeks gestation as our primary outcome. Preterm birth is defined as <37 weeks' gestation but most prematurity-related adverse outcomes occur at <34 weeks' gestation. Extreme pre-term births (24 - 28 weeks) have very poor outcomes (31, 32). Twin (and multiple) pregnancies carry a higher risk of miscarriage or preterm birth, but a healthy twin live birth ≥34 weeks will be considered a successful primary outcome (counted as one 'success' per randomised couple), as this reflects the patient perspective. The timing of assessment (births related to conception within 270 days of randomisation) will allow a fair comparison of treatment policy, and again reflects the patient perspective of achieving a healthy birth in a timely manner, taking into account current variation in treatment waiting times across the NHS. *[MRC/NIHR framework, core element 4 & 6: uncertainties & economic considerations].*

2. AIMS AND OBJECTIVES

The aim of UNiTY is to investigate the clinical and cost-effectiveness of up to three cycles of IUI versus one cycle of IVF in couples with UEI.

2.1. Internal pilot objectives

The trial includes an internal pilot phase to assess feasibility and acceptability. The decision to continue to a full trial will be based on pre-defined stop-go criteria (see Table 1), and informed by the findings from the pilot qualitative process evaluation (QPE).

The pilot objectives for the trial are:

- To assess the feasibility of recruitment to the UNiTY trial [*MRC/NIHR framework, core element 4 & 5: uncertainties & refinement]*
- To assess the feasibility of opening fertility centres to the UNiTY trial
- To explore and understand the feasibility, acceptability, ethical implications and context of the UNiTY trial interventions with couples and healthcare professionals (HCPs) *[MRC/NIHR framework, core elements 1-6: context, programme theory, stakeholders, uncertainties, refinement & economic considerations]*.

2.2. Main trial objectives

2.2.1. Clinical aims and objectives

The primary objective is to test the hypothesis that in couples with UEI, the policy of offering three cycles of IUI is not substantially worse than the policy of offering IVF by up to a 10% margin of non-inferiority in terms of live birth≥34 weeks *[MRC/NIHR framework, core element 4: uncertainties]*.

The secondary clinical objectives for the trial are:

1. To evaluate the rates of pregnancy loss for IUI versus IVF for couples with UEI.
2. To compare the health of babies born as a result of IUI versus IVF to couples with UEI.
3. To compare the complication rates of the two treatment arms.
4. To evaluate the TTP leading to a live birth for IUI versus IVF for couples with UEI.
5. To explore patient satisfaction in the two treatment arms.
6. To compare outcomes of couples over a longer period of 25 months post-randomisation when further interventions may have been provided.
7. To explore the different clinical features of IUI and IVF cycles.
8. To explore the reasons patients may not complete the full course of treatment or wish for different treatment options.

2.2.2. Economic aims and objectives

The health economics analysis within UNiTY aims to evaluate the cost effectiveness of up to three cycles of IUI compared to one cycle of IVF for couples with UEI. *[MRC/NIHR framework, core element 6: economic considerations].*

2.2.3. Healthcare Science aims and objectives

The embedded healthcare science work will investigate the variations in how male factors in infertility are assessed across the clinical partners involved in the trial. A quality assurance check for the sperm analysis performed prior to entry in the trial will be provided. Further, the prognostic value of both existing (WHO), and novel (including flagellar beat) markers for male factor infertility will be evaluated

in relation to treatment outcomes for both IUI and IVF. *[MRC/NIHR framework, core element 4: uncertainties]*.

2.2.4. Bioethics aims and objectives

The Qualitative Process Evaluation will help inform the ethical issues that will be explored in greater depth as part of the bioethics sub-study. Interviews will be carried out with trial participants (who have completed treatment), clinicians and commissioners to explore the intersection between costs of treatment and treatment choices. The bioethics sub-study aims to understand the perspectives of clinicians, commissioners and patients *[MRC/NIHR framework, core element 1, 3 & 4: context, stakeholders & uncertainties]*.

2.2.5. Patient Reported Outcomes Objectives

• Health related quality of life (HRQoL) (using the EQ-5D-5L overall score and thermometer scale) measured at baseline , and 9 and 19 months post randomisation, plus 25 months for couples who conceive within 450 days of randomisation;

• Satisfaction with treatment and care provision (using the CSQ-8 [36]) post-treatment.

3. TRIAL DESIGN AND SETTING

3.1. Trial design

UNiTY is a parallel, open, multicentre, non-inferiority RCT with integrated economic, healthcare science and bioethics evaluations. It includes an internal pilot phase (9 months) with embedded qualitative process evaluation.

3.2. Trial setting

The trial will take place in HFEA licenced fertility treatment centres in the UK. These may be NHS or private providers carrying out NHS funded treatments. Self-funded patients at these sites will be included where providers have suitable indemnity for this in place as determined by the Sponsor.

3.3. Sub-studies

Three sub-studies are included in the UNiTY trial. Please refer to section 16 for detailed information.

Qualitative process evaluation

A pragmatic qualitative process evaluation embedded in the pilot phase will explore and understand the feasibility, acceptability, ethical implications and context of the intervention, as well as the evaluation design, with couples and HCPs. In addition, it will explore ethical acceptability, potential health equity and equality concerns regarding access to the trial. The results will dynamically inform decision-making around progression to the full trial and the bioethics sub-study.

Healthcare science

Accurate diagnosis of the partner providing sperm is a key factor in diagnosing UEI and assessing suitability for IUI. UNiTY will investigate the variations in male factor assessments across the centres taking part in the trial, and assess and moderate the clinical investigations done prior to trial entry. There will also be a mechanistic investigation of whether these measures can be improved in the future through the use of novel sperm-imaging to predict outcomes.

Bioethics

Embedded within the main trial, this bioethics evaluation using qualitative methods explores further ethical issues with couples who have completed the trial protocol. Building on the process evaluation, interviews will gather the reflections of participants, clinicians and commissioners on the trial processes, and will explore potential health equity and equality concerns regarding access to the trial and the proposed intervention.

3.4. Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: No higher than the risk of standard medical care.

3.5. Patient and public involvement

Section 1.1.5 details the involvement patients and the public have had in the design of the trial.

Beyond this, the trial team will include PPI representatives throughout the trial, ensuring representation from a range of backgrounds. Individuals will review participant-facing documents, and sit on committees. A PPI panel will be convened to review the trial as it progresses and advise the trial team.

As well as the usual benefits for PPI participation, counselling will be available in the event that the discussion of infertility and fertility treatment is more difficult than anticipated for contributors.

4. ELIGIBILITY

4.1. Inclusion criteria

Couples with a diagnosis of UEI, referred to fertility centres for assisted conception, will be considered for the UNiTY trial.

Unexplained infertility for the purpose of this trial is defined as the ***absence*** of the following after complete investigations:

- Partner providing eggs infertility due to:
  - Tubal disease
  - Deep endometriosis +/- ovarian endometriosis
  - Significant uterine abnormality requiring surgery (including cavity distorting fibroids, fibroids >5cm or multiple fibroids)
  - Uterine septum with history of previous pregnancy loss
- Partner providing sperm infertility due to:
  - Total progressively motile sperm count ≤10Million
  - Normal sperm morphology of ≤2%*

* *Where centres routinely see the majority of partners providing sperm with normal sperm morphology ≤2%, their processes for assessing morphology will be verified to ensure they are correctly following WHO guidelines alongside the External Quality Assurance (EQA) provided through Sub-study 2: Healthcare Science.*

4.2. Exclusion criteria

- Partner providing eggs is 39 years or older on the date of randomisation
- Either partner is under 18 years old on the date of consent
- Partner providing eggs body mass index (BMI) is <19.0 or >34.9 kg/m^2
- Either or both partners have a diagnosis of an ongoing sexually transmitted infection
- Either partner is taking any prohibited medication(s)/intervention(s)
- The couple has two or more consecutive IVF treatment failures
- Either partner unable to provide informed consent
- Either partner unable to complete trial follow-up
- If self-funded, inability to pay for IVF

If couples do not meet the requirements for NHS-funded IVF in their area, but do meet the trial eligibility criteria, they can proceed as self-funded participants.

The age limit for partners providing eggs for NHS-funded IVF treatment is 40 years. In order for couples to have multiple cycles of IUI followed by IVF before turning 40, and without jeopardising their funding, partners providing eggs will need to be <39 years of age on the date of randomisation. Research teams will discuss this with all couples during screening, particularly those in which the partner is close to the age eligibility limit to be sure they understand the possibility of losing NHS funding.

4.3. Equality and Diversity

This trial aims to recruit an ethnically and socially diverse trial population and will adhere to the INCLUDE guidelines outlined by the NIHR.

Couples who do not speak English will be screened and approached. Written information will be translated by an interpreter, reinforced by video content in multiple languages. This has been found to be a more engaging and reliable way for couples to give true informed consent based on the trial team's clinical experience and from PPI feedback. Interpreters must also be available to facilitate the informed consent process for participants who don't speak English. This has been found to be a more engaging and reliable way for couples to give true informed consent based on the trial team's clinical experience and from PPI feedback.

Interpretation services (either available within the clinic or a medical specialist interpreter/translation company) will be available for the RCT and for the qualitative studies.

A separate trial-specific plan for achieving and maintaining equality and diversity in trial participation, PPI and public engagement will be followed throughout the study.

4.4. Co-enrolment

Co-enrolment may have an impact on outcomes and pose challenges to the participant pathway on both research studies. Due to this, co-enrolment will be considered on a case-by-case basis by the Trial Management Group (TMG). In all instances, the recruiting centre should contact the UNiTY Trial Office prior to offering the second trial, or before approaching a couple about UNiTY who are already enrolled into another study.

5. CONSENT

Consent for the UNiTY trial is given by both partners in the couple before any trial procedures take place. This will be gained following all HFEA Code of Practice or other recommendations that apply. One form must be completed by each partner, which can be done online (either in person or remotely) or on paper.

It is the responsibility of the Principal Investigator (PI) to ensure that informed consent is obtained for each partner prior to performing any trial related procedures. This task can be delegated by the PI to other members of the local research team, if local practice allows and this responsibility has been documented in the site signature and delegation log.

Both an Illustrated Participant Pathway and Participant Information Sheet (PIS) will be provided to facilitate this process. The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the couple. They will also explain that participation is voluntary and that the couple is free to decide to take part and may withdraw from the trial at any time. The couple will be given sufficient time to read the PIS, ask any questions and discuss their participation with others outside of the site research team. As described in section 4.3, couples for whom English is not their first language will have information and consent forms provided to them, and access to an interpreter who can facilitate explaining the trial to the couple.

For all participants receiving trial treatment, details of the informed consent discussions will be recorded in their medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to couple, version number of the ICFs signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit the participant who is receiving trial treatment will have their willingness to continue in the trial ascertained and documented in the medical notes. Throughout the trial the couple will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participant who is receiving treatment's decision to continue, participants will be given time to consider and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be localised to the headed paper of the local institution if paper copies are used. Audio information will be made available in multiple languages.

We will also add additional statements to the ICF for the participant to acknowledge that they understand that the Trial Office might in the future, for other related research, collect participant data available in NHS routine clinical datasets, including primary care data (e.g., Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (e.g., Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. The participant will acknowledge that they understand that the Trial Office might send their name, address, date of birth and NHS number to the relevant national registry, and then for the national registry to link this to their data and send the information back to the Trial Office. The acknowledgement by the participant will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

Online consent

Given most couples will be used to completing documents online, this is expected to be the primary method used to obtain informed consent for couples entering the UNiTY trial. If, after discussion with the research team, the couple would like to take part in UNiTY, they will both be asked to provide their email addresses in order to complete the online consent process. A link to the REDCap database https://bctu-redcap.bham.ac.uk/ will then be emailed to both partners for them to complete online the latest version of the Informed Consent Form (ICF). Each partner will sign and date their respective consent form; once completed these will also be signed and dated by the consenting clinician. If electronic consent is preferred, a simple typed signature is acceptable within the guidelines of the MRC Joint Statement on Consent. There will be details on the online PIS on how to contact the research team if they have any further questions.

A completed consent form is saved as a pdf on the database, which can only be seen by site staff and the central trial team. This pdf can be downloaded for filing in the egg providing partner's medical notes, and copies are automatically emailed to the participants. Documentation of online consent will be evidenced by printed copies of the ICF filed in the Investigator Site File (ISF). The site team can review the forms and contact the couple if there are any questions or concerns with form completion. All screened potential participants are assigned a Couple Trial ID which is used as their unique trial identifier throughout the trial.

Paper consent

This process will be available in case online consent is not an option for couples. The couple will be given the opportunity to ask questions before initialling, signing and dating the latest version of their respective ICF. The PI or delegate will then sign and date the ICF. Each participant will be given a copy of their ICF, copies will be filed in the medical notes and the originals placed in the ISF. Data from ICFs will be uploaded on the REDCap database for electronic review. Once the couple is enrolled into the trial, their Couple Trial ID will be entered on the ICF maintained in the ISF.

6. ENROLMENT, RANDOMISATION and BLINDING

6.1. Identification and approach

Potential participants will be identified via review of medical records by clinicians and nurses within (HFEA) licenced fertility treatment centres. Couples with potential unexplained infertility will not be screened until all their investigations have been completed and a diagnosis of UEI has been confirmed. Eligible potential participants will be approached about the trial by members of their direct care team including clinic doctors and staff at assisted conception units who are responsible for their care and who are named on the local delegation log. As HFEA guidelines prohibit fertility doctors from approaching patients relating to trial participation, research nurses are in this context considered part of the direct care team subject to local confirmation.

6.2. Screening and enrolment

Enrolment will take place upon confirmation of eligibility and after informed consent of both partners of the couple has been obtained. Details of all couples approached about the trial will be recorded on the screening CRF; which is stored on the REDCap database and accessible by the Trials Office.

6.3. Couples self-funding IVF

After screening, couples who are self-funding must have paid the fertility centre for IVF treatment before they can be randomised into the trial. This is to ensure that they have the funds available as per the eligibility criteria. If the couple is randomised to receive IUI, the payment will be retained in case it is needed to fund IVF after trial treatment is completed. If the couple do not go on to have IVF the funds will be returned to them.

6.4. Randomisation

Randomisation will be provided by BCTU using a secure online system (available at https://bctu-redcap.bham.ac.uk/). Unique log-in usernames will be provided to staff who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the UNiTY Site Signature and Delegation Log. Database users will be emailed a link to complete their account set-up including setting up their passwords. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. It is important to note that the time between randomisation and treatment will (at a minimum) be a number of days as consent for the relevant treatment regime will need to be taken after randomisation and before treatment can start, according with the HFEA Code of Practice. Therefore we do not expect temporary unavailability of the online system to negatively impact trial procedures.

6.4.1. Randomisation process

After eligibility has been confirmed, informed consent has been given and, if applicable, payment has been received, the participant can be randomised into the trial using the online system. All questions and data items on the online Randomisation Form must be answered prior to a potential participant being randomised into the trial. The couple should only be randomised if (in the opinion of the site PI) there is a high likelihood of treatment starting (defined as date of ovarian stimulation) within 3 months of randomisation in both groups.

Following randomisation, a confirmatory email will be sent to the research team at the relevant HFEA licenced fertility treatment centre and the UNiTY Trial Office.

The couple do not need to be present for the randomisation process. In this case, it is the responsibility of the local research team to notify the couple of their allocation and how they proceed on that treatment pathway.

The local research team should add the participant to the UNiTY Participant Recruitment and Identification Log which links participants with their Couple Trial ID. PIs or their delegates must ensure this document is stored securely and it must not be submitted to the Trial Office. The UNiTY Participant Recruitment and Identification Log should be held in strict confidence.

6.4.2. Randomisation method

Couples will be randomised at the level of the individual in a 1:1 ratio to either three cycles of IUI or one cycle of IVF.

A minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations over specific characteristics of the partner providing the eggs and randomising centre. The following variables will constitute the minimisation variables:

(i) Ethnicity of the partner providing the eggs (Asian, Black, Mixed, White, Other)

(ii) BMI of the partner providing the eggs (19.0-24.9, 25.0-29.9, 30.0-34.9 kg/m^2)

(iii) Age of the partner providing the eggs (<35, 35-37, ≥38 years), and

(iv) Randomising centre.

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the minimisation algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.5. Blinding

Due to the differing natures of the intervention, it is impossible to blind either the care providers, investigators or participants to their allocated group. While we cannot completely rule out some element of behaviour change (and hence performance) bias due to knowledge of allocated interventions, we expect the extent of such bias to be relatively small given the nature of the treatments. We have a strict, objective primary outcome, so we do not expect detection bias to be a factor.

6.6. Informing the participant's GP and other parties

If the participants have agreed, the GP of the participant providing the eggs should be notified that they are in the trial, using the UNiTY GP Letter.

7. TRIAL INTERVENTION

7.1. Trial interventions and schedule

Both interventions should start no more than 3 months after randomisation which should be sufficient time to complete treatment consent forms, for relevant medication to be ordered and appointments to be scheduled.

7.1.1. IUI strategy

Ovarian stimulation

IUI with the aromatase inhibitor letrozole will be commenced at a dose of 5mg (2 tablets) once daily from day 2 – day 6 after commencement of period. Follicular tracking will be according to local protocol, but this is usually commenced around day 10 – day 12 using transvaginal ultrasound. When at least one follicle reaches a diameter of ≥17mm, ovulation triggering using human chorionic gonadotrophins should be administered. This will ensure that IUI can be performed at a planned time convenient to the patient and staff. Luteal support will be provided according to local protocols.

Insemination

Single insemination should be planned 24-40 hours post the ovulation trigger injection (33, 34). Patients will be advised to have 10-15 min bed rest after the insemination is performed (35). Protocols will be managed according to local policy to minimise the chance of multiple pregnancy. Where no policy exists (e.g. in clinics with no current IUI provision), the suggested policy will be that when more than 2 follicles >15mm are present at the time of HCG triggering, the cycle should be cancelled and the couple advised to refrain from unprotected intercourse.

Multiple cycles

Couples who do not have a baby (due to negative pregnancy test or subsequent pregnancy loss) after their first or second cycle of IUI will proceed to another cycle. The timings for when to start this will be a decision for the couple after consultation with a clinician.

If a couple has not completed 3 cycles of IUI at the conception measurement point of 450 days post randomisation, they will no longer be able to take up those additional cycles.

Subsequent IVF

While not part of the trial intervention, all couples who are not pregnant after three cycles of IUI or 270 days (nine months) post-randomisation will be offered a cycle of IVF as part of clinical care.

Funding

Couples in the UNiTY study will not have to pay for the three cycles of IUI. Those eligible for IVF NHS funding will discuss this with the research team prior to randomisation. They will know the parameters of their funding and whether the trial will impact this. This will inform the couple's decision to take part in the trial.

7.1.2. IVF strategy

Ovarian stimulation

The IVF cycle will be carried out as per the fertility clinic's normal practice. The IVF cycle type (agonist or antagonist), medication used, and monitoring schedule will be determined by the individual clinics.

Embryo transfer

Single embryo transfers (fresh or frozen) will be standard practice.

Further transfers

Couples who use frozen embryos from their cycle in subsequent cycles do so outside of the main trial intervention, but outcomes will be collected up to a maximum of 25 months post-randomisation (see section 8).

Funding

Couples eligible for NHS treatment will not have to pay for IVF in the trial. Self-funding couples will need to pay for treatment prior to randomisation to ensure they have sufficient funds. Self-funding couples will be reimbursed if not randomised to IVF.

7.2. Drug interaction or contraindications

7.2.1. Permitted medication(s)/intervention(s) (including rescue medication)

All standard medications associated with Medically Assisted Reproduction (newer term for assisted reproductive therapy) (MAR) ovarian stimulation will be permitted for the IVF cycle as it will depend on the Anti-Mullerian Hormone (AMH) level, or antral follicle count. The final stimulation dosage, medication, duration of stimulation and protocol employed will be recorded, as well as method of luteal support. For IUI, letrozole is the chosen medication with the duration of stimulation recorded, as well as method of luteal support if employed.

7.2.2. Concomitant medication(s)/intervention(s)

Both partners may be taking supplements, or concomitant medication as part of other routine treatment. Continuing or pausing these medications will be decided by the clinical team, and relevant concomitant medication will be recorded.

7.2.3. Prohibited medication(s)/intervention(s)

Prohibited medications would only be those of unwarranted / unknown effect in initial MAR treatment. This would include intralipid infusions and immunosuppressive treatment such as corticosteroids.

7.3. Intervention modification or discontinuation.

All patients receiving off-protocol treatment will remain in the study. Data will continue to be collected from the couple until the end of their study duration. Any fertility treatment accessed by participants after completion of trial treatments is not considered a protocol deviation.

To minimise the multiple pregnancy risk, when more than 2 follicles >15mm are present at the time of HCG triggering, IUI should be withheld (17), this will be recorded in the trial as one of the three attempts as this again pragmatically reflects what would occur in current practice.

7.4. Continuation of intervention after the trial.

If couples do not have a live birth through the trial interventions, further treatment will be discussed with their clinical team outside of the trial.

7.5. Intervention supply and storage

All medications used within UNiTY are routine for the two different treatment arms. As such standard local protocols for supply and storage of drugs will be followed.

7.6. Adherence

The primary analysis will examine treatment policy (all randomised participants regardless of adherence to intervention), but further analysis will investigate the intervention effect within the population of adherent couples (see Section 14). For this purpose, the adherent population will be defined as receiving three cycles of IUI (or one or two cycles if pregnant from earlier cycles) with no further fertility treatment in the IUI strategy group and one cycle of IVF with no further fertility treatment in the IVF strategy group.

Adherence to intervention will be monitored via periodic data review performed by TMG, DMC and TSC.

Definition of cancelled and complete treatment cycles

- IVF and IUI cycle cancellation – if the partner providing eggs has had a stimulation injection, but the rest of the procedure was cancelled prior to egg collection (IVF), or insemination (IUI).
- Complete cycles – if embryo transfer (IVF) or insemination (IUI) has taken place.

Cancelled cycles and trial data

When cycles are cancelled it will be at the discretion and cost of the provider (treatment centre) as to whether a complimentary cycle is offered. Any replacement cycles will be recorded as non-trial treatments.

8. OUTCOME MEASURES

8.1. Internal pilot outcomes

The decision to continue to a full trial will be based on pre-defined stop-go criteria, and informed by the findings from the pilot qualitative process evaluation.

Related to the objectives in section 2.1, the outcomes for the pilot are the number of randomised participants and number of sites open at the end of the pilot phase. The aim of the pilot is to enrol at least 176 couples and open at least 12 centres, as set by the trial Funder (see Table 1).

The decision of whether to progress from the internal pilot to the full trial will largely be based on the recruitment outcome, as this is expected to be the most challenging aspect of the trial. If recruitment is ≥100% of expected (green in Table 1), UNiTY will proceed to the main trial on discussion with the Funder. If recruitment is 67-99% of expected (amber), the trial team will explore and implement methods with the Trial Steering Committee (TSC) and the Funder to improve recruitment; if recruitment is <67% of expected (red), with no obvious remedial factors, there will be discussions with the TSC and the Funder around stopping the trial (see Table 1).

Any decision regarding the feasibility and acceptability of the RCT, and remedial measures, if necessary, will also be informed by the results from the embedded qualitative process evaluation.

Table 1: UNiTY Internal Pilot Targets

	Red	Amber	Green
Trial recruitment n (%)	<118 (<67)	118-175 (67-99)	≥176 (100)
Recruitment rate/ site/ month	<1.6	1.6-2.3	2.4
Number of sites opened	<8	8-11	≥12

8.1.1. Qualitative

- A qualitative assessment of UNiTY's feasibility, acceptability and appropriateness for couples and HCPs.
- To dynamically inform decision making as to whether UNiTY should proceed to the next evaluative phase (e.g., continue to a full trial, refine the study design, or stop the trial).
- For further information please see Section 16.1.

8.2. Main trial outcomes

8.2.1. Primary outcome

The primary outcome is the live birth of a baby at ≥34 week's gestation, conceived within 270 days of randomisation (approximately 9 months). Date conceived is determined as date of egg collection for couples who have undergone fresh embryo IVF, date of embryo transfer minus the number of days of culture for couples who have undergone frozen embryo IVF, date of insemination for couples who have undergone IUI, and 14 days after the first day of the last period for couples who have conceived naturally.

In line with the evaluation of treatment policy, initial or subsequent pregnancies may be included within this timeframe. This outcome will be assessed at 19 months post-randomisation.

8.2.2. Secondary outcomes

8.2.2.1. Clinical

Pregnancy outcomes

The following outcomes will be assessed at two time points: 19 months post-randomisation to allow for pregnancy outcomes to be obtained and concern pregnancies conceived within 270 days (approximately 9 months) of randomisation; and 25 months post-randomisation to allow for pregnancy outcomes to be obtained and concern pregnancies conceived within 450 days (approximately 15 months) of randomisation. This will enable us to determine the medium-term effect of the initial treatment policy decision.

- Singleton live birth ≥37 weeks;
- TTP leading to a live birth defined as time from randomisation to pregnancy in days (censored at 270 days);
- Cycle cancellation and reason (failure to respond / over-response);
- Biochemical pregnancy;
- Clinical pregnancy;
- Ongoing pregnancy at 12 weeks (range 11 to 14 weeks);
- Multiple pregnancy;
- Ectopic pregnancy;
- Miscarriage (defined as delivery before 24 weeks of gestation);
- Stillbirth (defined as intrauterine death ≥24 weeks);
- Termination;
- Number of embryos remaining (IVF group).

Outcomes in live births≥24 weeks

The following outcomes will be assessed at two time points: 19 months post-randomisation to allow for pregnancy outcomes to be obtained and concern pregnancies conceived within 270 days (approximately 9 months) of randomisation; and 25 months post-randomisation to allow for pregnancy outcomes to be obtained and concern pregnancies conceived within 450 days (approximately 15 months) of randomisation. This will enable us to determine the medium-term effect of the initial treatment policy decision.

- Gestational age at delivery;
- Gestation<28 weeks;
- Gestation<32 weeks;
- Gestation<37 weeks;
- Birthweight, grams;
- Small for gestational age (<10th centile);
- Mode of birth (unassisted vaginal, instrumental vaginal, elective caesarean section, emergency caesarean section);
- APGAR<7 out of 10 at 1 minute;
- APGAR<7 out of 10 at 5 minutes;
- APGAR<7 out of 10 at 10 minutes;
- Survival at 28 days (or discharge from hospital whichever is sooner).

Complications

The following outcomes will be assessed:

i.) for the first IVF treatment within 450 days post randomisation for a period of 60 days following the date of FSH injection;

ii.) for the first three IUI cycles within 450 days post randomisation for a period of 30 days following the date of ovarian stimulation for partial or cancelled cycles, or date of insemination for complete cycles.

- Ovarian hyperstimulation syndrome (mild, moderate, severe);
- Pelvic infection;
- Bleeding post oocyte retrieval (IVF only);
- Admission to High Dependency Unit (HDU)/ Intensive Therapy Unit (ITU), standard ward admission, A&E visit or Outpatient review.

The following outcomes will be assessed at 28 days post birth (or patient's discharge date from hospital whichever is sooner).

- Antenatal
  - Placenta praevia;
  - Antepartum haemorrhage;
  - Pregnancy-induced hypertension;
  - PET/Pre-eclampsia/HELLP;
  - Obstetric cholestasis;
  - Preterm pre-labour rupture of membranes;
  - Gestational diabetes;
  - Other significant complication
- Intrapartum
  - Chorioamnionitis;
  - Intrauterine growth restriction;
  - Macrosomia;
  - Infection
- Post-partum
  - Haemorrhage

The following outcomes will be assessed at 28 days post birth (or baby's discharge date from hospital whichever is sooner).

- Neonatal
  - Congenital or chromosomal abnormalities;
  - Admission to neonatal care unit;
  - Early infection (as assessed by treating clinician);
  - Retinopathy of prematurity;
  - Necrotising enterocolitis;
  - Intraventricular haemorrhage;
  - Respiratory distress syndrome;
  - Ventilation or oxygen support;
  - Other significant complication

Patient reported outcomes

- Health related quality of life (using the EQ-5D-5L questionnaire overall score and thermometer scale (36)) measured at baseline, during the first treatment cycle* of IUI and/or IVF, and 19 months post randomisation (and 25 months for couples who conceive within 450 days of randomisation);
- Satisfaction with treatment and care provision (using the CSQ-8 (37)) measured during the first treatment cycle* of IUI and/or IVF, and 19 months post randomisation (and 25 months for couples who conceive within 450 days of randomisation).

Consent will be taken from couples to allow longer-term assessment of pregnancy and live birth rate through routine data sources. Funding to carry out this work through to 5 years post-randomisation will be requested through a separate application.

*The ideal timepoint during a treatment cycle to collect these questionnaires is between the date of insemination and the date of the pregnancy test for couples undergoing IUI, and between the date of embryo transfer and the date of the pregnancy test for couples undergoing IVF.

8.2.2.2. Economic

The main outcome of the cost-effectiveness analysis is cost per live birth at ≥34 weeks gestation based on the principal outcome of the trial. Some secondary outcomes assessed in the trial including (HrQoL) in terms of quality-adjusted life-year (QALY) will also be reported and presented in the form of a cost-consequences analysis.

8.2.2.3. Healthcare science outcomes

The healthcare science outcomes are covered in the Sub-Study section (see Section 16.2). The following outcomes will be assessed:

- Healthcare science characterisation of the standardisation of sperm analysis results.
- Measurement of prognostic value of existing sperm analysis markers for both IUI and IVF.
- Novel sperm flagellar markers with prognostic value for both IUI and IVF.

8.2.2.4. Bioethics

The aims of the bioethics sub study are:

- To explore the perceptions of participants, fertility professionals (e.g. doctors, nurses, clinic staff) and service commissioners around access to fertility treatment.
- To gain greater understanding of how the priorities of service providers intersect with patients' perspectives (e.g. commissioners might prioritise low-cost treatment, while for couples having a pregnancy/child might be a higher priority)
- To improve access to trials in this area and understand how funding restrictions could impact on trial participation.

9. TRIAL PROCEDURES

9.1. Schedule of assessments

Table 2: Schedule of Assessments

Trial process	Month 0	Month 2	Month 4	Month 6	Month 9	Month 19	Month 25	Ad hoc
Screening	X							
Consent	X							
Baseline data collection	X							
Randomisation	X							
IUI Treatment CRF		X	X	X				
IVF Treatment CRF		X			X[1]			
Laboratory CRF		X	X	X	X[1]			
Frozen Transfer CRF		X						
Clinical Pregnancy outcome						X	X[2]	X[3]
Post Treatment CRF						X[5]	X[5]	
EQ-5D-5L	X	X[6]				X	X[2]	
Health Resource use		X[6]				X	X[2]	
CSQ-8		X[6]				X	X[2]	
Complications - collected on Post Treatment CRF		X	X	X	X	X	X[2]	
Assessment of adverse events	Throughout participant's time on trial until 60 days after the outcome of the cycle is known							
Change of Status								X
Protocol Deviations								X
Non-trial treatment CRF								X

Natural Pregnancy Notification								X[4]
Qualitative process evaluation	X							
Qualitative bioethics							X	

Additional notes on Error! Reference source not found.

- Months 2-6 are an approximation for when couples will have the three cycles of IUI; this process may be longer.
- X[1] – Couples randomised to IUI but progress to IVF as part of clinical care. All couples randomised to IUI cannot progress to subsequent IVF treatment until 270 days (approximately 9 months) post randomisation.
- X[2] – to measure outcomes for all couples who conceive within 450 days of randomisation.
- X[3]- one Clinical Pregnancy Outcome CRF to be completed per positive pregnancy test.
- X[4]- to be completed for each pregnancy conceived during the trial outside of IVF or IUI treatment.
- X[5] – one Post-Treatment CRF to be completed 8 weeks after treatment starts (defined as the first day of ovarian stimulation).
- The qualitative sub-studies will approach participants at the indicated timepoints, but their interviews will happen in the subsequent weeks.
- X[6] - measured during the first treatment cycle of IUI and/or IVF. The ideal timepoint during a treatment cycle to collect these questionnaires is between the date of insemination and the date of the pregnancy test for couples undergoing IUI, and between the date of embryo transfer and the date of the pregnancy test for couples undergoing IVF.

9.2. Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a particular aspect of the trial without completely withdrawing. Couples who have decided not to adhere to their randomisation treatment allocation but are willing to be followed up in accordance with the schedule of assessments should not be treated as withdrawals. In this instance a protocol deviation form should be completed.

The changes in levels of participation within the trial are categorised in the following ways:

Partial withdrawal - One or both partners wish to withdraw from certain aspects of the trial, such as the intervention, follow-up, completion of questionnaires and/or data collection.

Complete withdrawal - No further data collection: The couple are not willing to be followed up in any way for the purposes of the trial AND do not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

Withdrawal from one of the sub-studies: Participants may withdraw from the QPE and/or the Bioethics Sub-study within 2 weeks of the data collection event but may still continue in the main trial. It is not possible to withdraw from the Healthcare science outcomes sub-study as this is mandatory for trial participation.

The details of changes in levels of participation in the trial (date, reason and category of status change) should be clearly documented in the participant's medical notes and captured on the Change of Status CRF. All withdrawals should be discussed with the UNiTY trial office before completing the CRF.

Participants found to be ineligible post-randomisation should be followed up according to all trial processes and a protocol deviation CRF should be completed.

Further information about withdrawal from the qualitative process evaluation and bioethics study can be found in section 16.

10.ADVERSE EVENT REPORTING

10.1. Definitions

Table 2: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	-	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

10.2. Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements

of the Health Research Authority (HRA). Definitions for adverse event reporting are listed in Table 2: Adverse event reporting definitions in Section 10.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

10.3. Adverse event reporting in UNiTY

The reporting period for AEs in UNiTY will be from the day the trial intervention starts until 60 days after the cycle outcome is known. For an unsuccessful cycle (i.e. biochemical pregnancy was not detected) SAEs should be reported for 60 days following the negative pregnancy test. For cycles resulting in pregnancy, SAEs should be reported for 60 days after the pregnancy outcome is known (i.e. live birth, still birth, termination or miscarriage). SAEs should only be reported for trial related treatments, with the exception of the first IVF cycle in the IUI arm. Any non-trial treatment related SAEs should be recorded in the medical notes but not reported to the trial office.

The safety profile for the trial population and interventions are well established, so although it is recommended that the severity, seriousness, and causality of all AEs for both participants and offspring should be recorded in the relevant medical notes, a strategy of targeted reporting of AEs will not affect the safety of participants. Related AEs will be captured as complications within the primary and secondary outcome measures. Only serious, related, and unexpected adverse events, beyond the routine expectations and known risks for fertility treatment, will be reported as SAEs.

10.4. Serious Adverse Advents (SAE) reporting in UNiTY

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the trials office on an SAE form as per Section 10.4.1 Serious Adverse Events not requiring reporting to the Trial Office.
2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 10.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office.
3. **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per Section 10.5 SAE Reporting process.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

10.4.1. Serious Adverse Events not requiring reporting to the Trial Office

At whatever time they occur during an individual's participation, from commencement of intervention up to 60 days after the cycle outcome is known, only serious and related SAEs will be reported to the trial office. SAEs that do not fall into these categories will be recorded on follow up CRFs.

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt". They will be recorded on the treatment CRFs as part of trial follow-up.

10.4.2. Serious Adverse Events requiring non-expedited reporting to the Trial Office

As the safety profile of the interventions are well established, the causal relationship between the intervention (or the participant's underlying condition), and the SAE, may be known. That is, such events are protocol-defined as "expected" (see Section 10.5.2 Assessment of expectedness of an SAE by the CInvestigator (CI)).

Such events should still be recorded by the trial team in the participant's notes and reported to the Trial Office on the relevant CRFs, but do not require expedited reporting (i.e. immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined. This includes:

- Hospital admissions due to OHSS

This information should be uploaded onto the trial database within four weeks of the event.

10.4.3. Serious Adverse Events requiring expedited reporting to the Trial Office

All serious and related AEs must be reported to the Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

10.5. SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office as per the requirements of protocol section 10.4.

To report an SAE to the Trial Office, the PI or delegate must complete, date and sign the trial specific SAE form on the REDCap database. Any other relevant, appropriately anonymised, data should be submitted to the Trial Office using the information below in accordance with the timelines given in Section 10.4.2 and 10.4.3.

To report an SAE, submit the SAE Form to the UNiTY trial team via the main trial database.

Where an SAE Form has been completed by someone other than the PI initially, the SAE form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

On completion of an SAE form, the database will assign a unique SAE reference number and notify the site and Trial Office via email as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence regarding the SAE and filed with the SAE in the ISF. The original SAE form should be updated with any relevant follow-up information.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the Trial Office.

10.5.1. Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see **Error! Reference source not found.**) of the event.

In defining the causality, the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

Table 3: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

As per Table 4, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the participant's medical notes. On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate(s) who will independently review the causality of the SAE on behalf of the Sponsor. Where the CI is also the reporting PI an independent clinical causality review will be performed. An SAE judged by the PI or CI or delegate(s) to have a reasonable causal relationship ("Related" as per **Error! Reference source not found.**) with the intervention will be regarded as a related SAE (i.e., SAR). The severity and causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

10.5.2. Assessment of expectedness of an SAE by the CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in Table 5.If the event is unexpected (i.e., it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

10.5.3. Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be added to the original SAE form. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is

Table 4: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures.
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and the original kept in the ISF.

10.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) will review any SAEs at their meetings.

The Trial Office will submit a progress report to the Research Ethics Committee (REC) and the University of Birmingham (UoB) Research Governance Team (RGT) annually starting 12 months after the date of the favourable opinion was given. An electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

The Trial Office will report all events categorised as Unexpected and Related SAEs to the Research Ethics Committee (REC) and UoB Research Governance Team (RGT) within 15 days of being notified. Details of all Unexpected and Related SAEs and any other safety issue which arises during the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

10.7. Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

10.8. Follow-up of pregnancy outcomes for potential SAEs

Since live birth is the primary outcome in the trial, congenital abnormalities or birth defects will be routinely collected and monitored. Data on congenital anomalies or birth defects will be recorded on the Clinical Pregnancy Outcome CRF.

11.DATA HANDLING AND RECORD KEEPING

11.1. Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Some data variables may be entered directly onto the CRF:

- Patient Reported Outcome Measures

Other data is non-CRF based

- Healthcare science sub-study videos and slides
- Qualitative process evaluation and bioethics study transcripts

Source data is kept as part of the participants' medical notes generated and maintained at site.

Table 5: Source data in UNiTY

Data	**Source**
Participant Reported Outcomes	The original participant-completed CRF is the source. Electronic versions will be stored on the trial database. Paper versions will be stored with the participant's trial record at site with copies provided to the trial office.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto CRFs.
Imaging/videos	The source is the original imaging usually as an electronic file. Data may be supplied to the Trials Office as a password-protected, anonymised, copy of the electronic file, or as an interpretation of the imaging provided on a CRF. Where data is interpreted, the CRF onto which it is transcribed becomes the source. Copy of the CRF should be provided to the trial office.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents.
Healthcare Science sub-study	The slides and videos obtained for this sub-study are the source data. Analysis will be performed directly on this material.
Qualitative transcripts	The audio file onto which the interview is recorded is the source documentation

11.2. Case Report Form (CRF) completion

The CRFs will include (but will NOT be limited to) the Forms shown in **Error! Reference source not found.**.

Table 6: Case report forms in UNiTY

Form Name	**Schedule for submission**
Informed Consent Form (one for each partner)	Prior to randomisation
Screening CRF	Prior to randomisation
Baseline CRF	Prior to randomisation
Baseline participant questionnaire: - EQ-5D-5L	Prior to randomisation
Treatment CRFs: - IVF treatment CRF - IUI treatment CRF - Laboratory CRF - Frozen Transfer CRF	During or as soon as possible after treatment
Outcomes CRF: - Post-treatment CRF	8 weeks after treatment starts (defined as the first day of ovarian stimulation) in order to capture all potential complications/outcomes.
Outcomes CRF: - Clinical Pregnancy outcome CRF	As soon as possible after each follow up assessment time point (19 months and 25 months post randomisation)
Outcome participant questionnaires - EQ-5D-5L (one questionnaire to be completed for each partner) - CSQ-8 (one questionnaire to be completed for each partner) - Health resource use (one questionnaire to be completed per couple)	As soon as possible after each follow up assessment time point (during the first treatment cycle of IUI and/or IVF, 19 months and 25 months post randomisation)
Non-trial treatment form	During or as soon as possible after treatment
Natural pregnancy notification CRF	As soon as possible after becoming aware of participant's pregnancy
Serious Adverse Event Form	If expedited: emailed within 24 hours of site research team becoming aware of event If non-expedited: emailed within 4 weeks of site research team becoming aware of event
Change of Status Form	As soon as possible after the point of reduced participation
Deviation Form	As soon as possible after a protocol deviation has occurred

A CRF should be completed for each couple or individual participant as documented at the top of each document. CRFs repeat to account for multiple treatment cycles and multiple pregnancies.

In all cases it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI, or delegate(s). The Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the CRF.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. Missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to GCP requirements and trial-specific guidelines, which will be provided separately.

All CRFs will be entered into REDCap by site teams. Paper copies of the forms are provided only for sites who wish to complete forms in an area with no immediate internet access.

The following guidance applies to data and partial data, on REDCap and if paper copies of forms are used:

- Only CRFs provided by the Trial Office should be used.
- Entries should be made in dark ink and must be legible.
- Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated.
- Time format – all times should be in accordance with the 24hr clock
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

Data for the UNiTY sub-studies, namely qualitative transcripts, and videos and slides of semen samples, will not have a CRF. Analysis will be directly performed on source data. Collection and processing of this data will be done in accordance with GCP, the relevant sections of this protocol and separate trial-specific instructions.

11.3. Participant completed questionnaires

Participant questionnaires can be completed using the participant's favoured mode of communication (letter, telephone, email, online), with a reminder if no response is provided within 2 weeks.

11.4. Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Data entry will be completed by the sites via a REDCap trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries

will be raised via the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be routinely requested.

11.5. Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

Operational processes: the data will be processed and stored within BCTU

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

11.6. Archiving

All records created by following trial procedures and all documents listed in guidance relating to the conduct of the trial must be retained and archived for the specified period.

The trial master file (TMF) is composed of a sponsor file, held by the sponsor organisation, and an investigator site file, held by the site investigator. Documents are archived following any regulatory requirements and any local procedures.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; UNiTY trial data will be stored securely and confidentially for at least 10 years (acknowledging that participant medical records will be stored for 50 years as standard under HFEA). BCTU has standard processes for both hard copy and computer database legacy archiving.

12.QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2. Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.2.1. On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the UNiTY trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.2.2. Central monitoring

The Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent requests for missing data or clarification of inconsistencies or discrepancies.

12.3. Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

12.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13.END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of queries. This includes the capturing of all qualitative data and lab results in the UNiTY sub-studies. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC and the Sponsor within 90 days of the end of trial. Where the trial has been terminated early, the Trial Office will notify the REC within 15 days of the end of trial. The Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14.STATISTICAL CONSIDERATIONS

14.1. Sample size

The HFEA suggests that the primary outcome rate in the IVF group will be approximately 28% (1). To ensure the IUI group will be within a 10% margin of non-inferiority (i.e., no lower than 18%) with 90% power (one-sided alpha of 0.025, equivalent to a two-sided alpha of 0.05), the trial will require 942 participants (assuming a conservative 10% loss to follow-up).

A three IUI cycle rate of at least 18% (approximately 6.4% per-cycle) would deliver 64% of the live births of IVF for 46% of the total costs, justifying the 10% margin of non-inferiority from a commissioning or self-funding couple financial perspective (see Table 8*Table 8*). A success rate matching IVF (28%) would be for 44% of the total costs of IVF (see Table 9).

The margin of non-inferiority is also justifiable if we consider that many of those allocated to IUI who do not achieve live birth will go on to receive an IVF cycle provided by the NHS, even considering further interventions and the possibility of natural birth in the IVF policy group *[MRC/NIHR framework, core element 1: context].* We will assess whether the initial IUI treatment policy is the superior approach in our medium-term assessment (25 months post-randomisation). For this assessment, we will have adequate (>80%) power to detect a 10% difference in live birth (≥34 weeks) rates (e.g., 45% vs 35%).

Table 7: Cost comparison, assuming a 10% margin of inferiority, between 3 cycles of IUI (assumed success rate per cycle of 6.4%) and 1 cycle of IVF (assumed success rate per cycle of 28%)

	IUI Cycle 1	IUI Cycle 2	IUI Cycle 3	IVF Cycle 1
Number of couples	100.0	89.6	80.4	100.0
Expected live births	6.4	6.0	5.6	28.0
		Total live births	18.0	28.0
		Number of cycles	281.2	100.0
		Cost per cycle	£605.33	£3,682.00
		Total cost	£170,225.54	£368,200.00
		Cost per live birth	£9,458.33	£13,150.00

Table 8: Cost comparison, assuming a 0% margin of inferiority, between 3 cycles of IUI (assumed success rate per cycle of 10.36%) and 1 cycle of IVF (assumed success rate per cycle of 28%)

	IUI Cycle 1	IUI Cycle 2	IUI Cycle 3	IVF Cycle 1
Number of couples	100.0	89.6	80.4	100.0
Expected live births	10.4	9.3	8.3	28.0
		Total live births	28.0	28.0
		Number of cycles	270	100.0
		Cost per cycle	£605.33	£3,682.00
		Total cost	£163,435.94	£368,200.00
		Cost per live birth	£5,842.99	£13,150.00

14.2. Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to receive three cycles of letrozole stimulated IUI versus those randomised to receive one cycle of IVF. For all outcomes, analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation (see Table 10 for proposed populations). For the primary outcome, given the nature of the non-inferiority design, supportive per-protocol and Complier Average Causal Effect (CACE) analyses (38) will be considered alongside the intention-to-treat population. All outcomes will be adjusted for the minimisation variables listed in Section 6.4.2 where possible.

For all major outcome measures, summary statistics and differences between groups, e.g. risk difference, relative risks, will be presented with 95% confidence intervals. For the primary outcome, this is equivalent to a one-sided 97.5% confidence interval and hence conservative in terms of the non-inferiority margin. For the trial to declare non-inferiority of the three cycles of letrozole stimulated IUI method, the lower margin of the absolute risk difference (see 14.2.1 for calculation method) confidence interval must not exceed 10%.

All secondary outcomes will be considered as exploratory; no adjustment for multiple comparisons will be made and hence significance should not be inferred from the confidence interval width.

14.2.1. Primary outcome

The primary outcome is a binary outcome, and we will use a mixed effect binomial regression model to estimate an absolute risk difference between groups and 95% confidence interval (primary method). Relative risks will be calculated in a similar fashion using a log-binomial regression model. Parameters for treatment group as well as the minimisation variables (listed in Section 6.4.2 will be included in the model as fixed effects (apart from randomising centre which will be included as a random effect). The p-value (relating to the non-inferiority hypothesis) as generated by the model estimating the absolute risk difference will be presented.

14.2.2. Secondary outcomes

The secondary outcomes that are binary (i.e., yes/no) will be analysed using the same methods as described for the primary outcome (see Section 14.2.1), with corresponding 95% confidence intervals (this includes the longer-term assessment at 25 months). For those secondary outcomes that are continuous (e.g. Gestational age at delivery, Birthweight, CSQ-8 score), mixed effects linear regression methods will be utilised to calculate an adjusted mean difference and 95% confidence interval. Time-to-event outcomes (e.g. TTP leading to a live birth) will be analysed using a mixed effects ('frailty') Cox Proportional Hazard model, allowing the same minimisation variables as fixed effects and randomising centre as a random effect. The treatment effect will be expressed as adjusted hazard ratio with 95% confidence interval. Regarding safety, the total number of participants experiencing SAEs will be given by allocation group along with a descriptive table of the events, and statistical significance will be determined by a chi-square test; other safety data including complications will be tabulated by group but are not expected to be formally analysed.

Table 9: Proposed analysis populations for primary outcome of live birth≥34 weeks

Timeframe	**270 days of randomisation (primary)**					**450 days of randomisation (medium term)**				
Group=3 cycles of IUI										
	Conceived			**Not conceived**		**Conceived**			**Not conceived**	
	<=3 cycles[1]	With further intervention (IUI, IVF, FET)	Natural pregnancy	At least 3 cycles	<3 cycles	<=3 cycles	With further intervention (IUI, IVF, FET)	Natural pregnancy	At least 3 cycles	<3 cycles
Primary: Intention-to-treat any pregnancy[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Secondary 1: Intention-to-treat first pregnancy only	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Secondary 2: Per-protocol[2]/CACE	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Group=IVF										
	Conceived			**Not conceived**		**Conceived**			**Not conceived**	
	IVF	With further intervention (IUI, IVF, FET)	Natural pregnancy	At least one IVF	No intervention	IVF	With further intervention (IUI, IVF, FET)	Natural pregnancy	At least one IVF	No intervention
Primary: Intention-to-treat any pregnancy[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Secondary 1: Intention-to-treat first pregnancy only	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Secondary 2: Per-protocol[2]/CACE	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No

Yes=inclusion within analysis population (or considered adherent for CACE)

FET=Frozen embryo transfer

[1]In the situation where e.g. an initial pregnancy did not result in a live birth ≥ 34 weeks, but a second one did then this outcome would supersede the result of the first pregnancy

[2]Per-protocol: only includes outcome relating to the randomised intervention (plus further intervention in the medium term period)

14.2.3. Planned subgroup analyses

Subgroup analyses will be limited to the variables that were used for the minimisation algorithm (see Section 6.4.2 excluding centre) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4. Missing data sensitivity and other supportive analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include multiple imputation techniques and 'tipping point' scenarios.

14.3. Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 25 months post-randomisation follow-up assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

15.HEALTH ECONOMICS

Identifying a cost-effective intervention for assisted reproduction is imperative in the current economic climate to optimise the use of limited public resources *[MRC/NIHR framework, core element 6: economic considerations]*. Previous studies have estimated the cost of three cycles of IUI (superovulation without donor) at £1,816 (39) and an IVF fresh cycle (using eggs and embryos that are never frozen) at £3,682 (40), both costs are adjusted to 2020 prices using Consumer Price Index (CPI) Health (41). As noted, if three cycles of IUI have a success rate matching IVF (28%) there would be a 36% reduction in cost per live birth. However, the additional cost of including IUI would need to be justified and shown to provide good value for the limited public healthcare resources. An economic evaluation is therefore required to assess the cost-effectiveness of three cycles of IUI compared to one cycle of IVF in the management of unexplained infertility.

15.1. Economic data collection

The economic analysis will be conducted from the perspective of the health care system, accounting for the direct costs incurred by the UK NHS as recommended by NICE (42), including individual level data on all health-related resource use. The main resource categories that will be monitored include the following:

1. Drug administration
2. Resource use of standard care
3. Resource use associated with adverse events and complications (including premature birth and neonatal care)
4. Resource use associated with outpatient or emergency visits and hospital admissions
5. Contacts with community and social care services, such as general practitioner, practice nurse and counsellors

To estimate the overall cost of each trial-arm, unit costs will be applied and attached to each resource item. Information on unit costs will be obtained from centres participating in the trial and UK national sources such as NHS Reference Costs (39), Unit Costs of Health and Social Care (43), the British National Formulary (BNF), and Office for National Statistics (ONS). Costs used in other relevant published sources will be sought for use in sensitivity analysis.

HrQoL data will also be obtained based on participants' responses to the EQ-5D-5L. A preference-based index of HrQoL will be derived using the recently published English value set, and QALYs will be calculated using the area under the curve approach.

15.2. Economic Analysis

A trial-based economic evaluation will be conducted to explore the relative cost-effectiveness of the two interventions. Given there is crossover anticipated between the interventions, as those allocated three cycles of IUI will be followed by the commencement of one cycle of IVF (though not before eight months has elapsed from randomisation), a model-based approach for analysing this may be most appropriate to capture the changes and crossover here, but we will explore whether this is necessary.

The appropriateness and feasibility of undertaking a distributional cost-effectiveness analysis will also be explored to address equity concerns around the distribution of costs and outcomes. This is a relatively new approach, and thus the feasibility of undertaking this analysis may be hampered by lack of availability of appropriate data.

15.3. Presentation of the analysis

A preliminary cost consequence analysis will be carried out comparing all costs and outcomes for the intervention and current practice as assessed in the trial in a disaggregated format. The main

economic analysis will be in the form of a cost-effectiveness analysis based on outcome of cost per live birth at ≥34 week's gestation. The main analysis will adopt an NHS perspective. However, given the potential variation in time commitment of participants in each trial arm, the perspective will be expanded beyond the base case of the health care system to include the lost productivity of patients measured using the human capital approach based on participants occupations collected at baseline.

The QALY data collected will be reported separately and the economic analysis is not anticipated to be based on the results of the EQ-5D in terms of cost per QALY. This is because the final outcome of live birth is likely to override the process of getting there. Thus, QALYs will be reported separately to convey the information and impact of the process of fertility treatment and not the final outcome in terms of cost effectiveness.

Missing data will be addressed through multiple imputation. The recommended approach to discounting will be followed, if necessary, which would include discounting costs and benefits at 3.5% in accordance with NICE guidelines (44).

For the analysis, an incremental cost-effectiveness analysis will be conducted based on the main outcome of cost per live birth at ≥34weeks gestation. The results of economic analysis will be presented using cost-effectiveness acceptability curves (CEACs) to reflect sampling variation and decision uncertainty across different thresholds of willingness-to-pay per additional unit of outcome where appropriate. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key assumptions and analytical methods used, and to consider the broader issue of generalisability of the study's results.

15.4. Distributional cost-effectiveness analysis (DCEA)

The feasibility of carrying out a DCEA will also be explored (these are currently experimental and very data dependent) to examine equity concerns. If possible and feasible, this will involve undertaking an equity impact analysis (EIA), which will quantify the distribution of costs and effects by socioeconomic status, ethnicity, and location. The combined results of the economic analysis will give policymakers a better understanding of the cost effectiveness and equity impacts of IUI compared to IVF *[MRC/NIHR framework, core element 3: stakeholders].*

16.SUB-STUDIES

16.1. SUB-STUDY 1: Qualitative Process Evaluation

16.1.1. Aim

To explore and understand the feasibility, acceptability, ethical and equity implications, context of the intervention, and the evaluation design. The QPE which will occur during the pilot phase of the trial, will also inform the development and refinement of a programme theory for the UNiTY trial.

16.1.2. Objectives

(1) **With couples who have unexplained infertility**: to explore their views and experiences of the recruitment approach, randomisation, barriers and facilitators to participation, and acceptability of treatment allocations**.**

(2) **With healthcare professionals (HCPs)**: to explore their views and experiences of recruitment, randomisation, appropriateness and acceptability of treatment allocations, intervention and trial context, and perceptions of trial processes.

16.1.3. Outcomes

The key outcome of the QPE will be a qualitative assessment of UNiTY's feasibility, acceptability and appropriateness for couples and HCPs. This pragmatic QPE aligns with the new 2021 MRC/NIHR framework for developing and evaluating complex interventions (24). The six core elements of the framework will be considered (where appropriate to the trial and the intervention(s)) including: (i) how the intervention interacts with its **context**, (ii) the underpinning **programme theory**, (iii) how diverse **stakeholder** perspectives are included in the research, (iv) identifying the key **uncertainties**, (v) how the intervention can be **refined**, and (vi) the comparative **economic** resource and outcome consequences of the intervention. The answers to these questions will be used to dynamically inform decision making as to whether UNiTY should proceed to the next evaluative phase (e.g., continue to a full trial, refine the study design, or stop the trial).

16.1.4. Eligibility

Inclusion

- All couples (individually or as a couple) eligible for UNiTY who are approached about the trial, irrespective if they agree to participate or not.
- All HCPs caring for couples with UEI and involved in the delivery of the UNiTY trial
- Those able and willing to give informed consent

Exclusion

- Participants who would be unable to take part in an interview where we cannot support their language needs (interviews will be undertaken in a range of languages where we can support this with an appropriate interpreter).

16.1.5. Participant Identification and Treatment

Couples will be approached to participate in an interview after they are approached to participate in the trial, whether they consent to the trial or not. If they verbally consent to potentially taking part in an interview, they will be asked to provide their contact details (via a consent to contact form). The recruiting clinician or research team member, confirmed locally as part of the direct care team, will securely transfer these details on to the qualitative research team.

In addition, recruiting clinicians or research nurses will review their site-specific screening logs and notes of all couples approached about the trial. Where there is no documented evidence of discussion

about the qualitative process evaluation or where couples have asked to be contacted about the qualitative study at a later time, the research nurses will follow couples up directly via letter/email. The letter/email will be specific to their decision about participating in the trial (e.g., decliner or randomised). The notes review and follow up letters will be sent within approximately 4 weeks of the approach about the trial, from a member of their usual care team for couples who have declined, and from a member of their usual care team on behalf of the qualitative team for couples who have been randomised. Within the letter couples will be asked to contact the qualitative research team directly if they wish to know more and/or take part. Couples who have clearly declined participation in the qualitative study will not be contacted via letter.

HCPs will be approached directly by the qualitative research team after being identified from the delegation logs, snowballing within sites, and through collaborator events and established clinical networks.

16.1.6. Consent and Withdrawal

Written informed consent to participate will be sought wherever possible. However, for example, in cases where the study related paperwork has not been received, not fully completed, or there are issues around literacy, we will seek alternative forms of informed consent including electronically completed (e.g., electronic completion of the form and scanning/photo of the completed consent form) or verbal (e.g., where the consent form will be read out in full, and audio recorded at the start of the interview).

Informed consent (written, electronically completed and/or verbal (that is audio recorded)) will include agreement to participate, demographic data collection, audio recorded discussion, and anonymised data sharing.

At the beginning of each audio recording, participants who have completed written or electronic consent processes will be asked to verbally re-confirm consent. Where formal verbal informed consent is being sought at the start of a virtual interview, two separate audio file recordings for each participant will be created. The first audio file will just cover the consent discussion and record verbal consent. The consent form will be read out, and the participant asked to consent to each statement. Should the participant not consent to any of the statements the interview will be terminated at that point having explained to that participant that data collection cannot continue, as they did not consent to participate.

Once verbal consent has been obtained the first audio file will be closed. A member of the qualitative research team within the University of Birmingham will transcribe the consent audio file to create a formal record of consent or declined consent. This transcript will be stored securely and separately from the transcript of the main interview (if consent was gained). If the participant does give consent, then the study interview will commence and be recorded in a second audio file. Only this second file will be sent to a third-party company for transcription.

Interview participants will be free to withdraw at any time within two weeks of the data collection event without having to explain or justify their decision.

16.1.7. Inconvenience Allowance and Expenses

Participants will receive a £25 (per individual participant) electronic voucher (e.g., Amazon) for participation in an interview. This covers £20 as a thank you for their time and £5 for consumables such as electricity/internet access given that we anticipate most interviews will be held remotely.

16.1.8. Data Collection

Participants will be invited to participate in an interview via telephone or University of Birmingham approved video conference account (e.g., Teams, Zoom, Skype or WhatsApp) as per their preference.

Couples can participate in an individual interview or as part of a paired interview dependent on their preferences. Either partner can participate, and this is not dependent on the other partner participating. We aim to conduct interviews within four to six weeks of couples being approached to participate (decliners) or being randomised (couples who consent to randomisation). This will, however, remain flexible to accommodate the needs of the participants *[MRC/NIHR framework, core element 1: context, core element 3: stakeholders]*.

A discussion guide to facilitate the interviews will be developed based on existing literature, PPIE, and discussions within the trial team *[MRC/NIHR framework, core element 1, 3 & 4: context, stakeholders & uncertainties]*. Interviews will be conducted in a participant-focused manner allowing issues and perspectives important to participants to arise naturally (45). For participants, interviews will explore their views and experiences of the recruitment approach, randomisation, barriers and facilitators to participation, acceptability, and ethical appropriateness of allocation to IUI vs. IVF. For HCPs, interviews will explore their views and experiences of recruitment, randomisation, including perceived barriers and facilitators, equipoise, appropriateness and acceptability of treatment, and perceptions of trial processes. The professional perspectives of HCPs will also be explored on the ethical issues raised by offering IUI for UEI, such as balancing patient choice with cost, funding constraints on practice, and risk assessments *[MRC/NIHR framework, core element 6: economics]*.

All participants will be asked to complete a brief demographic questionnaire (online or paper based) prior to or at the end of the interview to facilitate purposive sampling and a description of the sample going forwards.

16.1.9. Anticipated Sample Sizes

We aim to undertake semi-structured interviews across the sites involved in the trial and will attempt to purposively recruit participants from the following groups (number of interviews per group provided in brackets):

a. couples who decline to participate (n~10-15)
b. couples randomised to IUI (n~10-15)
c. couples randomised to IVF (n~10-15)
d. HCPs involved in recruitment and randomisation (n~15-18)

Sampling will attempt to address the site populations in relation to ethnicity, culture, and language *[MRC/NIHR framework, core element 1: context, core element 4: uncertainties]*. For example, translation services will be provided for eligible participants who face a language barrier for interviews. Interviews will, where possible, be undertaken in different languages supported by a trained interpreter.

Anticipated sample sizes for couples are based on the number of interviews, not the number of participants. The number of interviews will remain flexible, and the adequacy of the final sample size carefully monitored to ensure the data will have sufficient information power to develop new knowledge in relation to the research questions (46).

16.1.10. Data Analysis

Interviews will be digitally-audio recorded, with data collection and initial analysis taking place iteratively (45). Audio files will be transcribed clean verbatim (and translated into English where needed) by an external specialist transcription/translation company and reflexive thematic analysis (45) used to facilitate a systematic and flexible approach to the analysis. A dynamic approach will be

used to facilitate real time feedback to the TMG to identify potential trial and trial process issues (e.g. with recruitment and randomisation), so that these can be addressed rapidly, and thus increase the likelihood of successful progression to the full RCT. QPE findings will be combined with knowledge from the existing literature, PPI, and findings from the bioethics sub-study (see section 16.3) to develop and refine a programme theory for the UNiTY trial *[MRC/NIHR framework, core element 2: programme theory].* The programme theory will be an important resource for us and/or others to build upon for future research.

16.1.11. Management of Risk

All participants will self-select to take part. Given the nature of the interviews focusing on issues related to recruitment, randomisation, and trial processes, it is unlikely that participants in this study will be distressed by this part of the discussion. However, the topic of infertility is potentially emotive and so participants may become distressed because of participating in an interview.

Trained qualitative researchers will undertake data collection guided by Dempsey *et al* framework of essential elements for conducting qualitative research given the potentially sensitive issues that may emerge in discussions (47). Distressing topics will be handled sensitively, and we will follow a study specific distress pathway including signposting to additional support as appropriate (47).

The welfare of the participants will always be placed ahead of the knowledge to be gained and emotionally distressing topics will be handled with sensitivity and sympathy. It will also be clearly stated in the PIS, by the person introducing the potential participant to the study, as well as being reiterated by the qualitative researcher at the beginning of the interview that participants are free to withdraw at any time up to two weeks after the data collection event without having to explain or justify their decision. The interviewer will also signpost the distressed participant towards services for additional support should this be appropriate. Information on support services is also provided in the PIS. We have sought PPI input to ensure that all participant facing materials and the interview questions are appropriate and acceptable *[MRC/NIHR framework, core element 3: stakeholder]*.

If a participant raises issues about their care that the qualitative research team deem as potentially harmful to them (or others), the researcher will advise them to contact their local Patient Advice and Liaison Service (PALS) (or equivalent) whose contact details are provided in the PIS. The lead for the qualitative sub-study, Dr Laura Jones, will also inform the CI. The CI, where appropriate, will ensure that the local unit PI is aware of the participant's concerns so that follow-up can be arranged if required. Should a participant have questions about their clinical care the qualitative research team will advise the couple to contact their clinical team and/or their GP.

16.1.12. Nesting Within the UNiTY Trial

Recruitment to the qualitative study will begin in parallel with the pilot trial, with qualitative data collection taking place for ~7 months. This will include dynamic feedback in real time to allow the TMG to be adaptive to any problems identified and increase the likelihood of the pilot moving to the full RCT *[MRC/NIHR framework, core element 5: refinement]*. Final analysis and initial write up will be undertaken in month 8/9, prior to the pilot review at the DMC and TSC meetings.

16.1.13. Relationship with the Bioethics Sub-study

The QPE will help inform the ethical issues that will be explored in greater depth as part of the bioethics sub-study (see section 16.3) *[MRC/NIHR framework, core element 4: uncertainties]*. Interviews for the bioethics sub-study will be performed with couples who have completed the trial protocol (even if they have not participated in the QPE). Findings from the QPE and the bioethics sub-study will jointly inform the development and refinement of the UNiTY programme theory *[MRC/NIHR framework, core element 2: programme theory].*

16.2. SUB-STUDY 2: Healthcare Science

16.2.1. Aim

To investigate the variations in how male factors are assessed across the clinical partners involved in the trial, both at the diagnostic and the therapeutic stages of treatment, and to evaluate existing and novel sperm quality measures as prognostic factors.

16.2.2. Objectives

(1) To assess the standardisation of semen quality assessment at different sites, using videos created at site together with dry smears made at site.
(2) To evaluate the prognostic value of existing, WHO markers of male factor infertility.
(3) To evaluate the prognostic value of additional novel markers of male factor infertility in microscopy, including flagellar beat.

16.2.3. Outcomes

(1) A characterisation of the standardisation of sperm analysis results across sites in the trial to uncover whether male factors are being correctly identified in diagnosis of UEI.
(2) A measurement of the prognostic value of existing sperm analysis markers for both IUI and IVF.
(3) A set of novel sperm flagellar markers with prognostic value for both IUI and IVF.

16.2.4. Eligibility

All partners providing sperm who are taking part in the study will have a trial semen analysis for every sample they provide for treatment, and this sub-study is a required step for external quality assurance. There are no additional inclusion or exclusion criteria. The data from this research semen analysis will not be used to change treatment allocation (e.g. withdraw from treatment if sample <10M).

16.2.5. Participant Identification and Consent

Information about this sub-study will be included in the trial Participant Information Sheet and partners providing sperm will consent as part of the main trial consent form. Consenting to this sub-study is not optional.

16.2.6. Site Data Collection

The healthcare science outcomes comprise measurement of the semen sample at four stages.

Routine Initial Diagnostic

The routine initial diagnostic sample will have been taken prior to trial screening, and the details of this sample will be collected at baseline.

Raw sample

An aliquot of the sample produced for treatment will be assessed following routine practice before being prepared for treatment.

Prepared treatment sample

The sample will be prepared for treatment as per each arm of the trial, protocols and media will be recorded on a per-site basis (rather than per-couple on an individual CRF). An aliquot of the prepared sample will be assessed before insemination.

Insemination sample

The total sperm inseminated (and volume of sample used for insemination) will be recorded.

At no stage are the actual individual sperm assessed for this sub-study to be used in treatment, this is routine, which remains unchanged as they are on a slide for assessment, and the treatment will

therefore remain unchanged as a result of this sub study. The required analyses are standard practice and we are not asking the local laboratory teams to do any assessment they are not experienced in.

In addition to the semen analysis performed at site, they will also prepare data for the central team:

Videos

To allow for the external quality assurance for sperm motility assessments, and for the measurement of additional sperm parameters, videos will be taken of both the raw and prepared treatment samples. Many sites currently use computer-aided sperm analysis (CASA) systems for doing these assessments, in which case they will have the equipment and software needed. For sites which currently do not use CASA systems, they will have a system (microscope, computer, camera) provided for the capture of these videos. Video capture will be following the trial procedure, which will be provided to site teams in separate trial-specific guidance. In brief:

1. Sample will be placed in a 10μm depth chamber on a heated stage at 37°C.
2. Analysed using negative-phase microscopy with a 10x or 20x objective.
3. If the concentration of the sample is greater than 15 M/ml, the sample should be diluted to this level.
4. Videos should be recorded for one second at a frame rate of at least 60 f.p.s. (with the exact frame rate recorded).
5. Ideally a minimum of 200 in focus sperm cells would be available for analysis.
6. If this is not achievable in 20 fields, then acquisition can be discontinued, and the dataset considered complete.
7. Care should be taken that the 200 sperm are away from the edges of the field of view, and that imaged sperm are well separated (i.e. there are not excessive numbers of crossing sperm).

Slides

Following standard WHO sperm smear protocols, slides will be made and shipped to the Centre for Human Reproductive Science, UoB.

16.2.7. Data Transfer

Videos

Videos will be recorded onto pairs of encrypted hard disk drives (HDDs) with no patient-identifying information (aside from Trial ID number). The use of pairs of HDDs will mitigate the risk of a single-point-of-failure before data is received and backed up on UoB secure Research Data Store.

Once central analysis on the videos has been performed, they will be retained following data retention procedures for the main trial.

Slides

Slides will be stored in slide boxes (provided by the central trial team) at room temperature and sent in batches, being delivered to the Centre for Human Reproductive Science, UoB, by experienced courier. Once the analysis has finished, slides will be discarded after digital assessment and not retained for more than 5 years after the end of the trial without further ethical approval.

16.2.8. Central Data Analysis

External quality assurance (EQA)

Videos and slides will be assessed in Birmingham for sperm quality. These results will be compared with the local site measurements to assess consistency both within each local site, and across each site in the trial.

Prognostic value of sperm quality measures

Sperm quality measures will be assessed against treatment outcomes for prognostic value. Videos will be assessed by eye following WHO gold-standard protocols (48) and by computer using the UoB-developed FAST software package (21). Slides will be assessed by eye for morphology following WHO gold-standard protocols (48). These quality measures will come from three sources, and be assessed in turn for differences, namely:

1. Local site WHO gold-standard sperm quality measures vs treatment outcomes.
2. EQA-adjusted WHO gold-standard sperm quality measures vs treatment outcomes.
3. Novel flagellar sperm quality measures vs treatment outcomes.

16.3. SUB-STUDY 3: Bioethics Study (49, 50)

16.3.1. Aim

To investigate ethical issues identified for and or by couples who have completed the trial protocol, and to understand the intersecting perspectives of clinicians, commissioners, and patients.

16.3.2. Objectives

1. To understand the intersection between costs of treatment and treatment choices from the perspectives of both patients and professionals.
2. To look at trade-offs in the trial and explore different perceptions of cost, TTP, medical risks, and success rates.
3. To understand how to design trials that incorporate equality and equity concerns into recruitment and subsequent experience of the trial process.

16.3.3. Outcomes

1. A greater understanding of patients' perceptions of access issues – how they weigh up cost of treatment, TTP, medical risks and treatment success rates.
2. Fertility professionals' (doctors, fertility nurses and related clinic staff) perceptions of these issues, as well as commissioners of services view on this and how their priorities intersect with patients' perspectives. This will give us the perspectives from the three main stakeholders in fertility treatment. For example, commissioners might prioritise low-cost treatment, while for couples having a pregnancy/child might be a higher priority. We hope to begin to unravel how the organisational aspects – funding, where it is delivered, how long one has to wait - interact with the 'success' of the treatment.
3. Improve access to trials in this area and how funding restrictions and criteria could impact on trial participation.

16.3.4. Eligibility

Inclusion

- All participants (individually or as a couple) who complete the UNiTY trial
- Professionals working at fertility clinics in England
- Individuals involved in commissioning fertility services (Integrated Care Boards – across England)
- Those able and willing to give informed consent

Exclusion

- Participants who would be unable to take part in an interview where we cannot support their language needs (interviews will be undertaken in a range of languages where we can support this with an appropriate interpreter).

16.3.5. Participant Identification

When couples complete the main trial consent form, they can consent to being contacted about this bioethics study at the end of their main trial participation. This is optional, and one or both partners can consent. The recruiting clinician/research nurse will pass these details on to the qualitative research team.

At the end of main trial participation, couples or individuals will be approached to take part in an interview.

The fertility professionals will be recruited from the UNiTY trial sites and other fertility centres in England.

The commissioners will be recruited by approaching ICBs by email and asking them if they would like to participate in a short qualitative interview. We will also recruit through our own established networks and by snowball sampling.

16.3.6. Consent and Withdrawal

Written informed consent to participate, online through REDCap or on paper, will be sought wherever possible. However, for example, in cases where the study related paperwork has not been received, not fully completed, or there are issues around literacy, we will seek alternative forms of informed consent including electronically transferred (e.g. scanning/photo of the completed consent form) or verbal (e.g., where the consent form will be read out in full, and audio recorded at the start of the interview).

Informed consent (in all forms) will include agreement to participate, demographic data collection, audio recorded discussion, and anonymised data sharing.

At the beginning of each audio recording, participants who have completed written or electronic consent processes will be asked to verbally re-confirm consent.

Where formal verbal informed consent is being sought at the start of an interview, two separate audio file recordings for each participant will be created. The first audio file will just cover the consent discussion and record verbal consent. The consent form will be read out and the participant asked to consent to each statement. Should the participant not consent to any of the statements, the interview will be terminated at that point having explained to that participant that data collection cannot continue, as they did not consent to participate.

Once verbal consent has been obtained the first audio file will be closed. A member of the bioethics research team within the University of Manchester will transcribe the consent audio file to create a formal record of consent or declined consent. This transcript will be stored securely on University of Manchester servers and separately from the transcript of the main interview (if consent was gained). If the participant does give consent, the study interview will commence and be recorded in a second audio file. Only this second file will be sent to a third-party company for transcription. All audio files and transcripts will be stored on password protected University of Manchester computers, on the R research drive. The audio files will be destroyed once the transcripts are received, checked, and anonymised.

Interview participants will be free to withdraw at any time within two weeks of the data collection without having to explain or justify their decision.

16.3.7. Inconvenience Allowance and Expenses

Participants will receive a £25 electronic voucher as a thank you for their time in an interview. This covers £20 for participating and £5 for consumables such as electricity/internet access given that we anticipate most interviews will be held remotely. Participants who take part face to face will still

receive £25. Couples will therefore receive £50 if both partners take part, with £25 paid to each individual.

16.3.8. Data Collection

Participants will be invited to participate in an interview via telephone or University of Birmingham approved video conference accounts (e.g., Teams, Zoom, Skype or WhatsApp) as per their preference. The recording will be done by the video conferencing software, or if on the telephone by a separate encrypted recording device.

Couples can participate in an individual interview or as part of a paired interview dependent on their preferences. Either partner can participate, and this is not dependent on the other partner participating. We aim to conduct interviews within four to six weeks of couples completing the trial. This will, however, remain flexible to accommodate the needs of the participants.

A discussion guide to facilitate the interviews will be developed based on existing literature, PPIE, and discussions within the trial team *[MRC/NIHR framework, core element 1, 3 & 4: context, stakeholders & uncertainties]*. Interviews will be conducted in a participant-focused manner allowing issues and perspectives important to participants to arise naturally (45). For participants interviews will explore their views and experiences of the issues around access to treatment, treatment funding, how they perceive success rates and what issues arose for them when participating in the trial. For HCPs, interviews will explore their views and experiences on what they perceive as the barriers to trial recruitment, demographic reflections and their perceptions of equality and equity in trial recruitment.

For commissioners of fertility treatment, we will explore how they balance NICE guidelines, other funding pressures and how they commission treatment in this area, and how they perceive equality and equity issues in access to fertility treatment, and how the trial findings will impact on their commissioning decisions.

All participants will be asked to complete a brief demographic questionnaire prior to or at the end of the interview to facilitate purposive sampling and a description of the sample.

16.3.9. Anticipated Sample Sizes

We aim to undertake semi-structured interviews across the sites involved in the trial.

a. couples randomised to IUI (n~10-15)
b. couples randomised to IVF (n~10-15)
c. HCPs involved in providing fertility treatment (n~15-18)
d. Commissioners of fertility treatment (n~15-18).

Sampling will attempt to address the site populations in relation to ethnicity, culture and language *[MRC/NIHR framework, core element 1: context, core element 4: uncertainties].* For example, translation services will be provided for eligible participants who face a language barrier for interviews. Interviews will, where possible, be undertaken in different languages supported by a trained interpreter.

Anticipated sample sizes for couples are based on the number of interviews and not the number of participants. The numbers of interviews will remain flexible, and the adequacy of the final sample size will be carefully monitored to ensure the data will have sufficient information power and theoretical saturation reached to develop new knowledge in relation to the research questions.

16.3.10. Data Analysis

Interviews will be digitally-audio recorded, with data collection and initial analysis taking place iteratively.[3] Audio files will be transcribed clean verbatim (and into English where needed) by an external specialist transcription company and reflexive thematic analysis (45) used to facilitate a

systematic and flexible approach to the analysis. Findings will be combined with knowledge from the existing literature, PPI, and findings from the QPE sub-study to develop and refine a programme theory for the UNiTY trial *[MRC/NIHR framework, core element 2: programme theory].* The programme theory will be an important resource to build upon for future research.

Our analytic approach will be interpretive, approaching our interview data as both a resource and a topic (51). We will conduct qualitative thematic analysis that incorporates both substantive threads and maps ways in which those threads are juxtaposed and connected (52). Transcripts will be coded by the research team to determine themes and key ethical issues. The validity of the range of interpretations and suggested relationships between core themes will be explored and tested against the data using the constant comparative method (52).

To draw our data together and make recommendations, we will use symbiotic empirical ethics, an approach for incorporating empirical data into ethical deliberation that uses philosophical theory both to explore the data and to draw normative conclusions (53). This methodology can highlight new ethical problems and develop more nuanced moral norms. It aims to develop or refine theories to deal with the ethical conflicts that arise in practical settings. More generally, we will take a "philosophy as social research" approach, which seeks to reconnect philosophy with empirical realities, and in particular to conduct philosophical analysis by starting with prevailing beliefs, attitudes and commitments revealed in the qualitative empirical data (54). Therefore, the methods and data analysis approaches seek to remain as close to the lived-through experiences of our participants operating in complex environments as possible, thereby enhancing the relevance and feasibility of the study conclusions and recommendations.

16.3.11. Management of Risk

All participants will self-select to take part. Given the topic of infertility is potentially emotive, participants may become distressed because of participating in an interview.

Trained qualitative researchers will undertake data collection guided by Dempsey *et al* framework of essential elements for conducting qualitative research given the potentially sensitive issues that may emerge in discussions (47). Distressing topics will be handled sensitively, and we will follow a study specific distress pathway including signposting to additional support as appropriate (47).

The welfare of the participants will always be placed ahead of the knowledge to be gained and emotionally distressing topics will be handled with sensitivity and sympathy. It will also be clearly stated in the PIS, by the person introducing the potential participant to the study, as well as being reiterated by the qualitative researcher at the beginning of the interview that participants are free to withdraw at any time within two weeks of the data collection without having to explain or justify their decision. The interviewer will also signpost the distressed participant towards services for additional support should this be appropriate. Information on support services is also provided in the PIS. We have sought PPI input to ensure that all participant facing materials and the interview questions are appropriate and acceptable *[MRC/NIHR framework, core element 3: stakeholder]*.

If a participant raises issues about their care that the qualitative research team deem as potentially harmful to them (or others) then the researcher will advise them to contact their local Patient Advice and Liaison Service (PALS) (or equivalent) whose contact details are provided in the PIS. The lead for the bioethics sub-study, Dr Lucy Frith, will also inform the CI. The CI, where appropriate, will ensure that the local unit PI is aware of the participant's concerns so that follow-up can be arranged if required. Should a participant have questions about their clinical care then the qualitative research team will advise them to contact their clinical team and/or their GP.

16.3.12. Nesting Within the UNiTY Trial

Recruitment to the bioethics qualitative study will begin once the first participants complete the trial. Final analysis and initial write up will be undertaken in conjunction with the main trial analysis.

16.3.13. Relationship with the Qualitative Process Evaluation

The Qualitative Process Evaluation will help inform the ethical issues that will be explored in greater depth as part of the bioethics sub-study (see section 16.1). Interviews for the QPE will be performed with couples and individuals who have been approached about the main trial, but have both participated and declined. Findings from the QPE and the bioethics sub-study will jointly inform the development and refinement of the UNiTY programme theory *[MRC/NIHR framework, core element 2: programme theory].*

17.TRIAL ORGANISATIONAL STRUCTURE

17.1. Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

17.2. Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

17.3. Trial Management Group

The Trial Management Group comprises individuals responsible for the day-to-day management of the trial: the CI, statistician(s), trial team leader, trial manager, data manager, health economist and sub-study teams. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

17.4. Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

17.5. Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the UNiTY trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

17.6. Data Monitoring Committee

The role of the independent DMC is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

17.7. Finance

The research costs of the trial are funded by the NIHR HTA and awarded to Professor Kirkman-Brown, University of Birmingham. The trial has been designed to minimise extra 'service support' costs for participating HFEA licenced centres as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the SoECAT. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

The study will be eligible for portfolio adoption. The network has well established infrastructure that has previously delivered several large HTA funded studies nationally.

18.ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include Data Protection Act 2018, Human Fertilisation and Embryology Act 2008 and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial.

The protocol will be submitted to and approved by the REC/HRA prior to the start of the trial. All correspondence with the REC/HRA will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. In the event of a substantial amendment, REC/HRA approval will be sought prior to implementation of any changes. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approvals.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

19.DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected and analysed include date of birth, NHS number and medical history. Participant contact details will also be collected for the administration of the trial.

Participants will only be identified by their unique trial identification number or qualitative study ID on CRFs, audio recordings, sperm slides and videos, and on any correspondence with the Trial Office/qualitative team. Participants will acknowledge the transfer and storage of their informed consent form to the Trial Office. This will be used to perform central monitoring of the consent process. Participants will acknowledge the transfer of their personal data for the purpose of medical research to BCTU. The PI must maintain documents not for submission to BCTU in strict confidence.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party, other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer. Representatives of the trial office and sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. If any risks are disclosed to the participants or researchers, then the relevant authority will be informed e.g.:

- Occupational health for members of staff
- Hospital security for immediate threats
- GP and/or social services for disclosure of participants or families at risk e.g. suicide, domestic abuse
- Line managers for disclosure of harm to patients.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the UNiTY trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

20.FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

21.INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

Clinical Trial Limit of Indemnity £10,000,000 any one claim and in the aggregate including claims costs and expenses.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

22.POST-TRIAL CARE

Couples who become pregnant and give birth over the course of the trial will receive standard NHS antenatal and postnatal care.

Couples who do not become pregnant with the trial interventions will receive continued care from their fertility centres to discuss further options, as per standard care.

There are no interventions that couples will be prevented from accessing after the trial because of their participation in UNiTY.

23.ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant TMG, and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

24.PUBLICATION PLAN

On completion of the trial, the data will be analysed and a Final Study Report prepared. Results of this trial will be submitted for publication in a peer reviewed journal. The publication policy will be governed by the Trial Steering Committee *[MRC/NIHR framework, core element 3: stakeholders]*. Full details of the publication plan can be found in the Publication Plan Document. In brief:

24.1. Participant engagement

Results will be available via the trial website. Participants can also specifically request results from their PI after the results have been published.

24.2. Public engagement

We will communicate the trial progress and findings on a website. Our patient and public partners will advise on the dissemination of results, as well as sharing through their networks. The study team, supported by academic and patient and public partners will actively use their social media profiles to share approved short vignettes, graphics, and videos of the study findings to the widest possible audience.

24.3. Professional stakeholder engagement

We will work with the NIHR research networks, Academic Health Science Networks and Applied Research Collaborations. Our findings will inform evidence to support the professional evaluation of IUI and IVF. We will prepare a slide set for participating professionals to disseminate findings.

24.4. Academic stakeholders and outputs

The study protocol will be submitted for publication. We will aim to publish results in high impact factor peer reviewed journals. The National Institute for Health Research Library will promote key messages and reports.

We will promote findings and best-practice (through courses and guidelines) through the relevant Learned Societies, including the Associate of Reproductive and Clinical Scientists (of which the CI is Chair). National and internationally congresses such as the European Society of Human Reproduction & Embryology, and Fertility UK, will be targeted to disseminate knowledge through the academic community.

24.5. Authorship

Authorship will be determined by the trial publication policy within the publication plan.

24.6. Quality assurance

Ensuring quality assurance is essential to the good name of the study group. For reports of individual projects, internal peer review among members of the Trial Management Group is a requirement prior to submission of papers. All reports of work arising from the UNiTY study including conference abstracts should be peer reviewed by the Trial Management Group.

The internal peer review for reports of work arising from the UNiTY study is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Trial Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Trial Steering Group.

Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. The Trial Management Group undertakes to respond to submission of articles for peer review at Trial Management Group Meetings following submission (assuming the report is submitted to the CI at least two weeks prior to the meeting).

We will submit the trial protocol for publication in an open access journal for public scrutiny, before submission of the trial findings.

In all publications, authors must acknowledge that the trial was performed with the support of BCTU. The NIHR HTA should be notified before publication and their set acknowledgement wording should be included.

Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and sites.

The costs for dissemination include open-access fees for the final results publication, to enable all those without access to a medical library the opportunity to read and discuss the findings. These publications will be signposted on the trial website.

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