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Centre for Human Reproductive Science
FUTURE GENERATIONS

UNIVERSITY OF BIRMINGHAM

BCTU Birmingham Clinical Trials Unit

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**

Site Initiation Visit

Chief Investigator: Professor Jackson Kirkman-Brown

Sponsored by University of Birmingham

Important details

Funder: National Institute Health Research (NIHR) and Health Technology Assessment (HTA) programme

Sponsor: University of Birmingham

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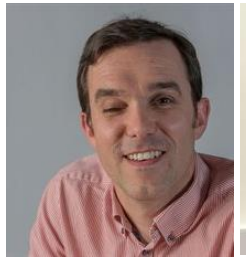


IRAS: 314070

Registration: ISRCTN 93757751

Recruitment period: September 2024 – August 2026

UNiTY Trial Team

Chief Investigator
Professor Jackson Kirkman-Brown

Birmingham Clinical Trials Unit (BCTU)

Team Leader
Clive Stubbs

Senior Trial Manager
Katie Kirkham

Main Trial

Data Manager
Sean Cole

Senior Analyst Programmer
Naomi Campton

Statisticians
Lee Middleton and Eleni Gkini

Qualitative Process Evaluation (QPE)

Qualitative Researcher
Prof Laura Jones

Research Fellow
Dr Eleanor Molloy

Healthcare Sciences

Research Fellow
Dr Meurig Gallagher

Bioethics

Qualitative Researcher
Dr Lucy Frith

Research Fellow
TBC

UNiTY Trial Design

Title	A randomized controlled trial evaluating the clinical and cost effectiveness of IVF versus IUI for UNexplained infertiliTY - parallel, open, multicentre, non-inferiority RCT.
Population	942 couples with a diagnosis of unexplained infertility
Intervention	Up to three cycles of Intra Uterine Insemination (IUI)
Control	One cycle of In-Vitro Fertilisation (IVF)
Primary Outcome	Live birth ≥34wks gestation conceived within 270 days of randomisation
Pilot	Internal 9 month pilot with embedded Qualitative Process Evaluation at 11 HFEA licenced fertility centres in the UK – both NHS and private providers
Sub-studies	1.) Qualitative Process Evaluation 2.) Healthcare sciences – Sperm analysis 3.) Bioethics
Timepoint	450 days post randomisation

Background

Approx. 28,000 IVF cycles using couples own eggs and sperm were carried out in 2019.

We conservatively estimate that 4000-9000 UK IVF cycles per annum are classified as UEI.

NICE guidance recommends three cycles of NHS funded IVF for couples with UEI when the partner providing eggs is under the age of 40 . Most often only a single IVF attempt is NHS funded in England.

The alternative, IUI, is practiced and recommended in many countries worldwide. However, NICE guidance, based on low quality evidence, recommends that IUI should not be offered for couples with unexplained infertility in the UK.

How does IVF and IUI differ?

Risk

The main risk associated with IVF is ovarian hyperstimulation syndrome (OHSS) and egg collection with the most common risks being bleeding and pelvic infection.

There are some concerns that the rates of multiple pregnancies may be higher in IUI compared to IVF, however, there is also evidence to say that the numbers are comparable.

Cost

The cost of IVF is considerable and parameters for access to funding mean that many couples in the UK need to self-fund their treatment.

The cost of IUI is less, as it requires less medication and monitoring and can be delivered at a local hospital rather than at a specialist IVF lab.

Time to pregnancy (TTP)

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

Current Guidance

NICE guidance, based on low quality evidence, recommends that IUI should not be offered for couples with unexplained infertility in the UK [1].

ESHRE guideline issued since this study was funded suggests IUI for unexplained infertility, but this still lacks the evidence-base this trial is designed to supply [2, 3].

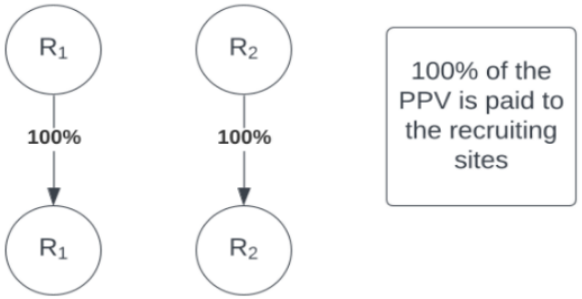
1. National Institute for Health and Care Excellence (NICE). Fertility problems: assessment and treatment. Clinical Guidance. 2013.
2. The Guideline Group on Unexplained Infertility, Romualdi D, Ata B, Bhattacharya S, Bosch E, Costello M, et al. Evidence-based guideline: unexplained infertility. Human Reproduction. 2023;38(10):1881-90.
3. The Guideline Group on Unexplained Infertility, Romualdi D, Ata B, Bhattacharya S, Bosch E, Costello M, et al. Unexplained infertility ESHRE evidence-based guideline on Unexplained Infertility

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**

Funding of Excess Treatment Costs (ETC)

- ETC for IUI are covered by the CRN at a Per Patient Value (PPV) of £2100 which will cover the cost of the maximum 3 cycles of IUI. This is paid regardless of whether randomised to IUI or IVF.
- IVF treatment is either NHS funded or couple funded.
- Self-funding couples must provide payment for 1 cycle of IVF to the fertility clinic before they are able to consent to UNITY.
- If randomised to IUI treatment, the clinic will retain the funds until the pregnancy outcome is known.
- If the couple has successful IUI, they will be refunded their IVF payment. If their IUI treatment is unsuccessful or they withdraw from the trial, the couple may go on to IVF treatment using the funds already held at the clinic, or request a refund.
- Sites will also receive £196.20 per couple recruited.



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Eligibility

Inclusion Criteria:

Couples with a diagnosis of Unexplained Infertility (UEI), referred to fertility centres for assisted conception.

UEI is defined as the ***absence*** of the following after complete investigations:

PARTNER PROVIDING EGGS:

- Tubal disease – including tubal patency testing for high-risk* couples.

*Chlamydia antibody testing can be considered a non-invasive test to differentiate between patients at low and at high risk for tubal disease.

- Deep endometriosis +/- ovarian endometriosis
- Significant uterine abnormality requiring surgery
- Uterine septum with history of pregnancy loss

PARTNER PROVIDING SPERM:

- Total progressively motile sperm count ≤10 million
- Normal sperm morphology of ≤2%

Eligibility

Exclusion Criteria:

- Partner providing eggs is ≥39 years on date of randomisation
- Either partner is <18 years
- Partner providing eggs BMI is <19.0 or >34.9kg/m^2
- Either partner has a diagnosis of an ongoing STI
- Either partner is taking any prohibited medications or interventions
- If self- funded, inability to pay for IVF
- Unable to give informed consent
- Unable to complete trial follow up
- Two or more consecutive IVF treatment failures

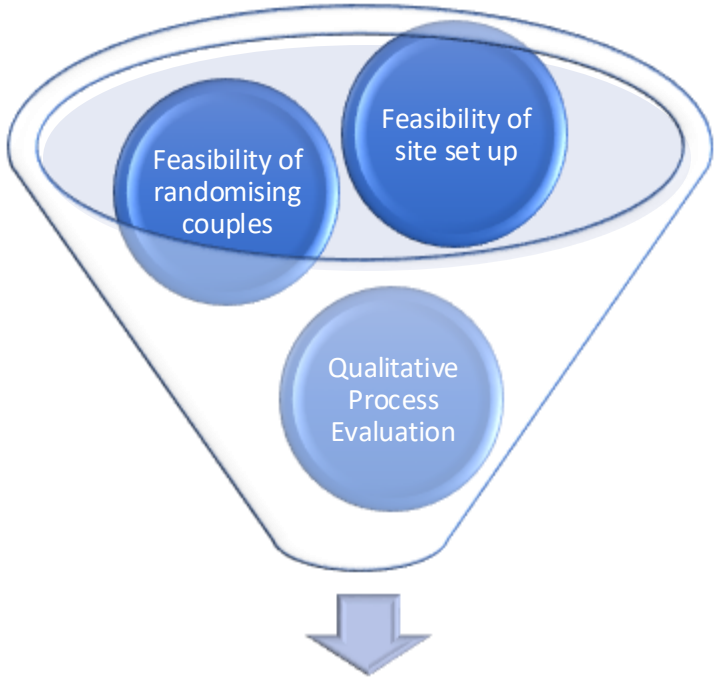
Internal 9 month Pilot Objectives

Internal randomised pilot

1. To assess the feasibility of randomisation to the UNiTY trial.
2. To assess the feasibility of opening fertility centres to the UNiTY trial.

Qualitative Process Evaluation (QPE Sub-study 1)

To explore and understand the feasibility, acceptability, ethical implications and context of the UNiTY trial interventions with couples and healthcare professionals.



Sub-study 1 – Qualitative Process Evaluation (QPE)

Aim: To explore and understand the feasibility, acceptability, ethical and equity implications, context of the intervention, and the evaluation design.

All eligible couples should be approached to take part in the UNiTY QPE.

Sites will collect contact details via a "consent to contact" form from those that agree to participate.

Recruitment to the QPE will be undertaken by a qualitative researcher - Dr El Molloy at the University of Birmingham, supervised by Prof Laura Jones.

UNiTY Consent To Contact Form

[Form to be completed by each partner separately]

How was consent to contact completed? *[Not shown on online survey. Default = **Online...** when "...how would they prefer to complete the consent to contact form?" (Screening) answered **Online...**, otherwise no default]*

◯ Online via an email by member of couple ◯ With researcher in clinic ◯ On paper and entered by researcher
◯ By phone and entered by QPE team

Partner providing *Tick one* ◯ Eggs ◯ Sperm

[If form completed by member of couple as survey (i.e. "How was consent to contact completed?" answered **Online...**), show informative text]

We would like to talk to couples (as individuals or together) who have unexplained infertility and have been approached about taking part in the UNiTY trial. You were eligible for the UNiTY trial and may or may not have taken part in the study. Either way, we would like to hear your thoughts about the trial, your reasons for taking part (or not) and your thoughts on the two different treatment options available as part of the trial. Your views will help us to improve NHS services for other couples with similar experiences. We would like to talk to couples; however, you can choose to speak to the researcher on your own, or alongside your partner, whichever you prefer.

If you would like to hear more, please complete your details below. A member of the team will get back to you. Taking part would involve a discussion (likely via phone or Zoom) with a member of the team and will take no more than an hour. If you're filling this form in on paper, please don't forget to sign the form at the bottom and give it back to the person who gave it to you. Filling in this form does not mean that you have to take part in a discussion with us.

Name: _____

Home phone/mobile: _____

Email: _____

Address: _____

Post code: _____

Preferred contact method: *Please tick ALL that apply.* ◯ SMS ◯ Email ◯ Phone call

Preferred language: _____

[If form completed by member of couple as survey (i.e. "How was consent to contact completed?" answered **Online...**), show "Would you like an interpreter to support you to take part in an interview?"]

Would you like an interpreter to support you to take part in an interview? ◯ No ◯ Yes

By completing and signing this form you are giving permission to be contacted by a member of the UNiTY research team based at the University of Birmingham.

Signature: _____ Date: D D - M M - Y Y Y Y

[If form completed by site staff or QPE team as form (i.e. "How was consent to contact completed?" answered **With research in clinic** OR **On paper and entered by researcher** OR **By phone and entered by QPE Team**), show "Would they like an interpreter to support you to take part in an interview?"]

Would they like an interpreter to support you to take part in an interview? ◯ No ◯ Yes

Sub-study 1 – Qualitative Process Evaluation (QPE)

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.

Eligibility:

Inclusion

- All couples (individually or as a couple) eligible for UNiTY who are approached about the trial, ***irrespective of 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).

Sub-study 1 – Qualitative Process Evaluation (QPE)

Information which you may wish to share with potential participants

- One off/single discussion
- Completing a consent to contact form does not mean they *have* to participate
- Remote interviews (e.g., Zoom / telephone)

§Couples can choose to participate individually or together

- Supported by interpreter (as needed)
- Discussion guide can be made available in advance
- ~60 minutes
- Audio recorded
- Withdrawal and distress support
- £25 voucher as a thank you for participation

Sub-study 1 – Qualitative Process Evaluation (QPE)

- Approach and offer **ALL** eligible participants the opportunity to take part in the UNiTY QPE
- Answer any questions briefly and offer short PIS
- Complete contact information via a "consent to contact" CRF on REDCap
- UNiTY QPE study team will pick up the consent to contact information and do **EVERYTHING** else
- You are **not taking informed consent** for the interview
- Let us know if you are interested in taking part in the HCP interviews – the QPE team will also be in touch with staff at your site about this.

Primary objective:

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.

Primary outcome:

Live birth of a baby at ≥34 weeks' gestation, conceived within 240 days of randomisation (approximately 8 months).

Secondary outcomes

Pregnancy outcomes (assessed at 19 months and 25 months):

- singleton live birth ≥ 37 weeks
- TTP leading to live birth defined as time from randomisation to pregnancy
- cycle cancellation
- biochemical pregnancy
- clinical pregnancy
- ongoing pregnancy at 12 weeks
- multiple pregnancy
- ectopic pregnancy
- miscarriage
- Stillbirth
- termination
- number of embryos remaining (IVF)

Secondary Outcomes continued

Outcomes in live births ≥24 weeks (assessed at 19 months and 25 months):

- gestational age at delivery
- Gestation <28/<32/<37 weeks
- Birthweight
- Small for gestational age
- Mode of birth
- APGAR<7 out of 10 at 1, 5 and 10 minutes
- survival at 28 days (or discharge from hospital, whichever is sooner)

Secondary Outcomes continued

Complications:

- Maternal
- Antenatal
- Intrapartum
- Post-partum
- Neonatal

Other adverse and serious adverse events related to treatment will also be recorded.

Patient reported:

- *Health related quality of life (EQ-5D-5L) and satisfaction with treatment and care provision (CSQ-8) measured post-treatment.*

Patient Reported Outcomes Measures

Economic:

Health economic analysis aims to evaluate the cost-effectiveness of up to three cycles of IUI compared to one cycle of IVF for couples with UEI.

UNiTY sub-study 2

Healthcare science

To investigate variations in how male factors in infertility are assessed across fertility centres in the trial.

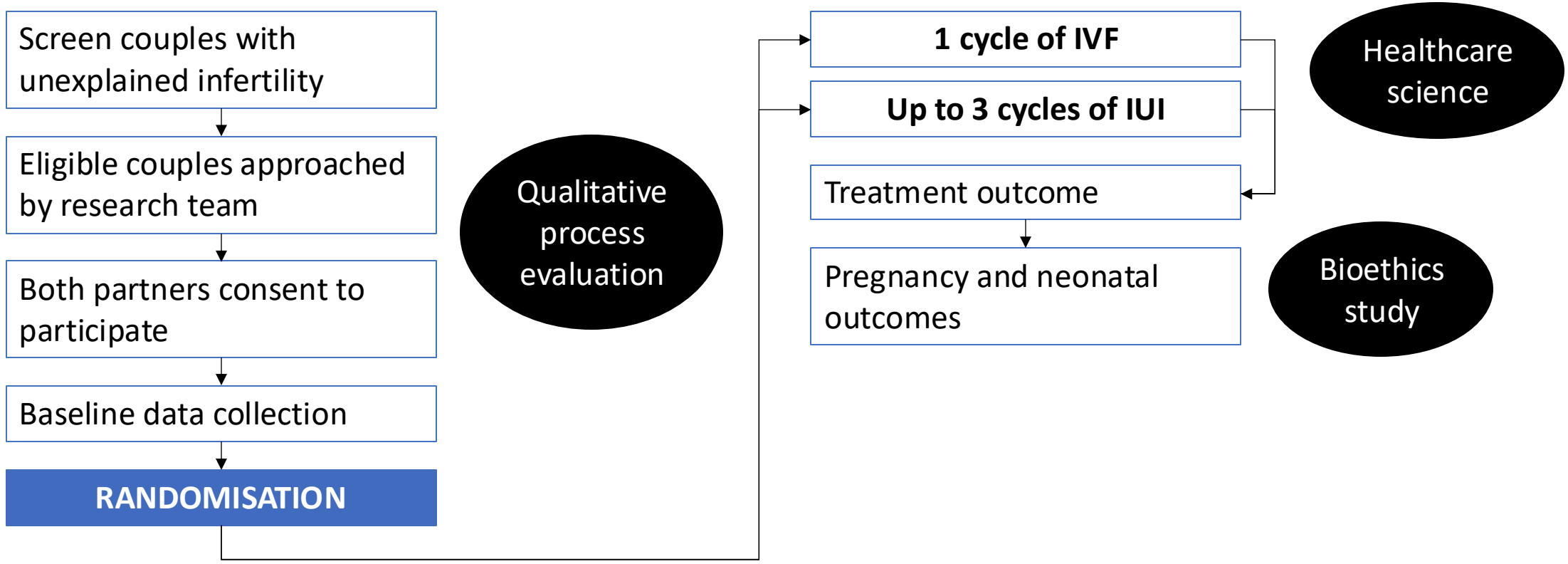
- To assess the standardisation of semen quality assessment at different sites, using videos created at site together with dry smears made at site.
- To evaluate the prognostic value of existing, World Health Organisation (WHO) markers of male factor infertility.
- To evaluate the prognostic value of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

UNiTY sub-study 3

Bioethics

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

Participant pathway



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	

Identification and approach

How will couples be identified?

Potential participants will be identified via review of medical records by clinicians and nurses after their investigations have been completed and a diagnosis of UEI has been confirmed.

Who can approach them?

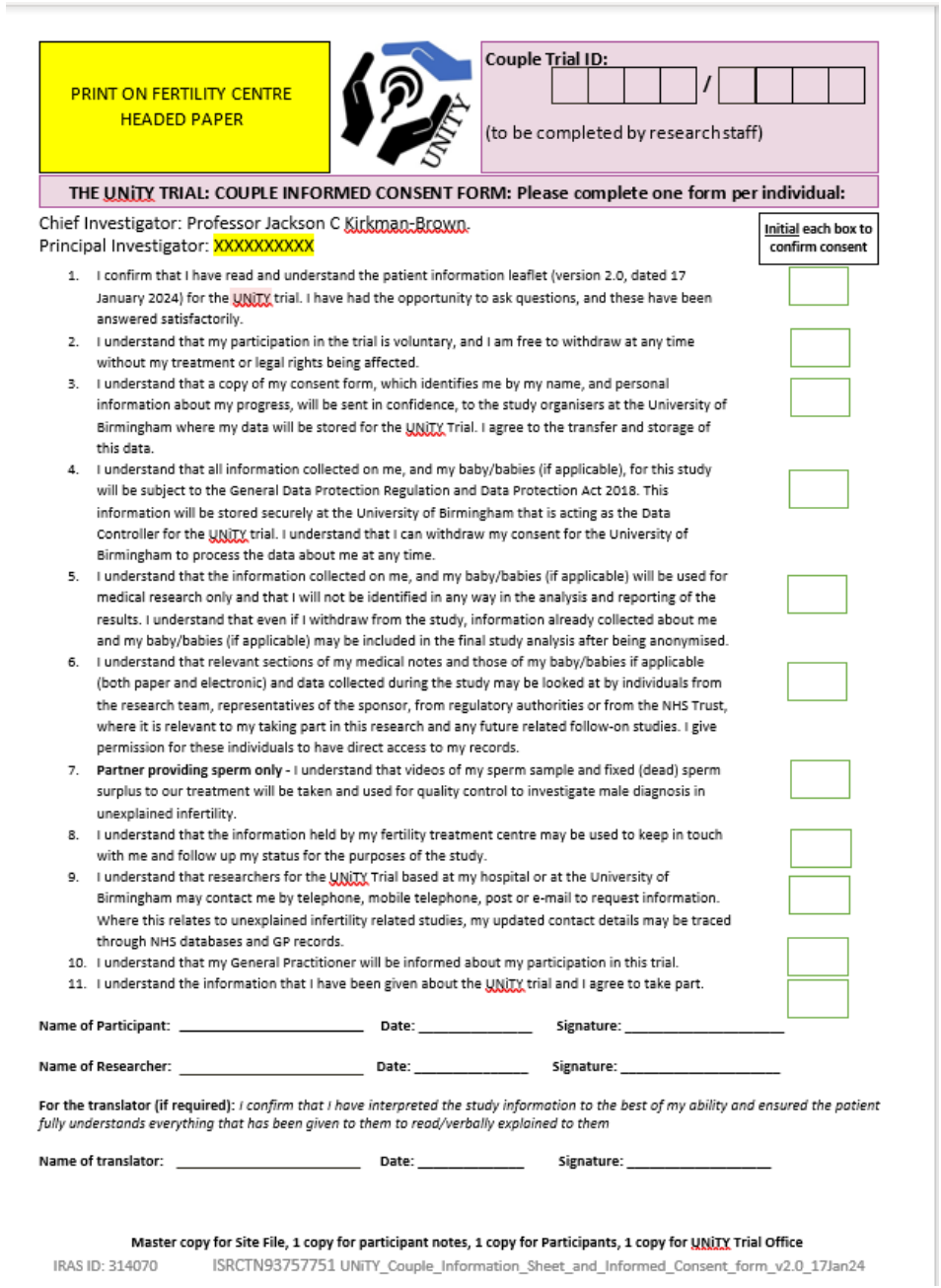
Members of their direct care team including clinic doctors and staff at assisted conception units who are responsible for their care and who are named on the local delegation log. Research nurses are considered part of the direct care team and can approach potential participants about the trial, subject to local confirmation.

Screening

Details of all couples approached about the trial will be recorded on the screening CRF entered directly onto the REDCap database.

Consent for the RCT

- Both partners must sign Informed Consent Forms (ICF) before any trial procedures take place
- A combined Patient Information Sheet and Informed Consent Form will be provided to the couple
- Consent can be done online via https://bctu-redcap.bham.ac.uk/ or on paper
- Consent can be delegated by the PI to other members of the research team if local practice allows and this is documented on the delegation log
- Consent discussion must be documented in the patients' medical notes



PRINT ON FERTILITY CENTRE HEADED PAPER

Couple Trial ID: ☐☐☐☐ / ☐☐☐☐

(to be completed by research staff)

THE UNiTY TRIAL: COUPLE INFORMED CONSENT FORM: Please complete one form per individual:

Chief Investigator: Professor Jackson C Kirkman-Brown.
Principal Investigator: XXXXXXXXXX

Initial each box to confirm consent

1. I confirm that I have read and understand the patient information leaflet (version 2.0, dated 17 January 2024) for the UNiTY trial. I have had the opportunity to ask questions, and these have been answered satisfactorily. ☐
2. I understand that my participation in the trial is voluntary, and I am free to withdraw at any time without my treatment or legal rights being affected. ☐
3. I understand that a copy of my consent form, which identifies me by my name, and personal information about my progress, will be sent in confidence, to the study organisers at the University of Birmingham where my data will be stored for the UNiTY Trial. I agree to the transfer and storage of this data. ☐
4. I understand that all information collected on me, and my baby/babies (if applicable), for this study will be subject to the General Data Protection Regulation and Data Protection Act 2018. This information will be stored securely at the University of Birmingham that is acting as the Data Controller for the UNiTY trial. I understand that I can withdraw my consent for the University of Birmingham to process the data about me at any time. ☐
5. I understand that the information collected on me, and my baby/babies (if applicable) will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that even if I withdraw from the study, information already collected about me and my baby/babies (if applicable) may be included in the final study analysis after being anonymised. ☐
6. I understand that relevant sections of my medical notes and those of my baby/babies if applicable (both paper and electronic) and data collected during the study may be looked at by individuals from the research team, representatives of the sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research and any future related follow-on studies. I give permission for these individuals to have direct access to my records. ☐
7. **Partner providing sperm only -** I understand that videos of my sperm sample and fixed (dead) sperm surplus to our treatment will be taken and used for quality control to investigate male diagnosis in unexplained infertility. ☐
8. I understand that the information held by my fertility treatment centre may be used to keep in touch with me and follow up my status for the purposes of the study. ☐
9. I understand that researchers for the UNiTY Trial based at my hospital or at the University of Birmingham may contact me by telephone, mobile telephone, post or e-mail to request information. Where this relates to unexplained infertility related studies, my updated contact details may be traced through NHS databases and GP records. ☐
10. I understand that my General Practitioner will be informed about my participation in this trial. ☐
11. I understand the information that I have been given about the UNiTY trial and I agree to take part. ☐

Name of Participant: _____ **Date:** _____ **Signature:** _____

Name of Researcher: _____ **Date:** _____ **Signature:** _____

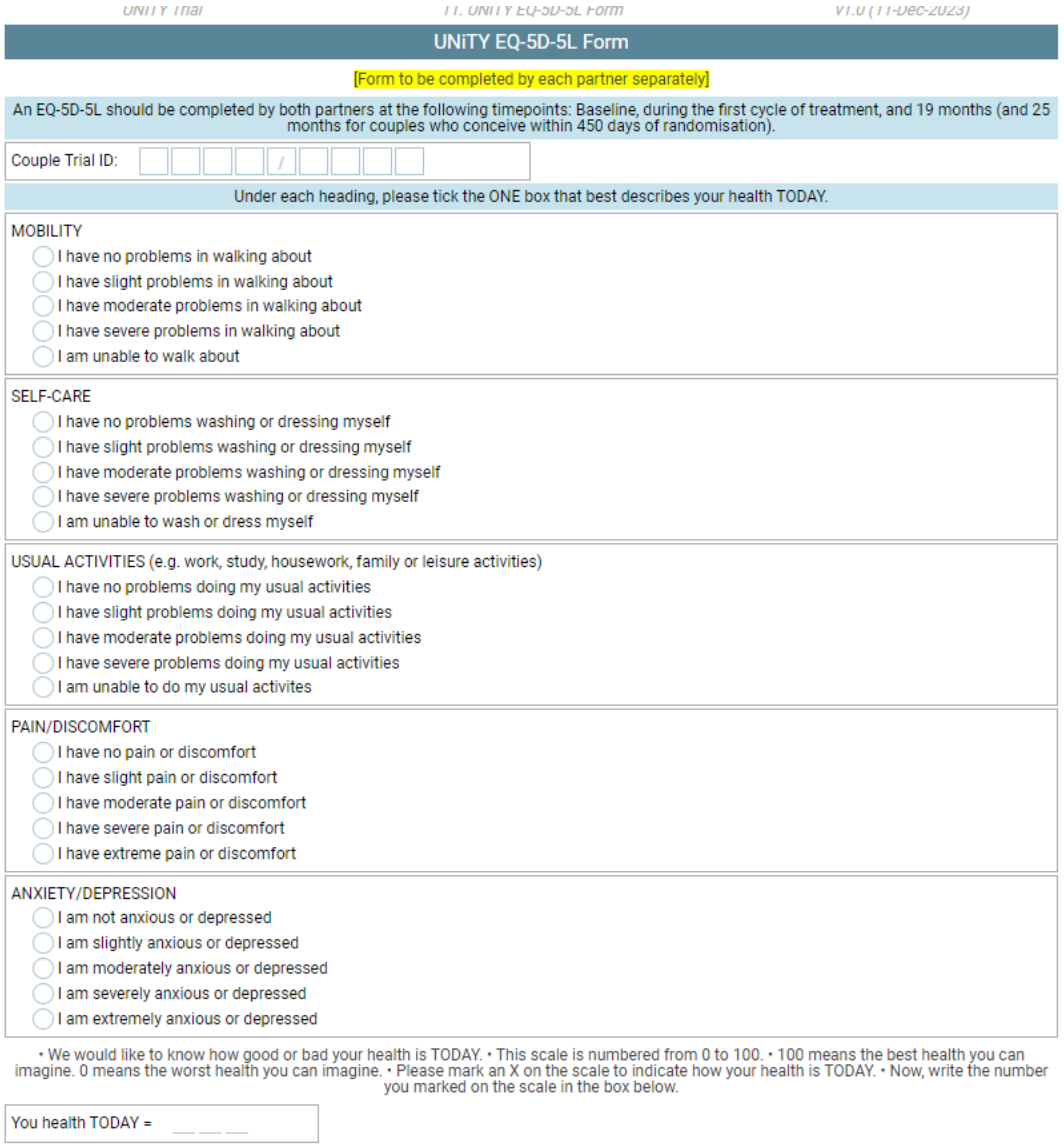
For the translator (if required): *I confirm that I have interpreted the study information to the best of my ability and ensured the patient fully understands everything that has been given to them to read/verbally explained to them*

Name of translator: _____ **Date:** _____ **Signature:** _____

Master copy for Site File, 1 copy for participant notes, 1 copy for Participants, 1 copy for UNiTY Trial Office

IRAS ID: 314070 ISRCTN93757751 UNiTY_Couple_Information_Sheet_and_Informed_Consent_form_v2.0_17Jan24

Baseline assessments



UNiTY Trial T1. UNiTY EQ-5D-5L Form V1.0 (11-Dec-2023)

UNiTY EQ-5D-5L Form

[Form to be completed by each partner separately]

An EQ-5D-5L should be completed by both partners at the following timepoints: Baseline, during the first cycle of treatment, and 19 months (and 25 months for couples who conceive within 450 days of randomisation).

Couple Trial ID: ☐☐☐☐/☐☐☐☐

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
- ◯ I have no problems in walking about
- ◯ I have slight problems in walking about
- ◯ I have moderate problems in walking about
- ◯ I have severe problems in walking about
- ◯ I am unable to walk about

SELF-CARE
- ◯ I have no problems washing or dressing myself
- ◯ I have slight problems washing or dressing myself
- ◯ I have moderate problems washing or dressing myself
- ◯ I have severe problems washing or dressing myself
- ◯ I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
- ◯ I have no problems doing my usual activities
- ◯ I have slight problems doing my usual activities
- ◯ I have moderate problems doing my usual activities
- ◯ I have severe problems doing my usual activities
- ◯ I am unable to do my usual activites

PAIN/DISCOMFORT
- ◯ I have no pain or discomfort
- ◯ I have slight pain or discomfort
- ◯ I have moderate pain or discomfort
- ◯ I have severe pain or discomfort
- ◯ I have extreme pain or discomfort

ANXIETY/DEPRESSION
- ◯ I am not anxious or depressed
- ◯ I am slightly anxious or depressed
- ◯ I am moderately anxious or depressed
- ◯ I am severely anxious or depressed
- ◯ I am extremely anxious or depressed

• We would like to know how good or bad your health is TODAY. • This scale is numbered from 0 to 100. • 100 means the best health you can imagine. 0 means the worst health you can imagine. • Please mark an X on the scale to indicate how your health is TODAY. • Now, write the number you marked on the scale in the box below.

You health TODAY = ☐☐☐

- Baseline Case Report Form – including minimization variables necessary for randomisation.
- Patient reported quality of life questionnaire – EQ-5D-5L – completed by both partners online or on paper.

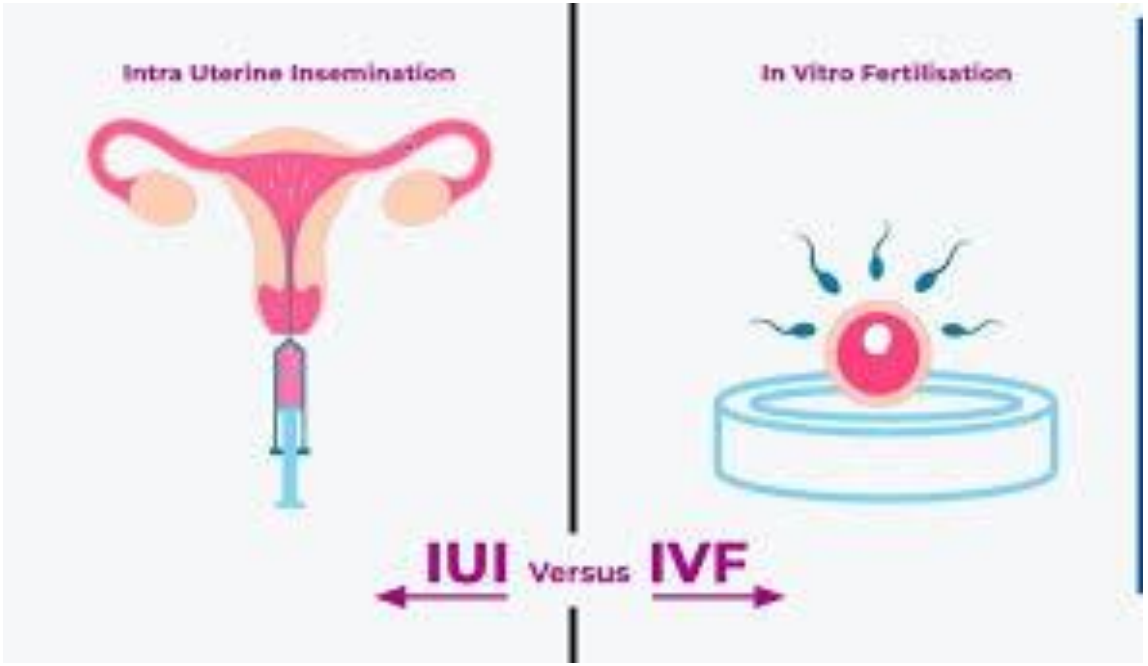
Randomisation

- Randomisation will be provided by BCTU using a 24/7 secure online system (available at https://bctu-redcap.bham.ac.uk/).
- Unique log-in usernames will be provided to staff who need 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.
- 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 and the UNiTY Trial Office.
- 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.

Screening

DEMO OF SCREENING FORM ON DATABASE

Trial Intervention and Control: IUI vs IVF



IUI Strategy

Ovarian stimulation

Letrozole 5mg commenced once daily from day 2 – day 6 after start of period.

Follicular tracking according to local protocol (usually commenced around day 10 – day 12 using transvaginal ultrasound).

When at least one follicle reaches a diameter of ≥17mm, ovulation should be triggered using human chorionic gonadotrophins to ensure that IUI can be planned at a 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 after the ovulation trigger injection.

Patients will be advised to have 10-15 min bed rest after the insemination is performed.

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.*

IUI Strategy continued…

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 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.

IVF Strategy

Ovarian stimulation

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.

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.

Sub-study 2 – Healthcare Science

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.

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).

Sub-study 3 - Bioethics

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.

Objectives:

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

Sub-study 3 - Bioethics

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

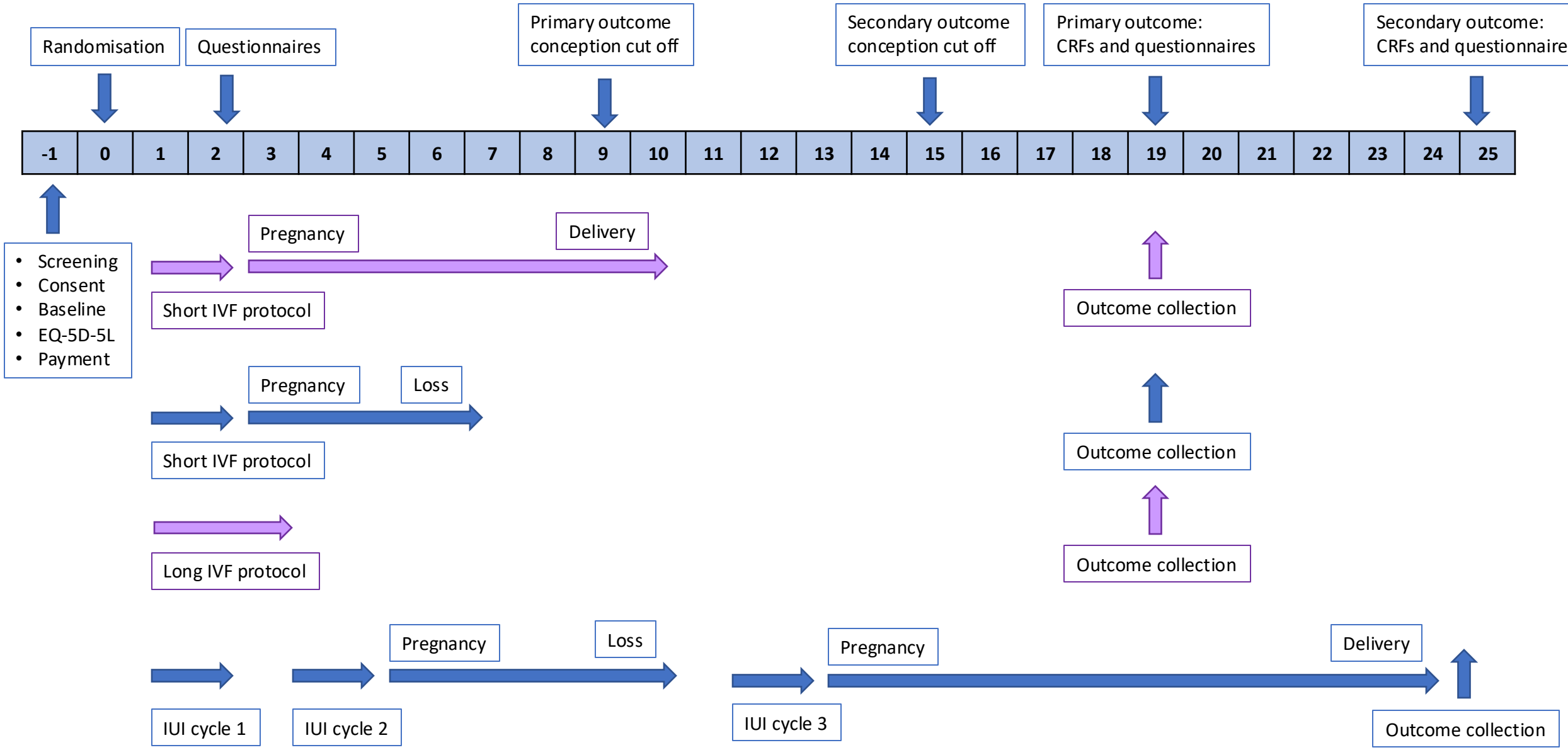
- Participants who would be unable to take part in an interview where we cannot support their language needs (interviews will be undertaken in a range of languages where we can support this with an appropriate interpreter).

Patient Reported Questionnaires

Assessment	Baseline	Post-treatment (1st Cycle)	Month 19	Month 25
Health Related Quality of Life EQ 5D 5L	✓	✓	✓	✓
Client Satisfaction Questionnaire CSQ8		✓	✓	✓
Health Resource Use Questionnaire		✓	✓	✓

Will be sent to couples according to their preferred method of completion (email, text or on paper).

Participant timeline



Safety Reporting overview

Severity Definitions	Mild Moderate Severe	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. A sign or symptom, which interferes with the participant's usual activity. 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.

Safety Reporting in UNiTY

Reporting period:

From the day the trial intervention starts until 60 days after the cycle outcome is known.

Examples:

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.

Safety Reporting in UNiTY

Only serious, related, and unexpected adverse events, beyond the routine expectations and known risks for fertility treatment, will be reported as SAEs.

The safety profile for the trial population and interventions are well established.

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.

Safety 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.
2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs. This information should be uploaded onto the trial database within four weeks of the event. This includes **Hospital admissions due to OHSS.**
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 on a trial specific SAE form on the database.

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.

Change of Status

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.

A participant may wish to cease to participate in a particular aspect of the trial without completely withdrawing.

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.

Green light requirements

- SIV and Lab training
- Site agreement
- Capacity & Capability
- Site Signature and Delegation of Duties log completed
- Training log completed
- GCPs and CVs for all staff on the delegation log
- Database training
- Protocol signed by PI
- Trial documents localised

Delegation log

Site ID / Name:		Principal Investigator:	

A	Screening potential participants	H	SAE sign off	O	
B	Confirm participant eligibility	I	Approach and consent to contact for Qualitative Process Evaluation and Bioethics	P	
C	Obtain informed consent	J	Preparation of videos and slides for external quality assurance of sperm motility and morphology	Q	
D	Participant randomisation	K	Investigator Site File maintenance	R	
E	Completion of CRFs	L	Other (please specify)	S	
F	Data query management	M		T	
G	SAE reporting	N		U	

** **PI Initials**

By initialling an entry, I confirm that the person completing the entry is authorised to perform the study procedures in the tasks section, and that the person is qualified to undertake these tasks. I also confirm that the person is appropriately informed about the study protocol and relevant study procedures

Name (please print)	Trial Role	Tasks Delegated by PI* (see legend above)	Initials	Signature	Date of signature	Date of Duties		PI Initials**	Date of PI Initials
						From (dd-MMM-yyyy)	To (dd-MMM-yyyy)		

The PI should sign below during the Site Close-Out visit.

I have reviewed the information on this log and have found it to be accurate. All delegated duties were performed with my authorisation.

PI Signature: _____ **PI Initials:** _____ **Site close out Visit Date:** _ _ / _ _ _/ _ _ _ _

Training log

- Keep updated and add staff that you train on WILL
- Send a copy to BCTU
- Database training must be done if database access is required

Site ID / Name:		Principal Investigator:	

Full name (please print)	Organisation/trainer name	Type of training	Date completed	Trainee Signature	Date of trainee signature	Trainer signature	Date of trainer signature
		Protocol/study specific training (e.g. SIV)					
		Database training					
		Laboratory training (only applicable for Lab staff)					
		Protocol/study specific training (e.g. SIV)					
		Database training					
		Laboratory training (only applicable for Lab staff)					
		Protocol/study specific training (e.g. SIV)					
		Database training					
		Laboratory training (only applicable for Lab staff)					

Investigator Site File (ISF)

- Sites will be provided with an ISF containing all essential documentation
- Sites are expected to maintain the ISFs by filing all new documents throughout the course of the study.
- Study documents not stored within the ISF should be in a secure location and there should be a file note stating the location in the ISF
- Superseded documents must be clearly labelled and retained in the ISF
- Sites will be provided with a document version control log which must be kept updated by the trials office

Site PI Responsibilities

✓Training of research personnel

✓The welfare and medical care of trial participants

✓Delegation of informed consent

✓Conduct of the study in compliance with the protocol

✓Management of the intervention

✓CRF sign off (can delegate this task)

✓Safety reporting

✓The accurate and timely completion of trial data

✓Archiving

✓Ensure that cover is in place if staff on extended leave

Central Monitoring

BCTU team will check incoming data for compliance with the protocol, data consistency and missing data including:

- Informed Consent Form completion
- Participant selection and recruitment process
- Protocol adherence
- SAE review
- CRFs and source documents
- Randomisation documentation

Sites will be sent data queries to resolve remotely via the database.

All couples will be checked for data acquisition and slide preparation for the Healthcare Science sub-study.

On-site Monitoring

On-site or remote monitoring visits may be triggered if there are any concerns on aspects of trial conduct with regards to quality management. These may include:

- abnormally high or low SAE reporting,
- a significant amount of missing data items e.g. greater than 10%,
- failure to supply the UNiTY trial office with documentation when requested,
- poor data quality,
- excessive number of participant withdrawals, or
- high number of non-compliances.
- Fertility centres that do not have established IUI clinics at the start of the trial may be selected for on-site or remote monitoring to ensure appropriate processes and oversight are in place regarding patient safety and delivery of treatment according to the protocol.

Protocol compliance and deviations

- Data reported should be consistent with the source data and any discrepancies will need to be explained.
- All study events must occur within the protocol specified timelines.
- Protocol and GCP non-compliances should be reported to BCTU on discovery via the Deviation form in REDCap.

End of trial and archiving

It is the responsibility of the PI to ensure all essential documentation and source documents at their site are securely retained for 25 years.

This includes but is not limited to:

- Signed ICFs
- Investigator Site Files
- Participant clinic/hospital notes
- Source data

Publication plan

On completion of the trial, the data will be analysed and a Final Study Report prepared. The NIHR Library will promote key messages and reports.

Results will be:

- submitted for publication in a peer reviewed journal.
- available via the trial website for participants and the public.

The study protocol will be submitted for publication.

We will promote findings and best-practice through the relevant Learned Societies and national and international congresses such as the ESHRE and Fertility UK.

Support and contacts

- Trial office unity@trials.bham.ac.uk
- Katie Kirkham k.l.kirkham@bham.ac.uk – Protocol queries, Research Governance, Study set up, SAE reporting
- Sean Cole s.cole@bham.ac.uk – Database enquiries, Research Administration
- Meurig Gallagher m.t.gallagher@bham.ac.uk – Lab enquiries
- Laura Jones and Eleanor Molloy unityqualstudy@trials.bham.ac.uk – QPE enquiries

Support and contacts

- Associate PI scheme
- Local CRN Study Support
- UNiTY Trial website
- UNITY TEAMS Channel
- Regular trial teleconferences
- Newsletters
- Certificate and rewards
- UNiTY Handbook – coming soon
- REDCAP Training Videos – coming soon
- UNITY Training Videos – coming soon
- Translated Trial Materials – coming soon