UNiTY

A randomised controlled trial evaluating the clinical and cost effectiveness of Intra Uterine Insemination versus In-Vitro Fertilisation for UNexplained infertiliTY

Trial Handbook

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About the study

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1. Contact Details

The UNiTY study is coordinated by the Birmingham Clinical Trials Unit.

UNiTY Trial Team
Birmingham Clinical Trials Unit
Institute of Applied Health Research
Public Health Building
University of Birmingham
Birmingham
B15 2TT
Tel: 0121 415 9109
Email: unity@trials.bham.ac.uk - **Please include the trial mailbox in all correspondence.**

During Office Hours:

Any queries whether urgent or not should be directed to the UNiTY Trial team during normal hours (usually between 9am and 5pm, Monday to Friday.)

UNiTY Team:

Chief Investigator for UNiTY is Jackson C Kirkman-Brown MBE PhD. J.kirkmanbrown@bham.ac.uk

Senior Trial Manager for UNiTY is Katie Kirkham. k.l.kirkham@bham.ac.uk Tel: 0121 415 9109.

Lead for Sperm Analysis sub-study is Dr Meurig Gallagher. m.t.gallagher@bham.ac.uk

Lead for the Qualitative Process Evaluation (QPE) sub-study is Dr Laura Jones. L.L.jones@bham.ac.uk, and Eleanor Molloy, e.molloy@bham.ac.uk

Lead for the Bioethics sub-study is Dr Lucy Frith, lucy.frith@manchester.ac.uk

Data Manager for UNiTY is Sean Cole. s.cole@bham.ac.uk Tel: 0121 415 9111.

2. Trial Summary and Schema

Aims: 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 Unexplained Infertility (UEI). It 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.

The trial will recruit 942 couples with a diagnosis of UEI from HFEA licenced fertility treatment centres in the UK. These may be NHS or private providers carrying out NHS funded treatments.

Inclusion criteria	Exclusion criteria
UEI 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%	• 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 and an inability to pay for IVF

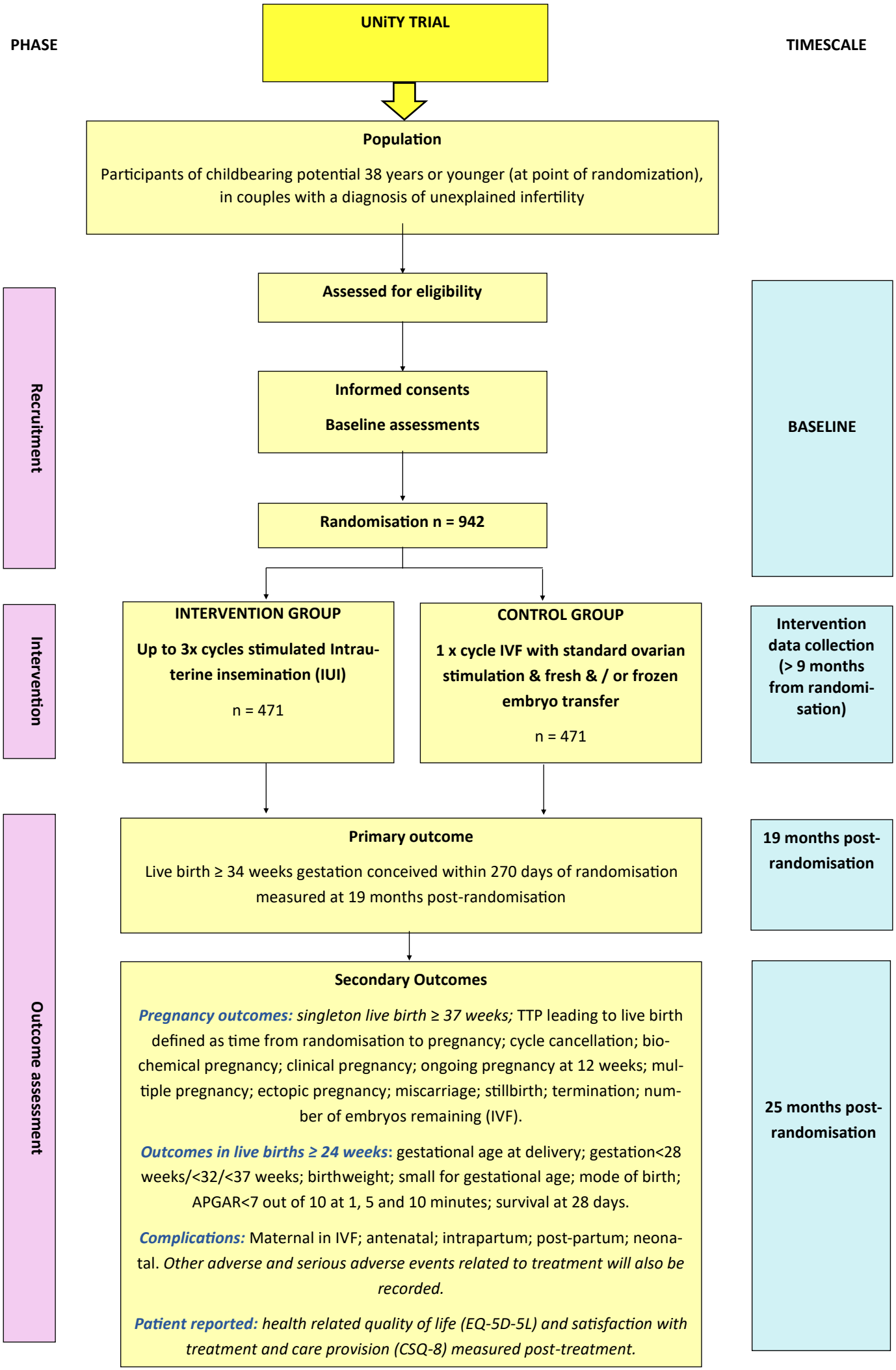
Intervention: Three cycles of letrozole stimulated Intra Uterine Insemination (IUI).

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

Couples will be randomised at the level of the individual in a 1:1 ratio

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.

Secondary outcomes include assessment of pregnancy outcomes and live births ≥24 weeks, complications for partner providing eggs and baby/babies, patient reported outcomes and health economics.


PHASE
UNiTY TRIAL
TIMESCALE
Population
Participants of childbearing potential 38 years or younger (at point of randomization), in couples with a diagnosis of unexplained infertility
Recruitment
Assessed for eligibility
Informed consents
Baseline assessments
BASELINE
Randomisation n = 942
Intervention
INTERVENTION GROUP
Up to 3x cycles stimulated Intrauterine insemination (IUI)
n = 471
CONTROL GROUP
1 x cycle IVF with standard ovarian stimulation & fresh & / or frozen embryo transfer
n = 471
Intervention data collection (> 9 months from randomisation)
Outcome assessment
Primary outcome
Live birth ≥ 34 weeks gestation conceived within 270 days of randomisation measured at 19 months post-randomisation
19 months post-randomisation
Secondary Outcomes
Pregnancy outcomes: 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).
Outcomes in live births ≥ 24 weeks: gestational age at delivery; gestation<28 weeks/<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.
Complications: Maternal in IVF; 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.
25 months post-randomisation

3. Identification and approach of potential couples

Potentially eligible couples will be identified by Site PIs, members of their clinical team and by research teams. 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.

3.1 First contact with potential couples

Couples will learn about UNiTY through the research teams and clinicians. Please ensure that the couple is provided with the combined Patient Information Sheet (PIS) and Informed Consent Form (ICF) and given as much time as needed to consider participation and with the opportunity to ask any questions.

3.2 Screening

Couples screened for the trial should be entered onto the screening form on the database, even if they do not proceed to enrolment. Details of all couples approached about the trial will be recorded on the screening CRF; which is stored on the REDCap database **https://bctu-redcap.bham.ac.uk/**

3.3 Enrolment

Enrolment will take place upon confirmation of eligibility and after informed consent of both partners of the couple has been obtained.

3.4 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.

3.5 Qualitative Process Evaluation (QPE)

All couples who are eligible and approached for UNITY, *whether they consent to the trial or not*, should also be asked if they would be interested in participating in a discussion about their feelings about the trial and the recruitment process. If they are happy to be contacted about this sub-study, they will be asked to complete a consent to contact form and the Qualitative Research Team at University of Birmingham will get in touch with them.

Healthcare professionals involved in the recruitment process may also be contacted to take part in a discussion.

Inclusion criteria	Exclusion criteria
• 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 healthcare professionals caring for couples with UEI and involved in the delivery of the UNiTY trial. • Those able and willing to give informed consent	• 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.

REDCap database

4. Trial Database

4.1 Database training & login

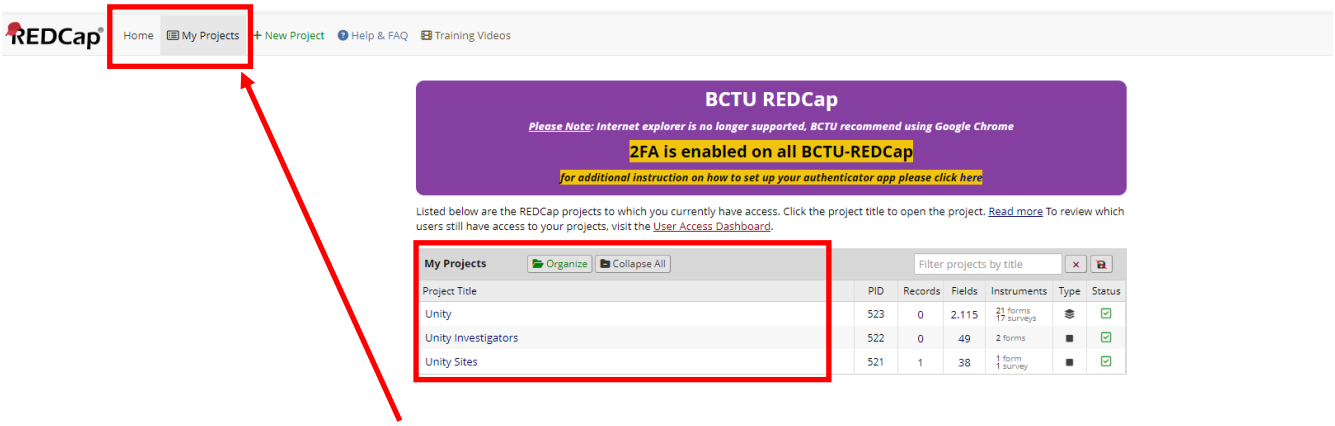
https://bctu-redcap.bham.ac.uk/

The UNiTY study team will provide training for the UNiTY REDCap database. In order to gain access to the UNITY database, please email the Trials Office

unity@trials.bham.ac.uk with the following documents:

- A current delegation log with you listed as being delegated the duty of CRF completion and signed by the PI.
- A training log showing that you have been trained in both protocol and database use.
- A current GCP
- A current signed CV

Navigate to https://bctu-redcap.bham.ac.uk/ on a modern browser such as Microsoft EDGE or Google Chrome.



Your REDCAP username will be provided by the UNiTY Trials Office and you will be prompted to set your own password when you log in for the first time.

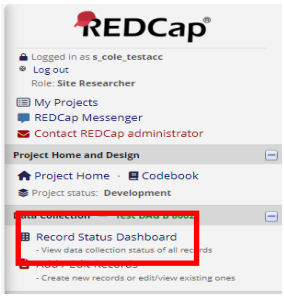
From the home page, click onto **'My Projects'** and then select the '**UNiTY'** Database from your projects selection.

If you forget your password, please click 'forgot your password?' as below and complete the necessary steps to reset your password.

If you require refresher training or you have a new team member, please contact the UNiTY trial team for training at unity@trials.bham.ac.uk. If you feel confident using the database and you received training directly from the trial team, we are happy for you to cascade the training to new team members.

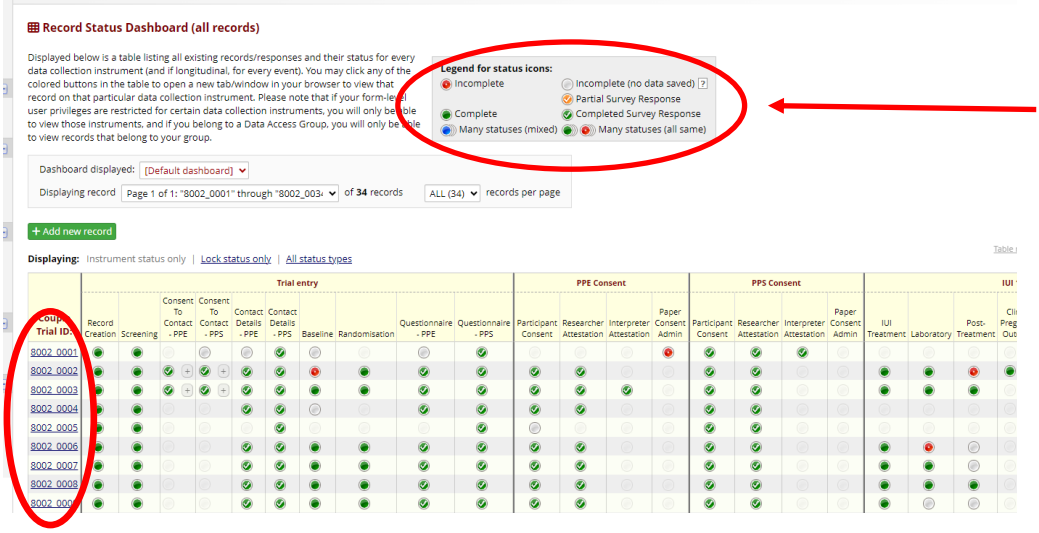
REDCap database

4.2 Overview



To view all couples approached to take part in the study at your site click 'Record Status Dashboard' on the left hand side of the screen after logging in. Once you have logged into REDCap, clicked on to the 'UNiTY' project, you will see your own site's UNiTY Dashboard.

When a Trial Entry Form is added the database will assign a 'Couple Trial ID'. The ID's will be formatted XXXX_YYYY, first 4 digits being the site ID (HFEA Centre Number) and the second 4 digits being the couple's trial ID.



The "Legend for status icons" indicates the 'status' of the forms.

Research team completed forms:

- Screening
- Consent to contact
- Participant consent
- Researcher Attestation
- Interpreter Attestation
- Baseline
- Randomisation

*Completed **at time of consent***

- IUI/IVF Treatment
- Laboratory
- Frozen Transfer
- Post-Treatment
- Clinical Pregnancy Outcome

Completed during and following treatment.

- Non-Trial Treatment
- Natural Pregnancy Notification
- Deviation
- Serious Adverse Event
- Change of Status

Completed as needed.

Couple completed:

CONTACT DETAILS

CONSENT TO CONTACT

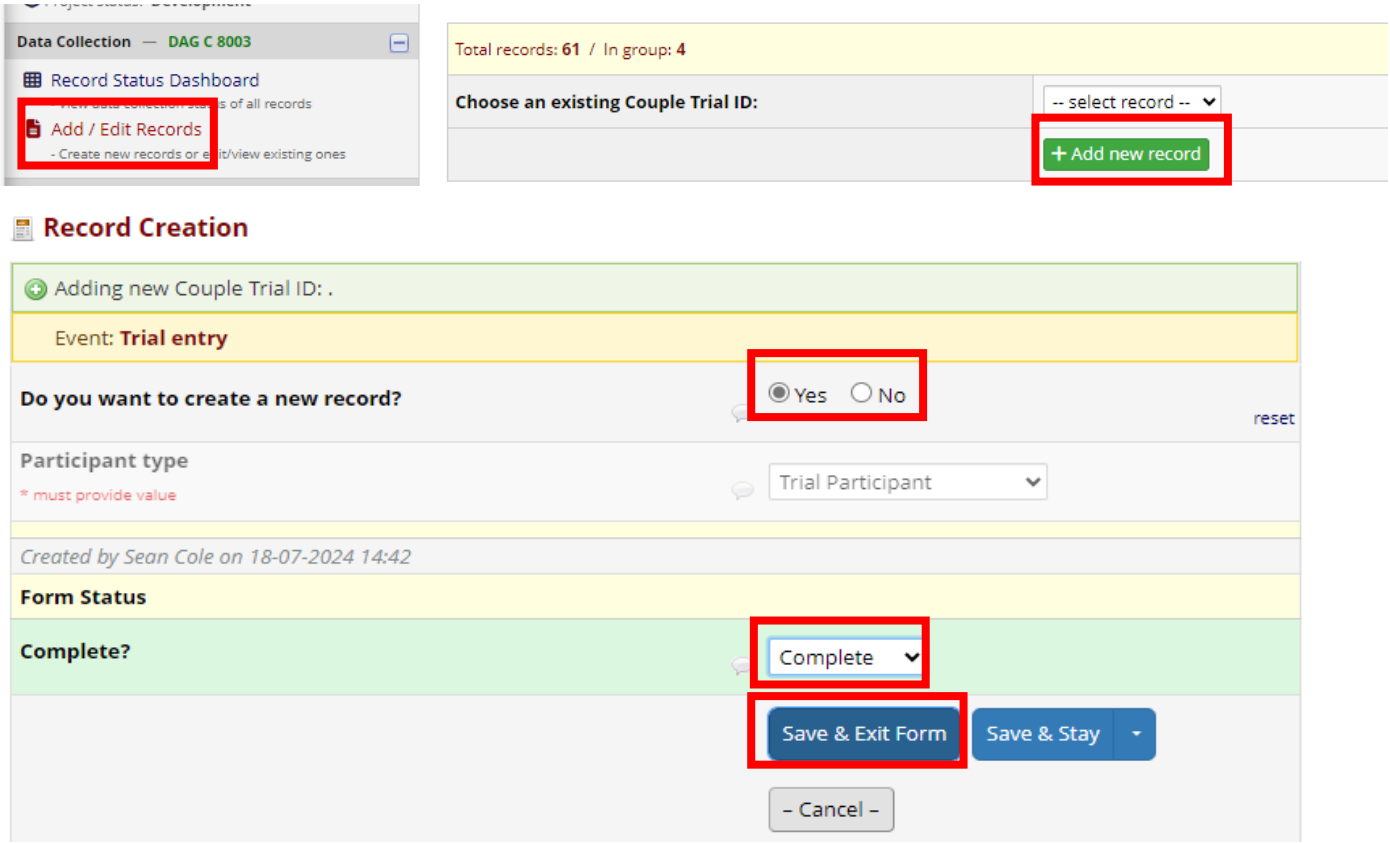
EQ-5D *(Quality of life questionnaire) — needs to be completed at baseline before you can randomise*

AFTER TREATMENT AND AT 570 DAYS AND 750 DAYS FOLLOWING RANDOMISATION

- EQ-5D (QoL)
- CSQ8 (Client Satisfaction)
- Health Resources Questionnaire

4.3 Record Creation

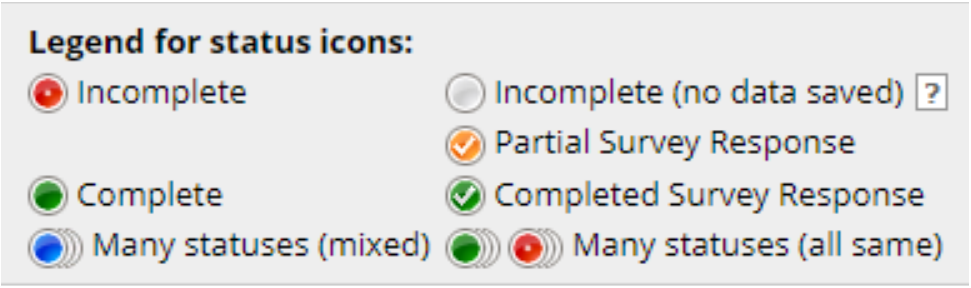
Click **'Add / Edit records'**, on left hand side of screen. Then click on the green **"+Add new record"** button (which will then generate the couple trial ID). Click **'yes'** to create a record for the couple on the database, set form status to **'complete'**, and click **'save & exit form'.**



When saving a form, you have the choice of marking it as **"complete"** or **"incomplete".**

Forms marked complete will have a green bubble on the record status dashboard, therefore we recommend that you only mark forms as complete if you have finished entering all the data.

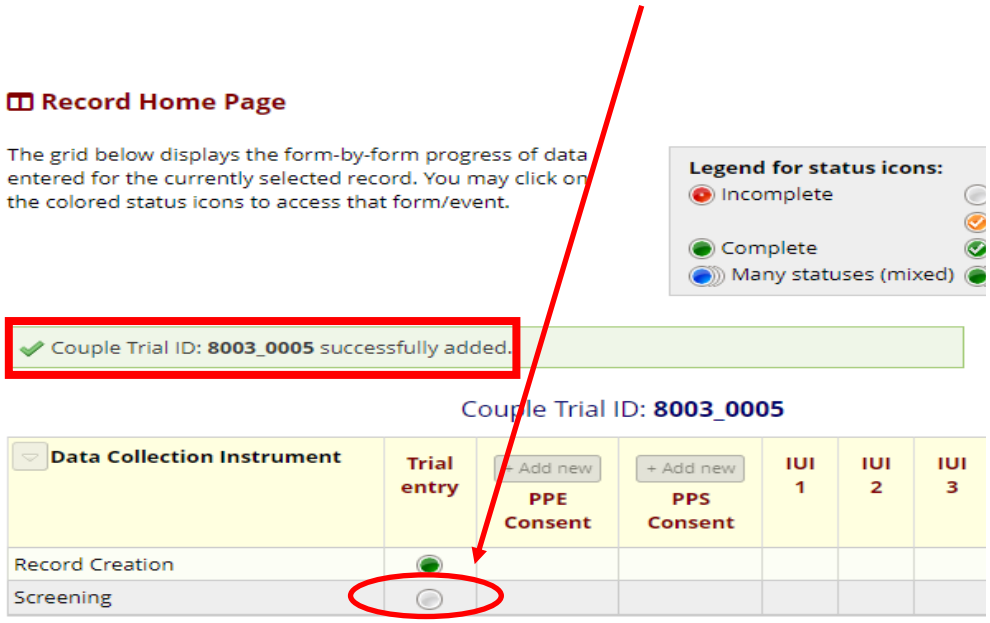
If at any time during data input you are waiting for another piece of data please ensure you leave the form status as 'incomplete' (red bubble on the record status dashboard) as this will help you and the UNiTY Trials Office to establish what needs to be checked.

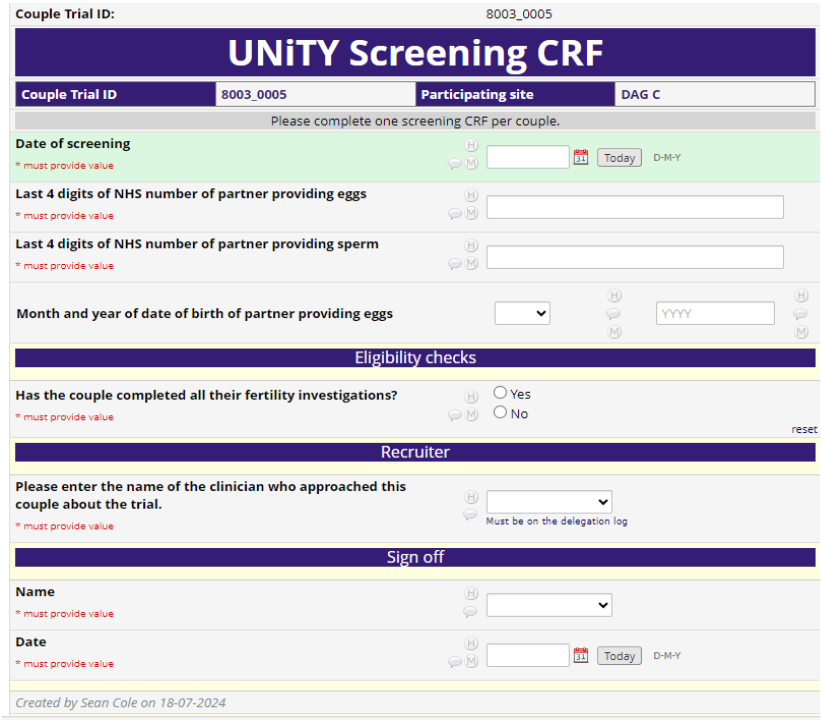


4.4 Screening

Once 'record creation' is completed, the couple trial ID will appear in a green heading and the Screening form will be generated. **Please screen all couples on the database who you are actively considering for the study**.

Open the '**Screening**' form by clicking on the clear 'bubble'

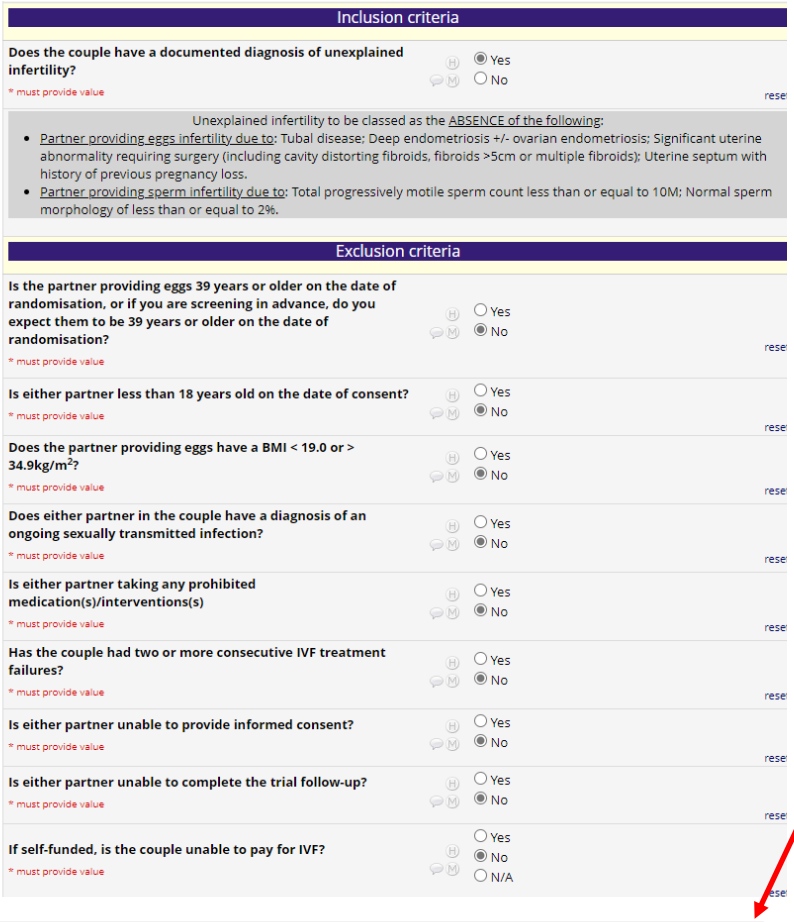




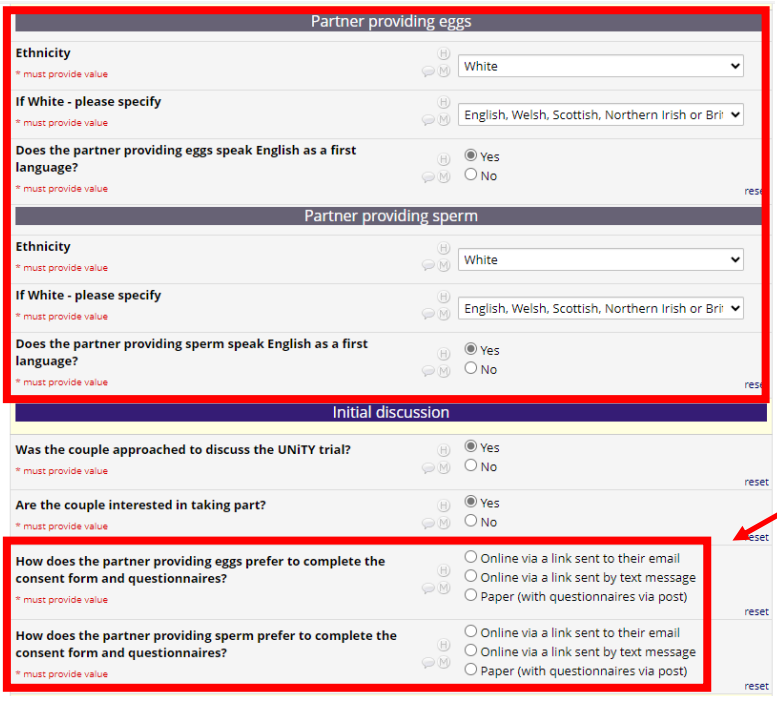
***Note**:* when you start answering the questions, more fields will appear, please complete all data fields that appear. If you save the form without completing all data fields, you will receive a pop-up dialogue box to remind you to enter missing data.

4.5 Complete the 'Screening' form

Please read *all* the questions *carefully* and answer them accurately for the date/time you are screening the couple.

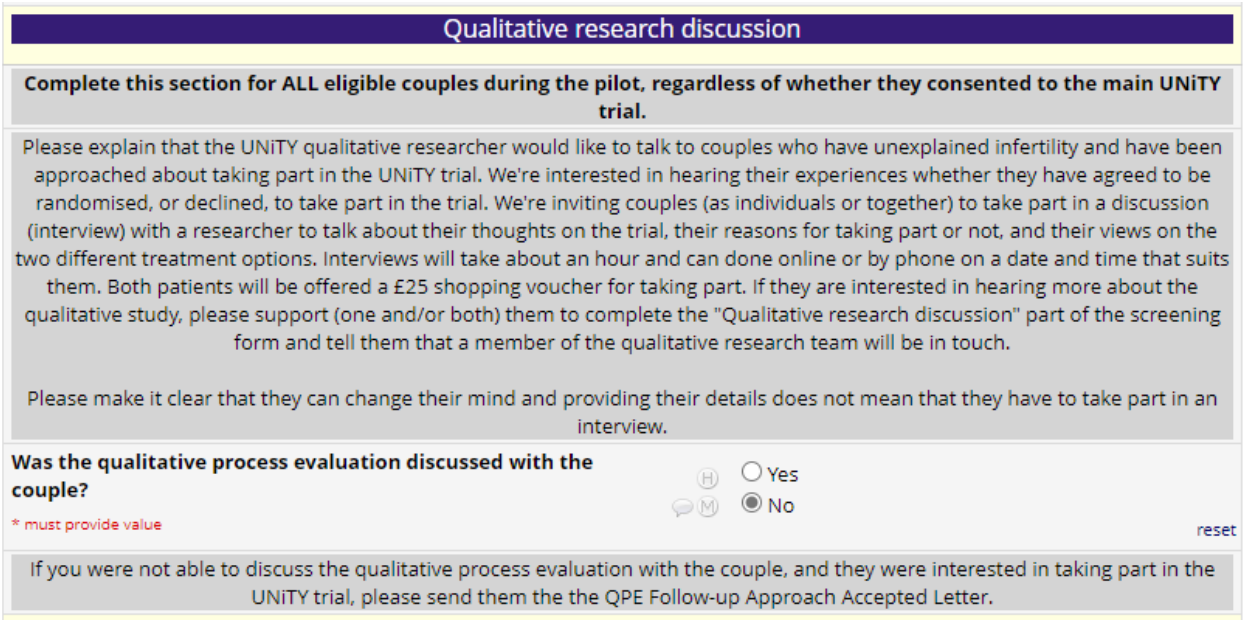


Once the inclusion and exclusion criteria have been answered, the form will generate the 'partner providing eggs' and 'partner providing sperm' ethnicity question. **This data is needed as it is a minimisation variable required for randomisation.**



Please enter the couple's preferred contact method. Couples will have an option of 'email', 'text message' or 'paper'. The consent form will be sent electronically if 'email' or 'text message' is selected. If paper is selected, you must upload a PDF of the completed consent form in order to proceed.

4.6 'Qualitative Research Discussion' on the Screening form



Qualitative research discussion

Complete this section for ALL eligible couples during the pilot, regardless of whether they consented to the main UNiTY trial.

Please explain that the UNiTY qualitative researcher would like to talk to couples who have unexplained infertility and have been approached about taking part in the UNiTY trial. We're interested in hearing their experiences whether they have agreed to be randomised, or declined, to take part in the trial. We're inviting couples (as individuals or together) to take part in a discussion (interview) with a researcher to talk about their thoughts on the trial, their reasons for taking part or not, and their views on the two different treatment options. Interviews will take about an hour and can done online or by phone on a date and time that suits them. Both patients will be offered a £25 shopping voucher for taking part. If they are interested in hearing more about the qualitative study, please support (one and/or both) them to complete the "Qualitative research discussion" part of the screening form and tell them that a member of the qualitative research team will be in touch.

Please make it clear that they can change their mind and providing their details does not mean that they have to take part in an interview.

Was the qualitative process evaluation discussed with the couple?

* must provide value

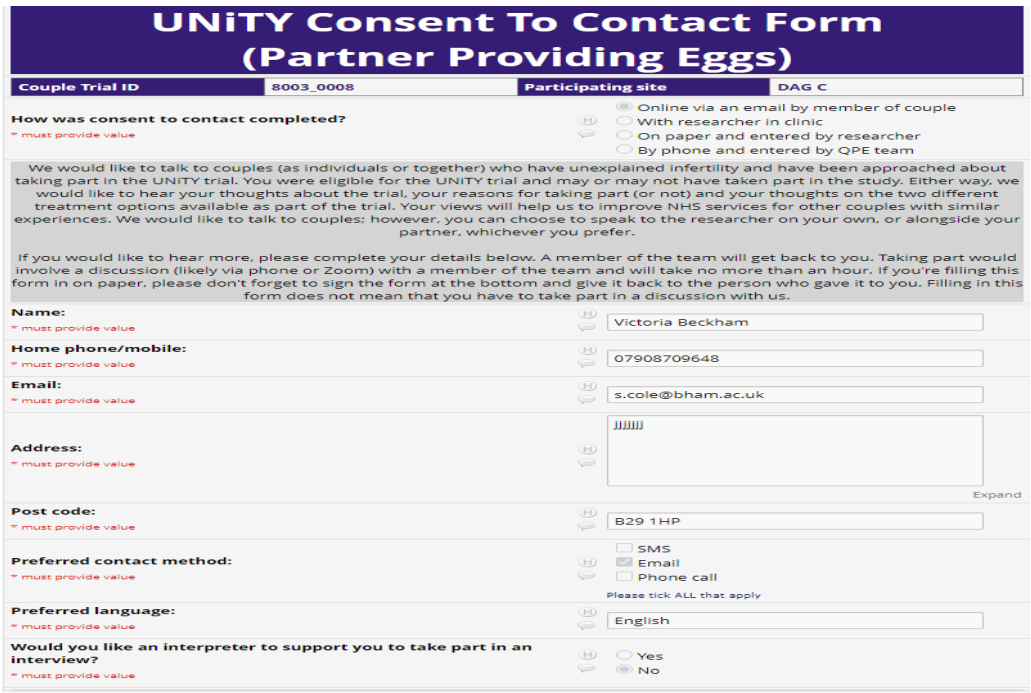
(H) ○ Yes
(M) ◉ No

reset

If you were not able to discuss the qualitative process evaluation with the couple, and they were interested in taking part in the UNiTY trial, please send them the the QPE Follow-up Approach Accepted Letter.

During the pilot, all eligible couples that have been approached for UNITY should be asked if they are willing to be contacted to take part in the QPE discussion sub-study. If one or both members of the couple are interested in taking part, a '**consent to contact'** form will be generated for the couple to complete. Once completed, this will be emailed to the University of Birmingham Qualitative Research team to follow up on.

This sub-study will run for the 9 month internal pilot and aims to gather experiences from patients and healthcare professionals to identify any problems in recruitment to the trial.



UNiTY Consent To Contact Form (Partner Providing Eggs)

Couple Trial ID	8003_0008	Participating site	DAG C

How was consent to contact completed?
* must provide value
◉ 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

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: * must provide value — Victoria Beckham

Home phone/mobile: * must provide value — 07908709648

Email: * must provide value — s.cole@bham.ac.uk

Address: * must provide value — jjjjjjj — Expand

Post code: * must provide value — B29 1HP

Preferred contact method: * must provide value
☐ SMS
☑ Email
☐ Phone call
Please tick ALL that apply

Preferred language: * must provide value — English

Would you like an interpreter to support you to take part in an interview? * must provide value
○ Yes
◉ No

If you were not able to discuss the QPE sub-study with the couple, you will be prompted to send the couple the 'QPE Follow-up Approach Accepted Letter', or 'QPE Follow-up Approach Declined Letter' (depending on whether or not the couple are taking part in the main trial.)

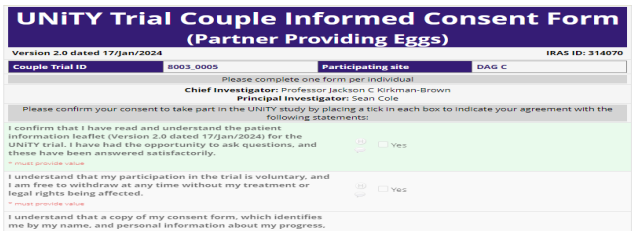
4.7 Participant Consent

Informed Consent Forms:

- Participant Consent forms are designed to be completed via email or text message however paper informed consent forms are available if preferred by the couple. If an interpreter assists with consent they must counter-sign the consent form.

Couples will have three options to complete the UNiTY Informed Consent Form (ICF):

- Email
- Text Message
- Paper



If you have entered the participant's preferred email address or mobile phone number on the screening form, a link to the consent form will then be sent via this method once the screening form is saved.

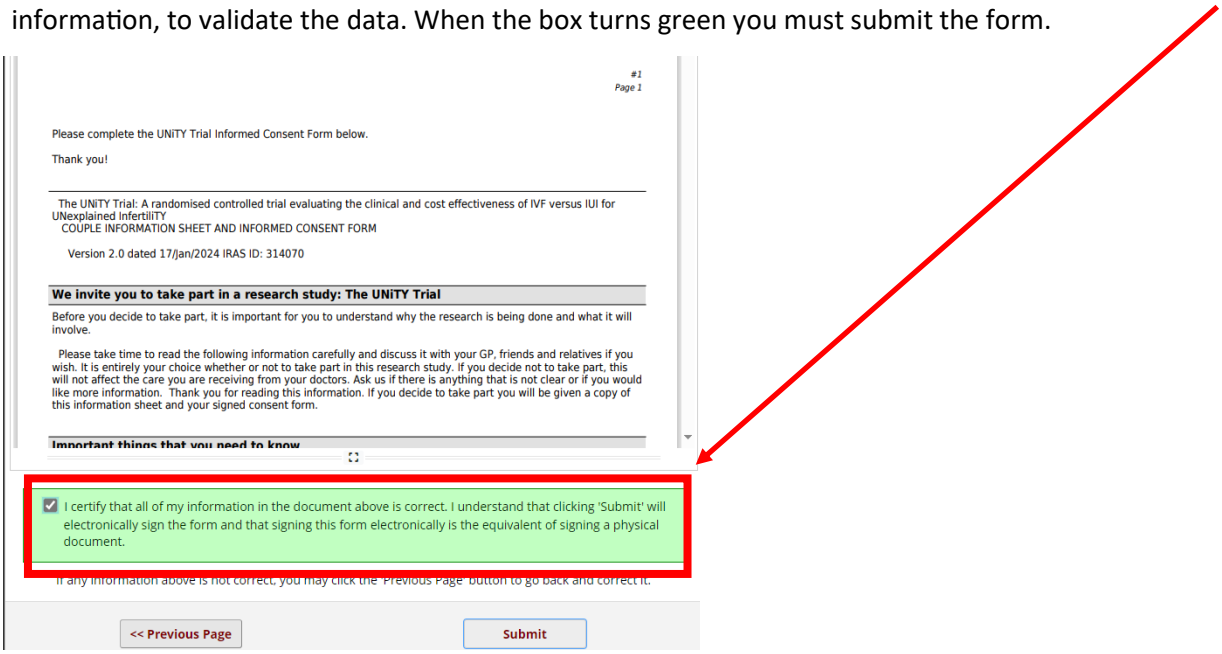
When entering the form from the email/text message hyperlink, the UNiTY Patient Information Sheet (PIS) will appear and participants must proceed through each section in order to reach the consent form.

The consent form contains a number of mandatory statements that must be answered 'yes' in order to proceed. If a paper consent form is completed, ensure that initials are used to denote agreement to each statement (not ticks).

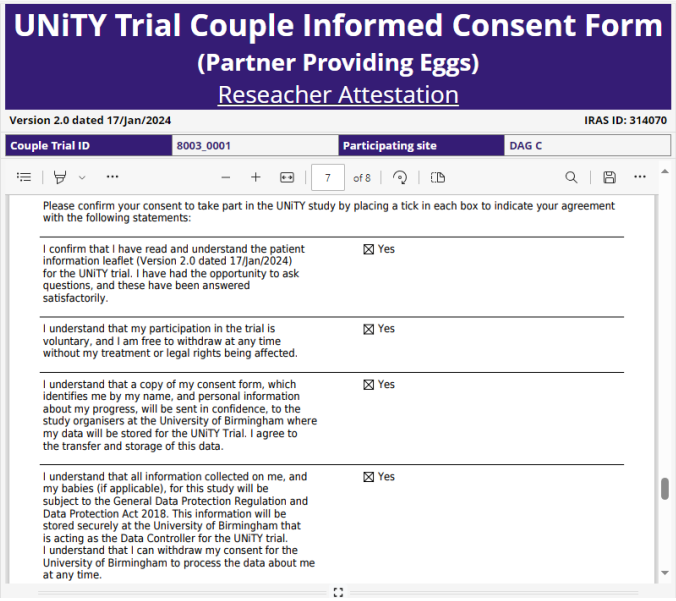
If the paper method is chosen, a fully signed copy must be uploaded to the database in order to proceed with randomisation — refer to page 15.

The member of staff obtaining informed consent, and an interpreter if one is used, must counter-sign the form before it is considered valid.

Once the online consent form is complete a PDF version will appear, and the participant will have to 'certify' the information, to validate the data. When the box turns green you must submit the form.



4.8 Researcher and Interpreter Attestation



UNiTY Trial Couple Informed Consent Form
(Partner Providing Eggs)
Reseacher Attestation

Version 2.0 dated 17/Jan/2024 — IRAS ID: 314070

Couple Trial ID	8003_0001	Participating site	DAG C

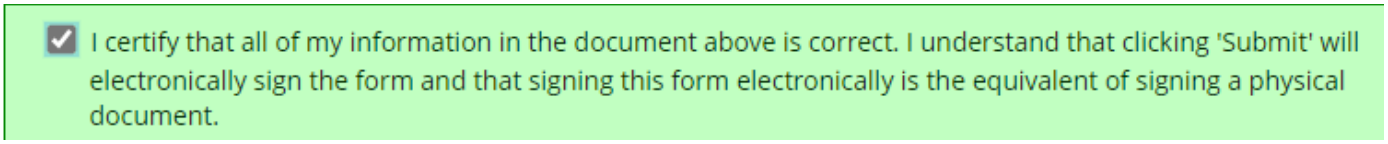
Please confirm your consent to take part in the UNiTY study by placing a tick in each box to indicate your agreement with the following statements:

I confirm that I have read and understand the patient information leaflet (Version 2.0 dated 17/Jan/2024) for the UNiTY trial. I have had the opportunity to ask questions, and these have been answered satisfactorily.	☒ Yes
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.	☒ Yes
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.	☒ Yes
I understand that all information collected on me, and my 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.	☒ Yes

Immediately after the couple have submitted their consent from electronically, the researcher will receive an email to the address they entered on the screening form. Please click on the link in this email. This will take you to an electronic copy of the consent form which you must check and counter-sign in order for the consent to be valid.

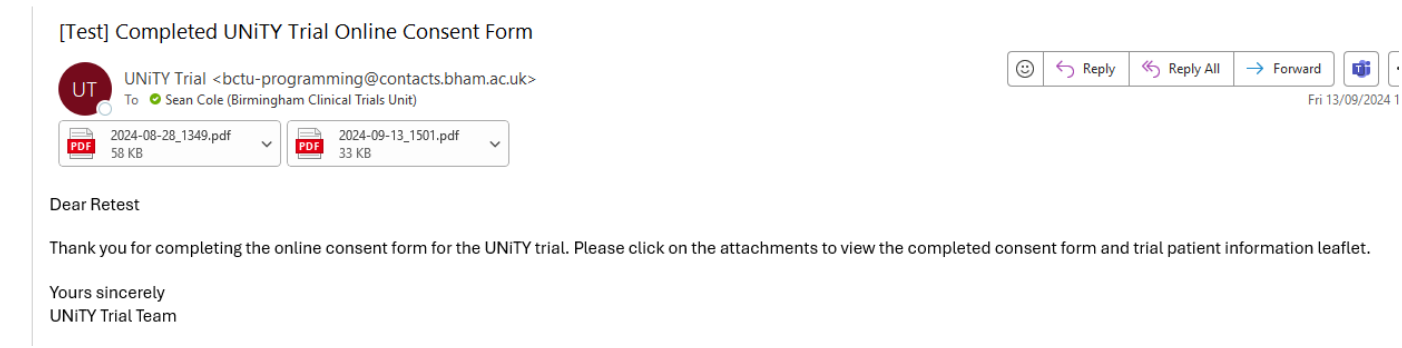
If an interpreter is used, they must also follow that same process. They will be emailed to the address provided on the screening form. Once the researcher has submitted the form.

The Researcher and Interpreter Attestation forms will also, like the consent forms, have the certify button seen below. This is confirming that the data has been checked and verified by the member of site staff that consented the couple.



☑ I certify that all of my information in the document above is correct. I understand that clicking 'Submit' will electronically sign the form and that signing this form electronically is the equivalent of signing a physical document.

Once the certify box is ticked and the form has been submitted an email will be sent to the couple with the PDF versions of their consent, researcher attestation, and interpreter attestation forms.



[Test] Completed UNiTY Trial Online Consent Form

UT — UNiTY Trial <bctu-programming@contacts.bham.ac.uk>
To Sean Cole (Birmingham Clinical Trials Unit)

Reply | Reply All | Forward
Fri 13/09/2024 1

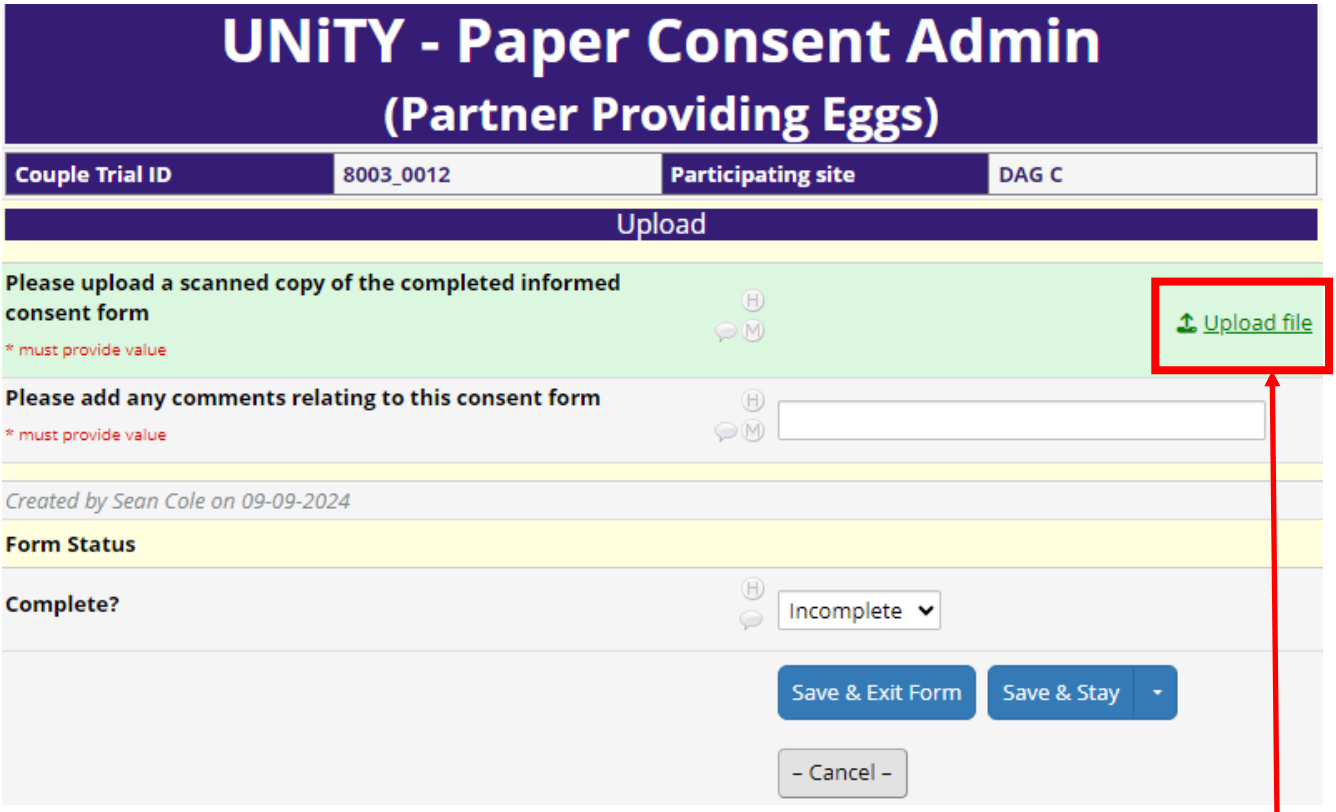
2024-08-28_1349.pdf 58 KB
2024-09-13_1501.pdf 33 KB

Dear Retest

Thank you for completing the online consent form for the UNiTY trial. Please click on the attachments to view the completed consent form and trial patient information leaflet.

Yours sincerely
UNiTY Trial Team

4.9 Participant Consent (paper method)

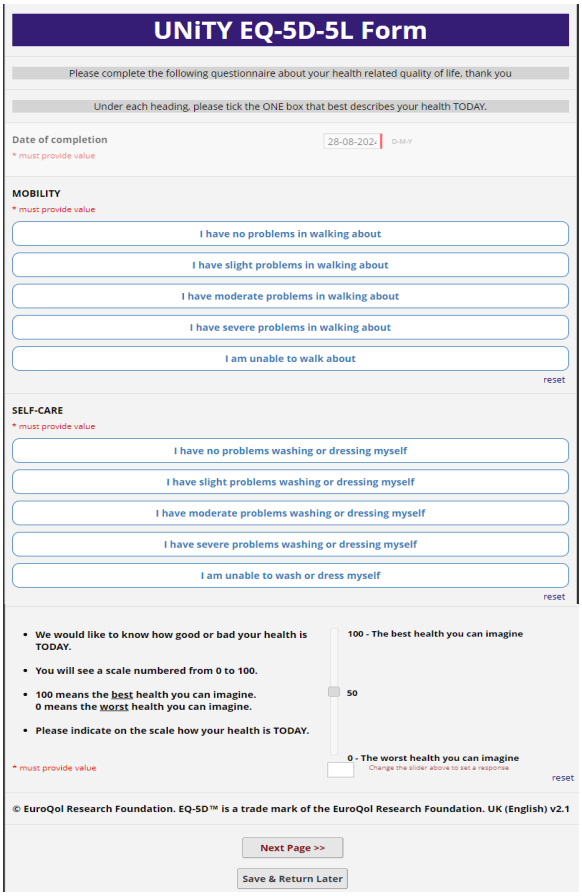


If the couple prefers to complete the consent form on paper, a PDF copy of the fully signed form MUST be uploaded to REDCAP in order for the database to allow you to proceed further.

Scan the consent form and save as a PDF. Clicking the green 'upload file' button will allow you to access all of your saved computer files. Find the consent form you have saved in your files and double click this to upload to the database. Once that is done add any comments in the prompt below and set form status to complete. Save & Exit the form.

The paper consent form will be checked by the BCTU Trial Office and queries sent to you via email.

4.10 EQ-5D-5L

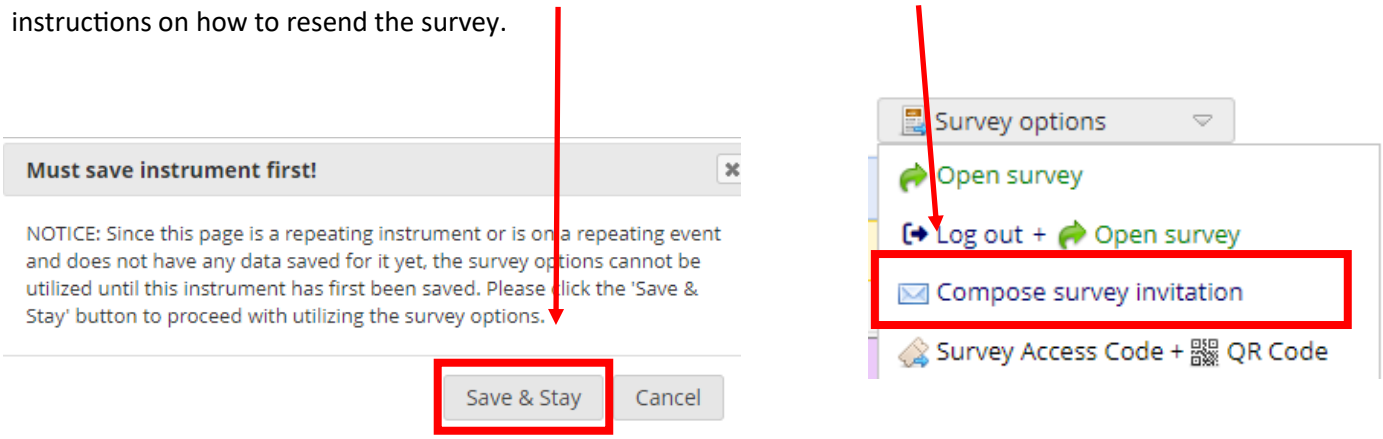


The EQ-5D-5L is a very short quality of life questionnaire which both members of the couple must complete separately. Completion is mandatory in order to proceed to randomisation, therefore please encourage the couple to complete this immediately after consenting. If they have selected a preference to receive this via email or text message, it will automatically be sent to their preferred contact method.

Alternatively, you can answer the questions directly onto the database if preferred.

4.11 Composing survey invitations

If you need to resend a form to a participant please click on the bubble of the form you need to send out, and you will see 'survey options' greyed out to the top of the CRF, right hand side. If you click this it will pop up below with an error, stating that if you 'save and stay' you will be able to select the options. Click 'save & stay' and this will enable the survey options drop-down list where you will see 'compose survey invitation' - see next page for further instructions on how to resend the survey.



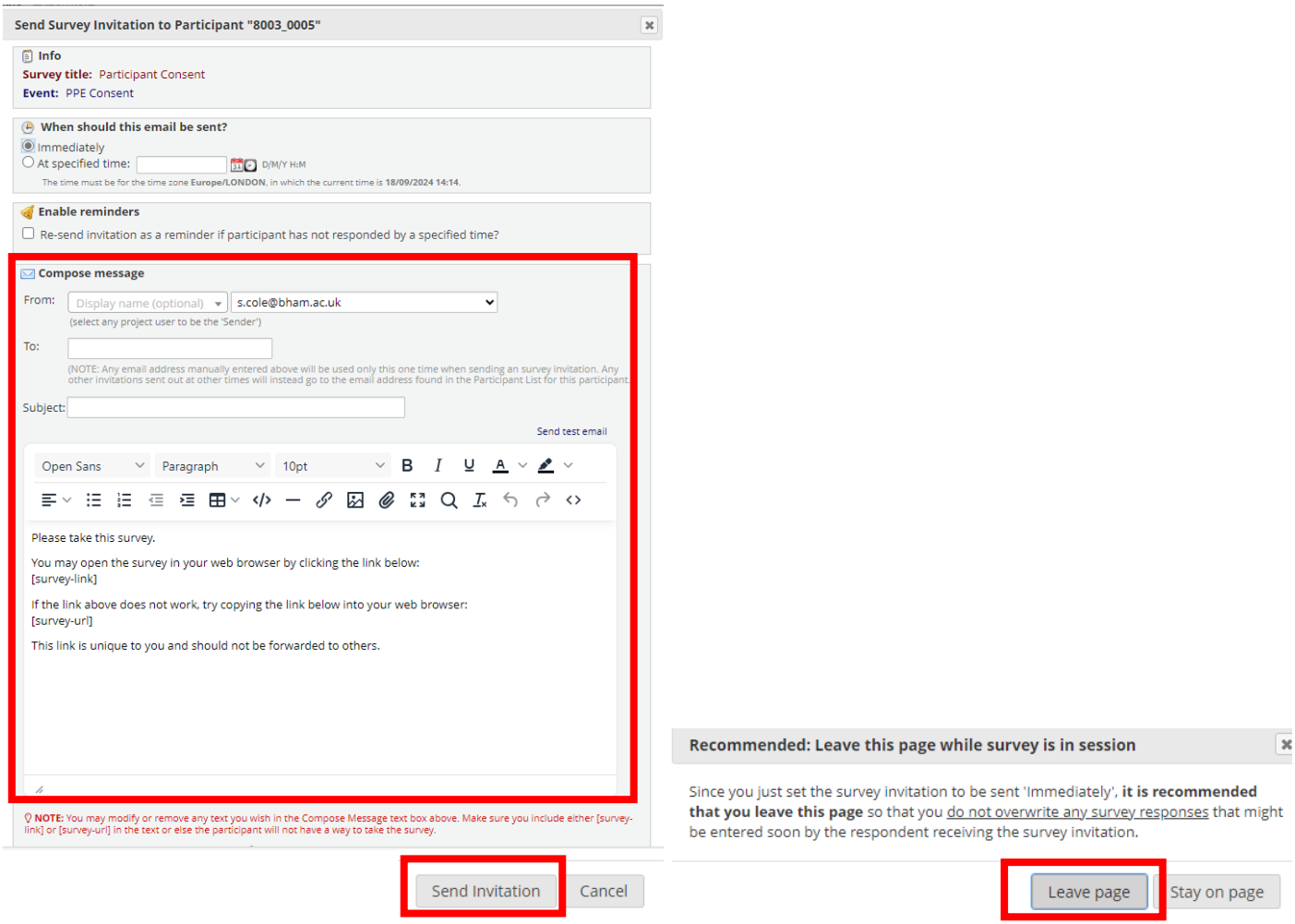
4.12 Sending survey invitations

When 'compose survey invitation' is selected the page shown below will pop up to confirm the correct participant to send it to and the survey title (questionnaire or form). In the case illustrated below, it is 'PPE Consent' meaning the Partner Providing Eggs will be sent the Consent Form via email. You can also:

- Choose when you want this email to be sent (i.e 'immediately' or 'at specified time).
- Enable reminders which will resend the reminders automatically if the participant has not responded by a specified time.
- Compose the message—Type the participant's email address into the 'To:' data field, and you can also write the subject, for example, **'Trial ID number____ - reminder to complete UNiTY ICF'** and can also change the contents of the email.

Once you are happy with the email please select 'send test email' which you will be able to send to yourself to view how this would look when participants receive it. **For this please ensure your own email address is typed in to the 'To:' area.**

When you have done this, please replace your own email address with the email address of the participant you wish to send to, select 'send invitation' and a prompt will pop up as below to state you must select 'leave page' if you wish to send this email immediately. Select 'leave page' and your email will be sent.



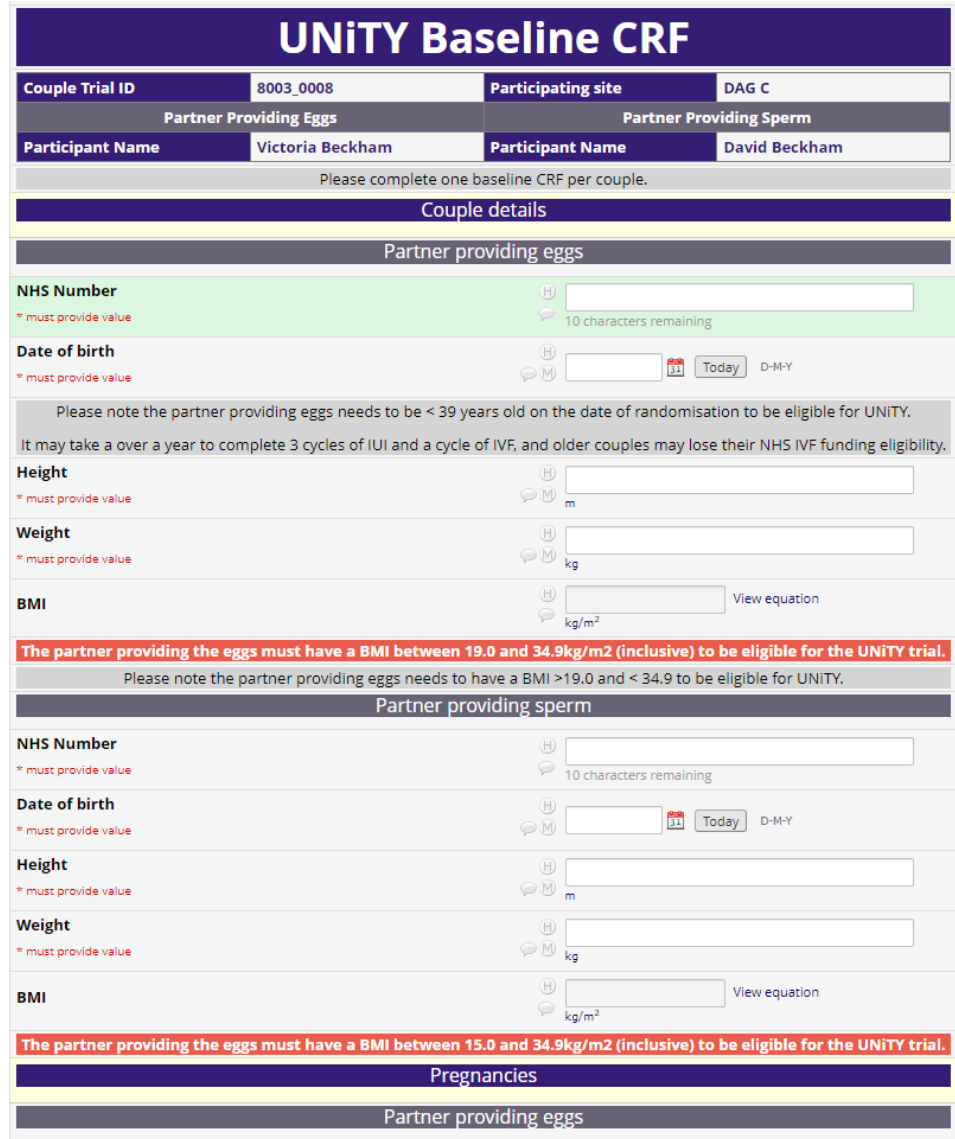
4.13 Baseline

This form collects the following essential information needed for randomisation.

- Partner providing eggs date of birth
- Partner providing eggs height
- Partner providing egg weight
- Partner providing sperm date of birth
- **Partner providing eggs ethnicity must be entered on the screening form**

You must complete this data immediately after consent in order to proceed to randomisation.

The rest of this form can be completed when you have more time.



UNiTY Baseline CRF

Couple Trial ID	8003_0008	Participating site	DAG C
Partner Providing Eggs		Partner Providing Sperm	
Participant Name	Victoria Beckham	Participant Name	David Beckham

Please complete one baseline CRF per couple.

Couple details

Partner providing eggs

NHS Number * must provide value — 10 characters remaining

Date of birth * must provide value — Today D-M-Y

Please note the partner providing eggs needs to be < 39 years old on the date of randomisation to be eligible for UNiTY.

It may take a over a year to complete 3 cycles of IUI and a cycle of IVF, and older couples may lose their NHS IVF funding eligibility.

Height * must provide value — m

Weight * must provide value — kg

BMI — View equation — kg/m²

The partner providing the eggs must have a BMI between 19.0 and 34.9kg/m2 (inclusive) to be eligible for the UNiTY trial.

Please note the partner providing eggs needs to have a BMI >19.0 and < 34.9 to be eligible for UNiTY.

Partner providing sperm

NHS Number * must provide value — 10 characters remaining

Date of birth * must provide value — Today D-M-Y

Height * must provide value — m

Weight * must provide value — kg

BMI — View equation — kg/m²

The partner providing the eggs must have a BMI between 15.0 and 34.9kg/m2 (inclusive) to be eligible for the UNiTY trial.

Pregnancies

Partner providing eggs

4.14 Randomisation

Data Collection Instrument	Trial entry	+ Add new PPE Consent	+ Add new PPS Consent
Record Creation			
Screening			
Consent To Contact - PPE (survey)			
Consent To Contact - PPS (survey)			
Participant Consent (survey)			
Researcher Attestation (survey)			
Contact Details - PPE (survey)			
Contact Details - PPS (survey)			
Baseline			
Randomisation			
Questionnaire - PPE (survey)			
Questionnaire - PPS (survey)			
Baseline: Pregnancy History - PPE			
Baseline: Pregnancy History - PPS			

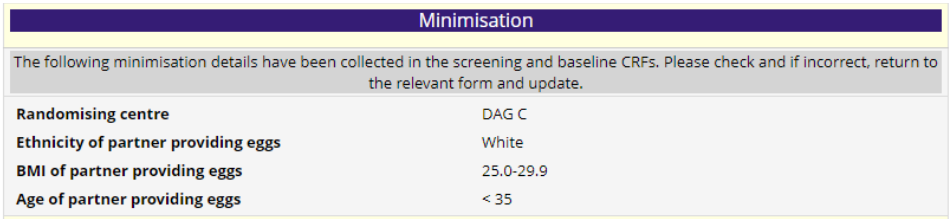
In order to enable randomisation to proceed, you must ensure that the following forms have been completed on the database:

- PPE consent form
- PPS consent form
- Researcher Attestation Form
- Interpreter Attestation Form (if required)
- PPE EQ-5D completed
- PPS EQ-5D completed
- Baseline minimisation variables completed

As you can see in the image to the left, once the above forms are complete, the randomisation form will generate for completion.

Complete the randomisation variables.

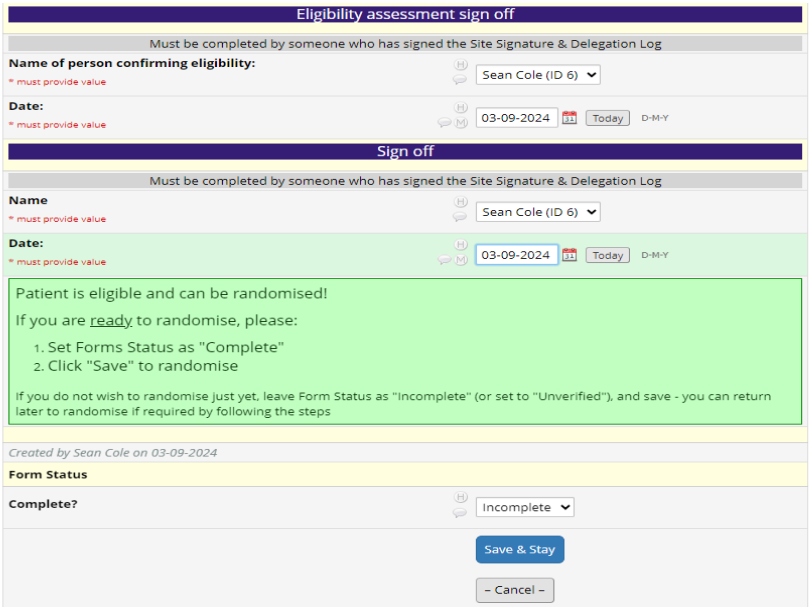
The minimisation data will populate once the data has been input, displaying where the couple were randomised, PPE ethnicity, PPE BMI and PPE age to enable you to check that these variables have been entered correctly.



Minimisation

The following minimisation details have been collected in the screening and baseline CRFs. Please check and if incorrect, return to the relevant form and update.

Randomising centre	DAG C
Ethnicity of partner providing eggs	White
BMI of partner providing eggs	25.0-29.9
Age of partner providing eggs	< 35



Eligibility assessment sign off

Must be completed by someone who has signed the Site Signature & Delegation Log

Name of person confirming eligibility: * must provide value — Sean Cole (ID 6)

Date: * must provide value — 03-09-2024 Today D-M-Y

Sign off

Must be completed by someone who has signed the Site Signature & Delegation Log

Name * must provide value — Sean Cole (ID 6)

Date: * must provide value — 03-09-2024 Today D-M-Y

Patient is eligible and can be randomised!

If you are ready to randomise, please:

1. Set Forms Status as "Complete"
2. Click "Save" to randomise

If you do not wish to randomise just yet, leave Form Status as "Incomplete" (or set to "Unverified"), and save - you can return later to randomise if required by following the steps

Created by Sean Cole on 03-09-2024

Form Status

Complete? Incomplete

Save & Stay

– Cancel –

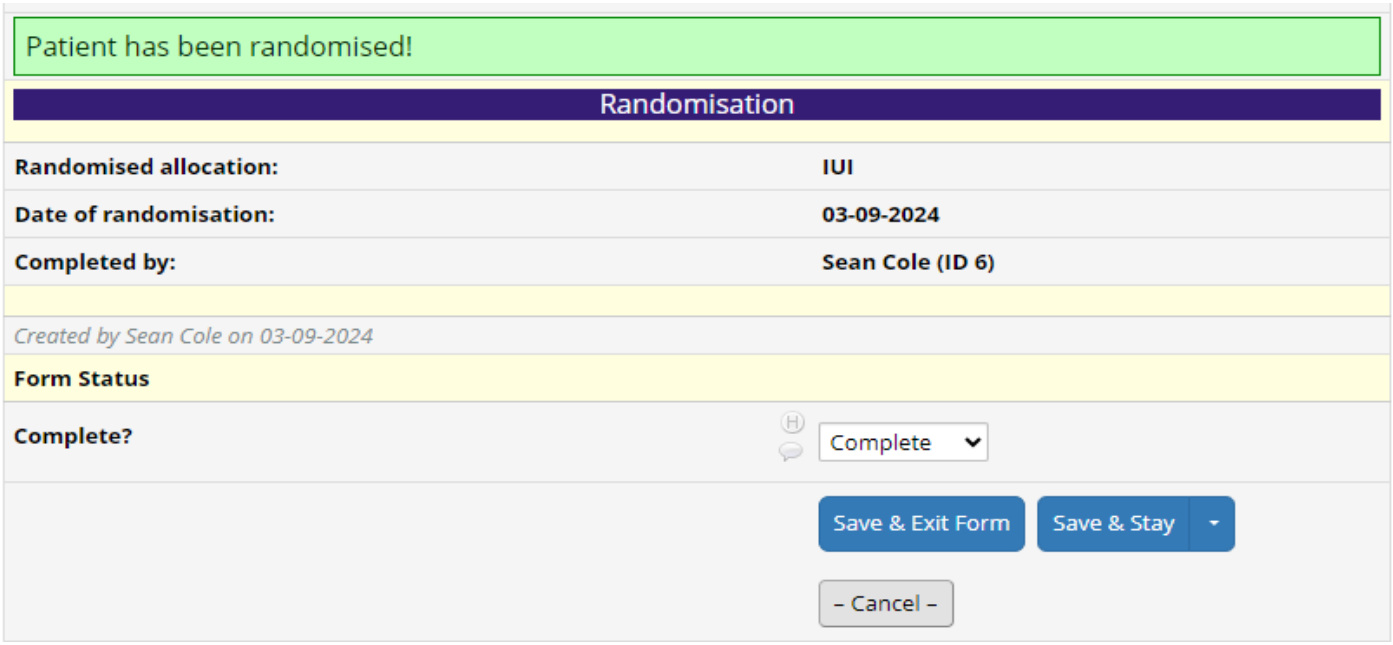
This Eligibility assessment sign off section of the Randomisation form allows the randomiser to document the member of staff assessing eligibility of the couple. Once all the questions on the randomisation form are answered a green box will appear stating 'patient is eligible and can be randomised!' The treatment will be allocated once the form status is set to complete and the form is saved.

Continued Randomisation

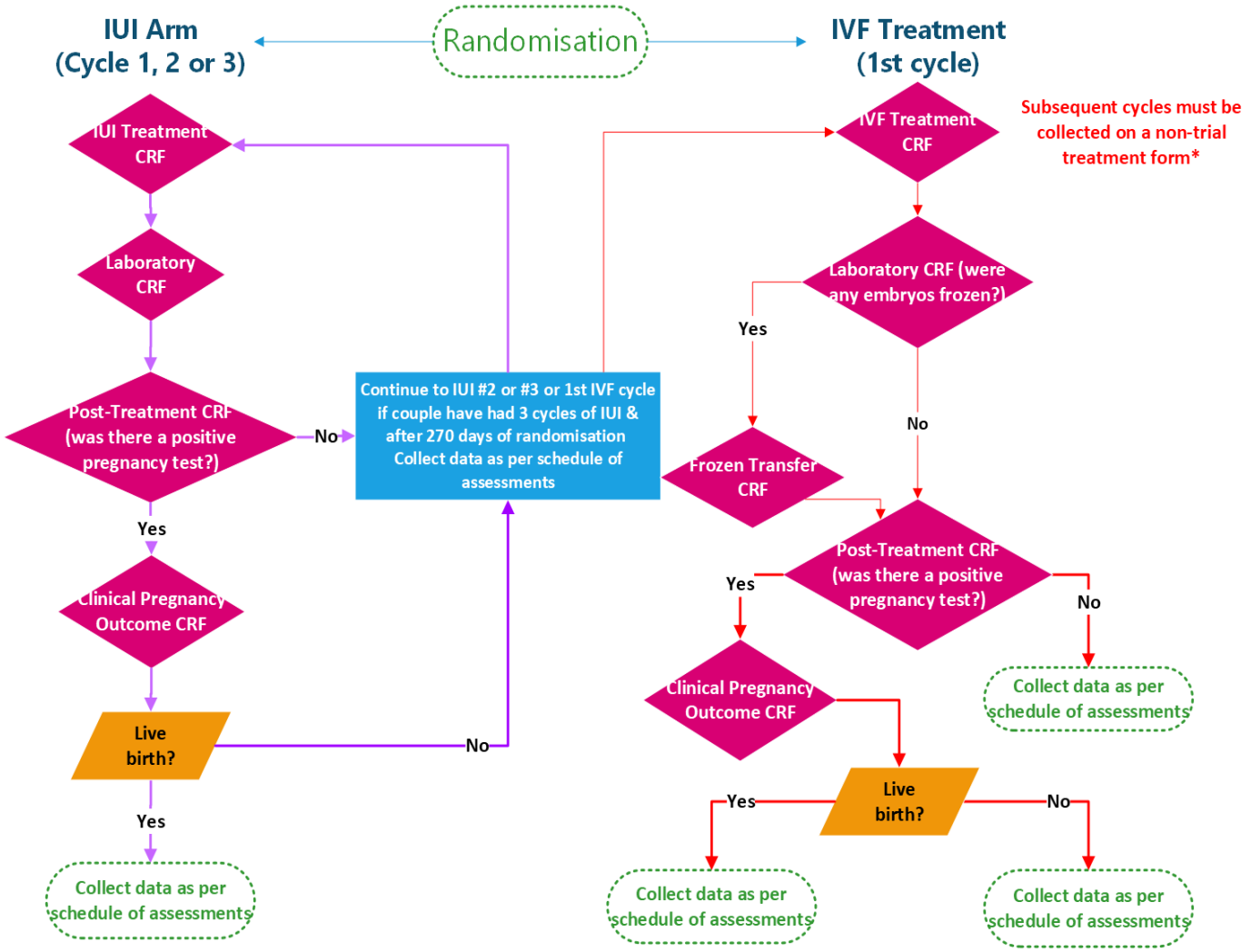
Once the form is saved a green box will appear informing you that the couple were randomised, with the details of the randomisation, as seen below:

- Randomisation Allocation
- Date of randomisation
- Name of site staff that completed randomisation of the couple.

When this appears, randomisation is complete. You will now receive an email confirming randomisation, please save this in your site file.



4.15 Flow diagram of forms to be completed after randomisation



Ad hoc CRFs

Non-trial treatment*

Serious Adverse Event (SAEs)

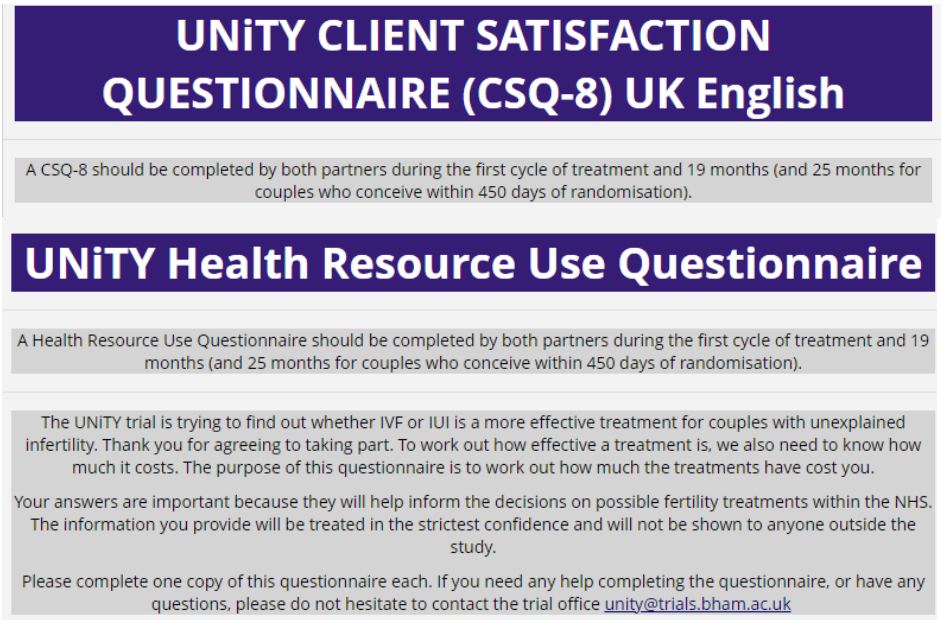
Deviation

Change of Status (CoS)

Natural Pregnancy Notification

4.16 Patient Reported Outcomes

EQ-5D, CSQ8 and Health Resource Use Questionnaires



UNiTY CLIENT SATISFACTION QUESTIONNAIRE (CSQ-8) UK English

A CSQ-8 should be completed by both partners during the first cycle of treatment and 19 months (and 25 months for couples who conceive within 450 days of randomisation).

UNiTY Health Resource Use Questionnaire

A Health Resource Use Questionnaire should be completed by both partners during the first cycle of treatment and 19 months (and 25 months for couples who conceive within 450 days of randomisation).

The UNiTY trial is trying to find out whether IVF or IUI is a more effective treatment for couples with unexplained infertility. Thank you for agreeing to taking part. To work out how effective a treatment is, we also need to know how much it costs. The purpose of this questionnaire is to work out how much the treatments have cost you.

Your answers are important because they will help inform the decisions on possible fertility treatments within the NHS. The information you provide will be treated in the strictest confidence and will not be shown to anyone outside the study.

Please complete one copy of this questionnaire each. If you need any help completing the questionnaire, or have any questions, please do not hesitate to contact the trial office unity@trials.bham.ac.uk

The EQ-5D (Patient Reported Quality of Life), Client Satisfaction Questionnaire (CSQ-8) and Health Resource Use Questionnaire must be completed by ***each member of the couple separately*** after the first cycle of treatment and at 19 months, and 25 months post randomisation. The aim of these questionnaires is to find out the quality of life of the couple, the quality of service the couple has received whilst in the trial and gathers data on the wider cost of their treatment.

If their preferred method of completion is stated as email or text message on the screening form, these questionnaires will be automatically sent to the couple by their preferred contact method after their first cycle of treatment (i.e. once the IUI or IVF CRF has been completed) and at 19 months and 25 months post randomisation.

If a participant has stated on the screening form that they would prefer to complete their questionnaires on paper, it is your responsibility to follow up with them at the right time-points.

5. Change of Status

COUPLES THAT DECIDE 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, IT IS A PROTOCOL DEVIATION AND THE TEAM WOULD EXPECT YOU TO COMPLETE A DEVIATION FORM.

Please complete a Change of Status form for participants that choose to withdraw from all or part of the trial.

There are four types of withdrawal for you to select from:

- **Death** (notification that one or both partners have died)
- **Partial withdrawal** (one or both partners wish to withdraw from certain aspects of the trial such as intervention, follow-up, questionnaires and/or data collection.)
- **Complete withdrawal** One or both partners decide to withdraw completely from the trial i.e no further data will be collected. This is only applicable to couples who have not yet started fertility treatment or have completed fertility treatment.
- **Loss to follow-up** (it has not been possible to contact the couple despite repeated attempts)

6. Serious Adverse Event (SAE)

All related and unexpected SAEs 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.

AEs must be reported from randomisation until 60 days after cycle outcome is known.

For unsuccessful cycles SAE's should be reported for 60 days following a negative pregnancy test. For cycles resulting in pregnancy, SAEs should be reported for 60 days after the pregnancy outcome is known.

SAEs should only be reported for trial related treatments, and 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. Only serious, related, and unexpected adverse event, beyond the routine expectations and known risks for fertility treatment, will be reported as SAEs.

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

Serious Adverse Advents (SAE) reporting**:**

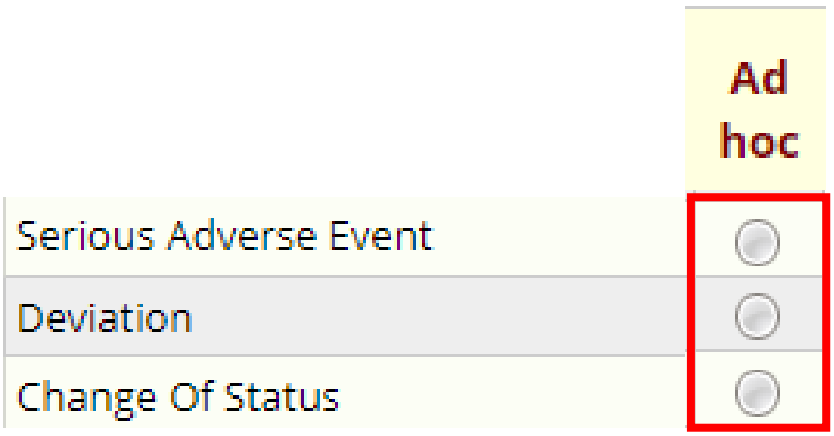
1. Record safety reporting-exempt SAEs in the medical notes but **not report** them to the trials office on an SAE form.

2. Report SAEs to the trial office in a non-expedited manner. This can only be done for the pre-defined subset of SAEs and should be uploaded onto the 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.

To report an SAE, submit the SAE form to the UNiTY trial team via the main trial database within 24 hours of becoming aware. A member of staff listed on the delegation log for SAE reporting must complete the form, and the PI (or delegate) listed as responsible for SAE sign off must sign the form.

When a couple is randomised, their ad hoc forms will be available to generate on your site's patient dashboard. These forms can be created any time during the trial after the couple are randomised. Click on the bubble of whichever form is relevant to the circumstances and this will take you into the CRFs for completion.



Bubbles will be underneath 'Ad hoc' section on patient table

7. Protocol Deviation

If there has been a deviation from the protocol, please let the UNiTY Trial Office know as soon as possible by completing a Deviation form on the database.

Protocol deviations may relate to: inclusion/exclusion of participants, informed consent, randomisation, confidentiality and data protection.

Please complete a Deviation form if the following occurs:

- A couple have decided not to adhere to the randomisation treatment allocation but are willing to be followed up in accordance with the schedule of assessments.
- Couples are found to be ineligible post-randomisation.

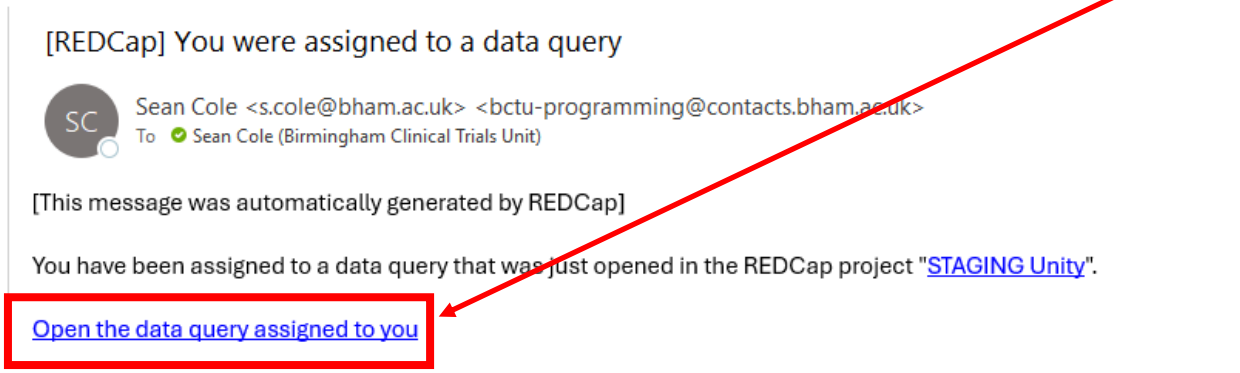
In both cases couples should be followed up according to all trial processes and a deviation form completed.

8. Data Queries

The UNiTY Trials Office will be checking all forms once the form status' have been set to 'complete' and the bubbles display the colour green on the dashboard. Any missing or inconsistent data will be queried as by the UNiTY Trials Office.

All data that is queried will be assigned to the Lead Researcher at that specific site, and the UNiTY Trials Office would expect that queries are completed every fortnight to give ourselves the best chance of collecting accurate data.

When the Trials Office opens the query, it will be sent immediately to the site staff that the query was assigned to and they will receive an email with links directly to the query, as seen below.



When the above link has been clicked, a box will appear as seen below. This will give site staff an opportunity to provide the UNiTY Trials Office with a response to the query. Site staff can 'reply with response'. **Only the UNITY Trials Office can 'close the query'**. Available selections from the drop-down responses are:

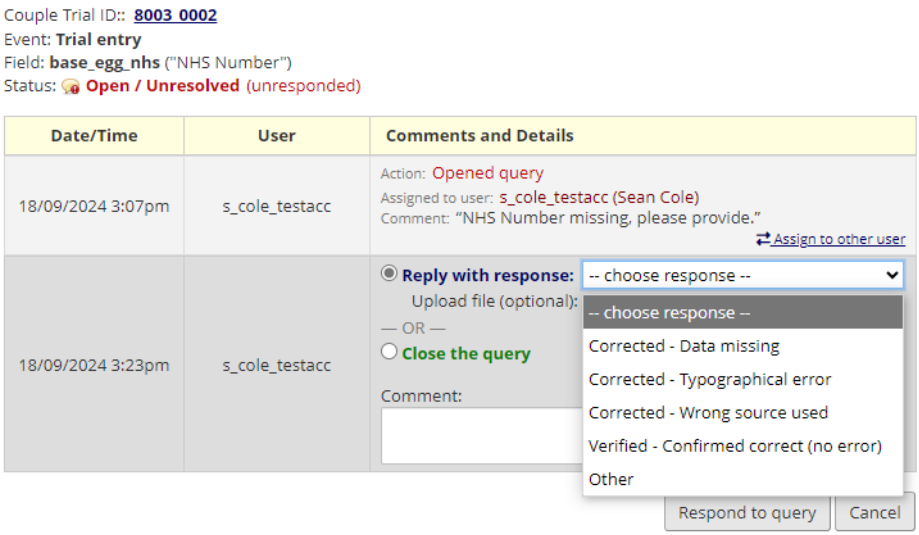
Corrected—Data missing

Corrected—Typographical error

Corrected—Wrong source used

Verified—Confirmed correct

Other



Icons below show when a query needs resolving vs when it is resolved and closed.

9. Advanced reports

There is a function on the left hand menu called 'Advanced Reports'. This function can be used to search for things in a simpler fashion, there are a few advanced reports that site staff will be able to run at site if need be. These are broken up in to three parts:

CRF Management

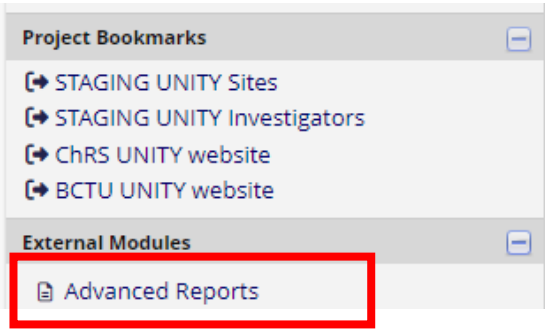
- **Form Status**—this will give you a list of your site's participants with their 'events' which means the specific form i.e. 'IUI 1' which is the first cycle of IUI. This function will tell you if the form is expected or not and if it is due or the date it is due. It will also inform you if the data has been entered or not.
- **Return Rates**—return rates function will display a table of your site's events and forms that are 'expected', 'due', or 'entered' with the number of each specific forms that are expected, due, or entered. It also gives you a percentage of your responses vs your expected responses.

Queries

- **Queries Summary**—the queries summary report will display a table of how many queries your sites has 'open' or 'closed', which is a quick and easy way to gather this data quickly. We recommend that you check this report regularly (every 2 weeks).
- **Queries Summary by Form/DQR**—this report is the same as above except it will list the specific form or DQR that has been queried, with a total.
- **Queries by participant**—this report will display a similar table with the specific participant the query relates to.
- **Queries by participant by form/DQR**—this report is the same as above except it will show you which form and which participant the query is for.
- **Queries by Participant by form/DQR (full details)** —this report will break down which form the query is on, which question the query relates to. It will also display the data category of the queries, so whether the query is a critical data item (CDI) or not. You will see the query comments on this report also, along with the status of the query whilst also showing which member of staff the query is assigned to. The Trials Office would encourage sites to use this function as the main source of information.

Recruitment

- **Recruitment by site and month**—this report will display a table showing your site's recruitment per month, how many couples you have recruited and the month recruited, with a total number also displayed.



10. UNiTY Database Training videos

Links:

- Video 1 – log in, navigating home page and adding couple = https://youtu.be/Na2ZPlgdkm0?si=3GEydU3qAIGAmzzh
- Video 2 – Screening = https://youtu.be/bwwr3K4t294?si=u0ueMYB9fqf3yyrW
- Video 3 – Electronic Consent = https://youtu.be/OtGaEyBe52Y?si=ot26jVuvyqh-0PrL
- Video 4 – Paper Consent = https://youtu.be/kwgiqMAigfg?si=2DTcuPdn7w5KYP54
- Video 5 – Researcher & Interpreter Attestation = https://youtu.be/TF2p5-dWHVM?si=_egNL0BV7wmHDoEQ
- Video 6 – Baseline & Randomisation = https://youtu.be/JAIiHnA3ulE?si=W7oNUQrqSITKAGsC
- Video 7 – Advanced Reports = https://youtu.be/Jo5DUinnT0Y?si=i1hjKeL0cKg9Oiiv

11. Laboratory Information

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UNiTY FAST Documentation

A. Videos of the insemination sample with FAST

Aliquots of the insemination sample (**NOT** the raw sample) should be taken for imaging with FAST following the instructions below.

1. Smear

A sperm smear should be made of the insemination sample:

a. Clean both surfaces of two frosted slides by wiping off with ethanol.

b. Label the frosted portion with the UNiTY couple ID and the cycle number (IVF/IUI1/IUI2/IUI3)

c. Apply a 5-10 µl aliquot of prepared sample, to the end of the slide. Use the second slide to pull the drop of sample along the surface of the slide (see figure).

d. Allow the slides to dry in air. Place in slide box and keep in the fridge until transfer to Birmingham.

To get the feel for the motion, place the dragging slide at an angle of 45° and move it into contact with the aliquot of semen *(a)*, which runs along the edge of the slide *(b)*. Bring the dragging slide slowly back (over approximately 1 second) along the length of the slide to produce the smear (c).

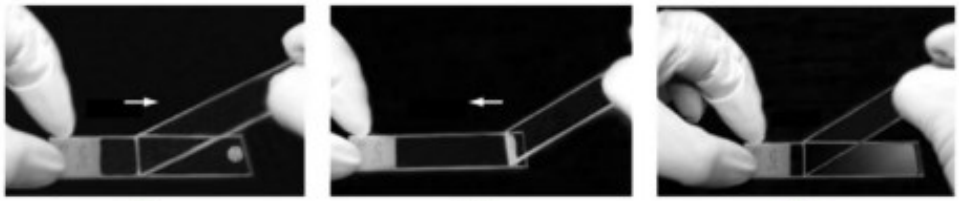

Image from WHO6 Manual

2. Concentration

If the insemination sample has been prepared at a concentration > 15 M/ml then it must be diluted down below this threshold using additional sperm preparation media.

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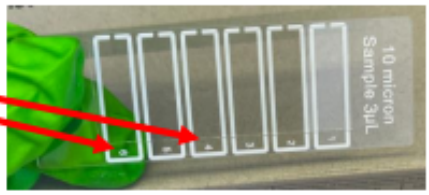
3. Imaging chambers

Place 3µl of the insemination sample in two chambers of the fixed-depth slide by pipetting onto the open numbered section.

Connect the sample with the slide opening by drawing the pipette tip so that they touch.

You **do not** need to 'push' the sample into the slide by pipetting directly under the coverslip.



4. Heated stage

Place the filled sample in the **pre-warmed** heated stage for imaging.

The heated stage should then be placed under the objective on the microscope.

5. FAST – Start Experiment

Now prepare FAST for imaging.

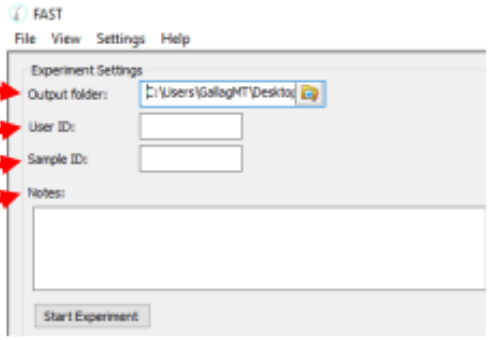
The Output folder should be prepopulated with your hard drive location.

Your initials go in the 'User ID' field.

The UNiTY couple ID goes in 'Sample ID'

In 'Notes' put which cycle this is for (IVF / IUI1 / IUI2 / IUI3)

When you have completed these fields, click 'Start Experiment' to record videos.



After clicking 'Start Experiment' you will see the video feed of the sperm, and you can focus the microscope. Make sure there is enough light that you can clearly make out the beating tails of the sperm.

If there is a background flow, wait 5 minutes to allow it to settle down. If after ~5 minutes there is still background flow, fill another chamber and image in that.

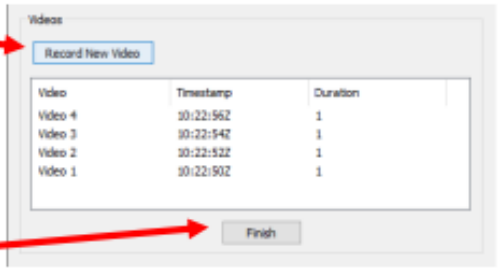
6. Capture videos

Click 'Record New Video' to capture a video of the swimming sperm.

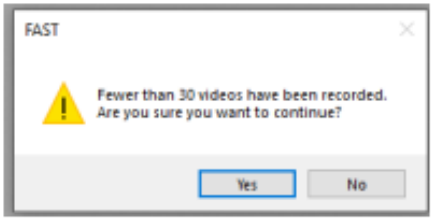
After each video, move the field so you are imaging new sperm.

Once you have taken 15 videos in a single chamber, move to the other chamber and take 15 more videos.

After you have taken 30 videos across two chambers, click 'Finish'.



If you click 'Finish' before you capture 30 videos you will get a warning. Click 'no' to go back and continue to take videos until you reach 30 fields.



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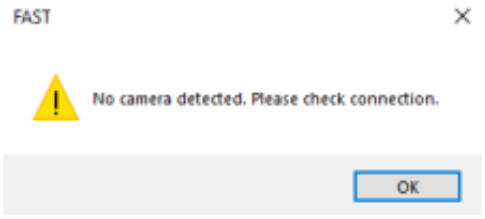
B. Launching FAST

1. Launch FAST

To launch FAST double click the FAST logo on the desktop.

C. Trouble Shooting

Occasionally you may come across an error. The below should help you troubleshoot.

"Background flow in the imaging chambers does not stop"	Occasionally a chamber doesn't fill properly, meaning that there is a background flow that doesn't go away. If you find this, first try filling a new chamber and imaging in that. If this is a repeated problem then try 'overfilling' by pipetting 4 µl instead of 3 µl onto the slide.
	Make sure you have filled in the Output Folder, User ID, Sample ID, and Notes boxes as in A.5. above.
	Unplug the USB cable connecting the camera and replug it back in, making sure that there is a green light showing on top of the camera. If this does not fix the problem, check the connection that the cable makes with the camera.

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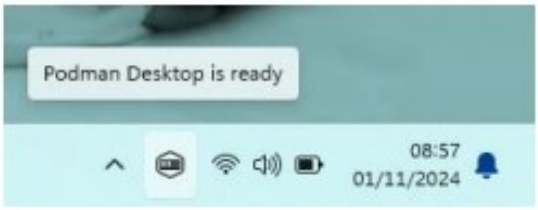
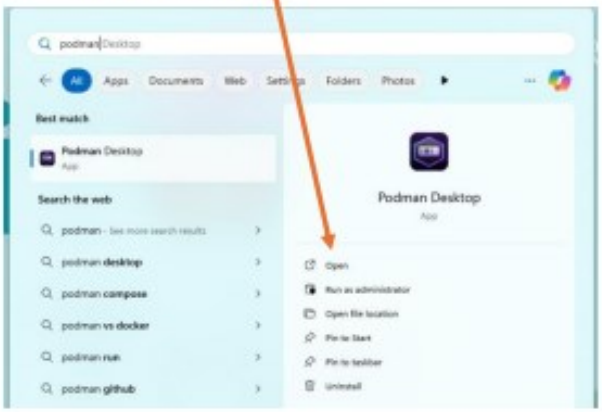
This indicates that a program called 'Podman desktop is not running correctly.

First check to see if this icon is in the taskbar:



If it is, right click and click quit.

Next, press the windows key and type podman desktop, click to open.



For any other problems please try turning the machine off and on again, following Section B.

For all other problems please get in touch with Dr Meurig Gallagher at m.t.gallagher@bham.ac.uk or by phone on 07474 403 387.

12. Frequently Asked Questions

Any issues with the database should be reported in the first instance to s.cole@bham.ac.uk and unity@trials.bham.ac.uk however please see some frequent queries and some troubleshooting resolutions below.

Please still email all database queries to the above email addresses.

- **Before logging in, please ensure you have checked that your delegation log, CV and GCP certificate have been sent to unity@trials.bham.ac.uk and s.cole@bham.ac.uk**

- **What do I do if I cannot log in?** - Please ensure you are using a modern browser (EDGE or Chrome) and check for typos in your username or password by refreshing the page and trying to log in again. If you have forgotten your password, please click 'forgot your password' button located by the 'log in' and complete the steps accordingly to change your password. If you can still not log in, please contact s.cole@bham.ac.uk.

- **What shall I do if I am assigned to the incorrect role?** - When logging into REDCAP at the top of the menu on the left hand side it will show you what role you are logged in as which should be **'site researcher'** role or **'PI'** for PIs. If you are logged in as any other role, please log out and contact s.cole@bham.ac.uk in the first instance with the role you are logged in as, **please do not complete any data on the database if you are in the incorrect role.**

- **The form will not allow me to save, why?** - Normally when this happens it is because the database has timed out on the browser, please ensure if you are completing CRFs you are not on the same page for more than 5 minutes without inputting any data.

- **I can't see the randomisation bubble**—There are 2 reasons this could be:

◊ You may not have permission to randomize—this may be because you have not been delegated this task on the delegation log—please supply an updated log to the Trials Office and we can update your permissions.

◊ Essential information has not been completed. The randomisation form will only generate once both couples have a fully signed and valid consent form (signed by the participants, the researcher, and interpreter if necessary), the contact details form has been completed, the EQ-5D has been completed by both partners and the minimization variables on the Baseline form have been completed.

- **The Record Status Dashboard is only showing some of our records**—you can set this to your preference. If the dashboard is only showing the first 20 participants, there is a box above the dashboard with a few drop-down options. The bottom right drop-down under '___ records per page' where you can select from 10 to 1000 records, or all of them if that is your preference.

- **I can't see Laboratory form, Frozen transfer form or Clinical pregnancy form**—check that the relevant IVF or IUI treatment form has been completed, this will generate the Laboratory form. If a frozen embryo is input onto the lab form, the Frozen transfer form will generate. If a positive pregnancy test is recorded on the post treatment form, this will generate the clinical pregnancy outcome form.

12. FAQ continued

- **The couple or researcher hasn't received the text or email**— check the correct spelling of their email or phone number on the screening form. You can also resend emails via instructions in sections 4.11 and 4.12.
- **The couple has had 3 IUI cycles and then go on to have IVF, where do I record the first cycle of IVF?** - on an IVF Treatment form (not a non-trial treatment form as the first IVF cycle is always recorded on the IVF form).
- **The couple has conceived naturally, where should this be recorded?**—enter the data on a Natural Pregnancy Notification form.
- **The couple has changed their mind and wants to have a different fertility treatment**—Couples that decide 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, it is a protocol deviation and the team would expect you to complete a deviation form. Carry on completing the CRFs as normal (as long as the couple has not expressed a wish to withdraw from data collection).
- **Link to REDCAP FAQS—**On the left hand menu, near the bottom there is a function called 'Help & FAQ' which will bring up a bunch of frequently asked questions that only relates to REDCAP, and the trial team would encourage you to read through this.
- **Tubal patency**—The new ESHRE unexplained subfertility guideline states that Chlamydia antibody testing for tubal patency can be considered a non-invasive test to differentiate between patients at low and at high risk for tubal occlusion. But anyone with risk factors also needs formal tubal patency testing. The decision to recruit couples without definitive testing for tubal patency must be recorded in the medical notes and on the trial case report forms. If teams wish to test all couples this also fits with being a pragmatic trial and is fully supported as a decision by the team.