SepTiC

Sepsis Trials in Critical Care

Randomisation User Training

v1.0 01-NOV-2023

Sponsor: Imperial College London

Funder: NIHR

IRAS ID: 1005848

REC ref: 23/LO/0339

Chief Investigator: Prof Anthony Gordon

Study Coordination Centre:

Imperial Clinical Trials Unit

IRAS ID: 1005848

REC ref: 23/LO/0339

Imperial College London

FUNDED BY NIHR | National Institute for Health Research

Coordinating Centre / Trial Management Team

- Trial coordinated by Imperial Clinical Trials Unit
- Chief Investigator: Prof Anthony Gordon
- Trial Manager: Janis Best-Lane
- Trial Monitor(s): Ravinder Dhaliwal and Paulina Kuswik

  - Email: septic@imperial.ac.uk
  - Address: Room 503, 5th Floor, Medical School Building,
    Imperial College London, St Mary's Campus, Norfolk Place,
    London, W2 1PG

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Introduction to SepTiC

+ A multi-centre, pragmatic, multi-factorial, open-label randomised controlled trial, with an embedded randomised, double-blind, parallel group trial.

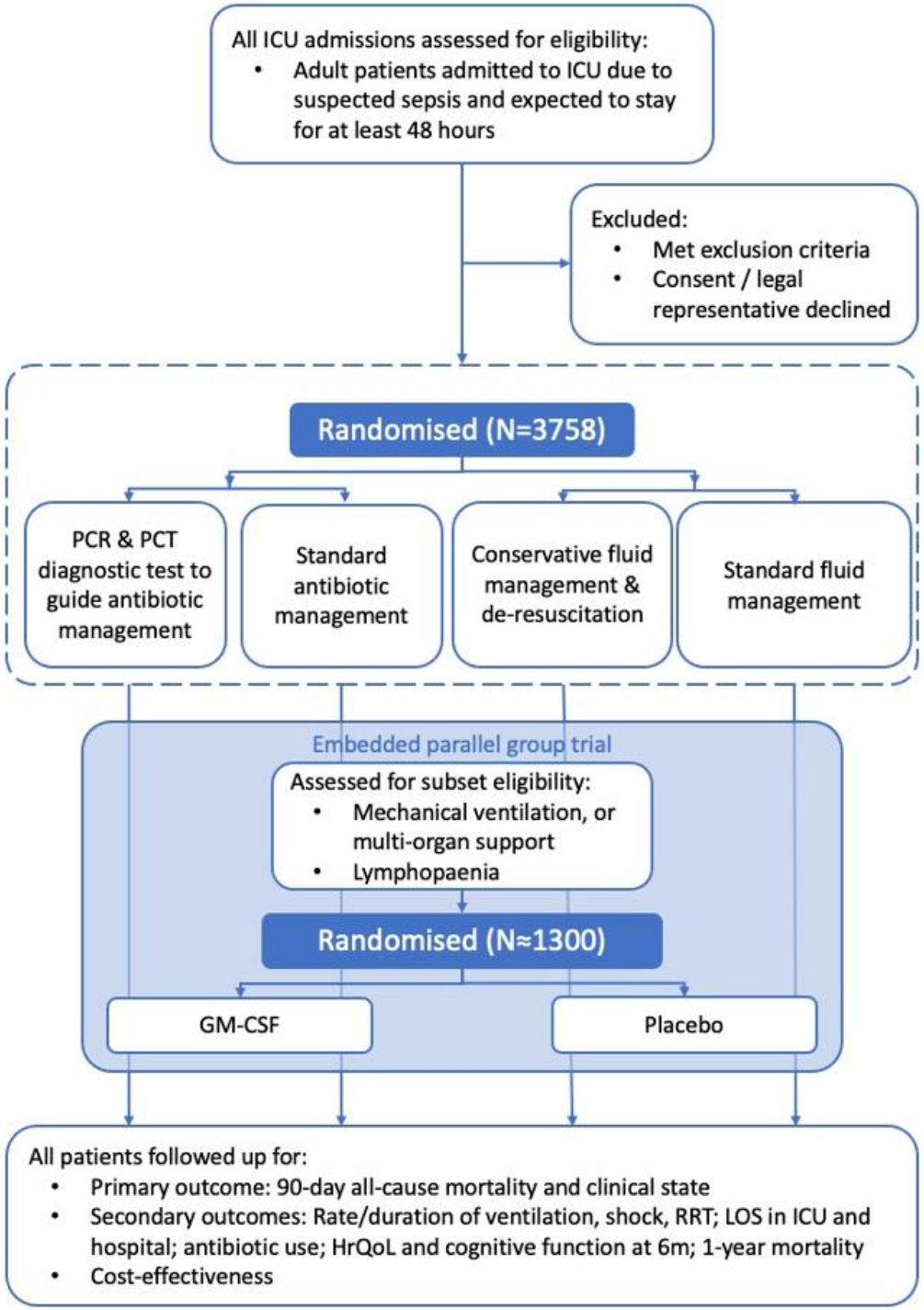
Research questions

1. Do rapid PCR-based microbiological diagnostics plus procalcitonin improve outcomes and antibiotic stewardship compared to standard care in patients admitted to ICU with sepsis?
2. Does conservative fluid therapy with active removal of accumulated fluid (de-resuscitation) improve outcomes compared to standard care in patients …with sepsis?
3. Does GM-CSF compared to placebo improve outcomes in a high-risk subset of patients …with sepsis?
4. What is the relative cost-effectiveness of each of these interventions compared to current standard of care?

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Study Flowchart



Imperial College London

SepTiC
Sepsis Trials in Critical Care

Inclusion Criteria

+ Adult patients (≥16 yrs) admitted to ICU due to suspected sepsis and expected to stay for at least two calendar days (i.e. expected to still to be in ICU the day after tomorrow)

+ Receiving intravenous antibiotics for suspected sepsis

+ According to local clinical judgement, patient has received adequate initial early fluid resuscitation

Exclusion Criteria

+ More than 24 hours since ICU admission *(not for GM-CSF)*
+ Previously admitted to ICU due to sepsis on this hospital admission
+ Not expected to survive 90 days, due to pre-existing chronic disease
+ Not expected to survive initial resuscitation (24 hours)
+ Neutropaenia due to chemotherapy / malignancy (but not due to sepsis)
+ A source of infection that will require a prolonged course of antibiotics, for >21 days (e.g. infective endocarditis, osteomyelitis, hepatic or cerebral abscess, tuberculosis)
+ DKA / HHS / DI / SAH (in last 21 days)
+ Weight <40Kg

GM-CSF Trial - Inclusion criteria

+ Intubated, mechanically ventilated & expected to continue for another 24 hours

Or

+ Two organ support (Vasopressors, RRT)

AND

+ An absolute lymphocyte count <1.2 x10^9 /L on two consecutive calendar days

(at least 12 hrs apart with no values >1.2 x10^9 /L in between)

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Additional Exclusion criteria – GM-CSF

+ More than 120 hours (5 days) since ICU admission
+ Already receiving G-CSF or GM-CSF
+ A total white blood cell count (WBC) >50 $x10^9$ /L
+ Allergy or adverse reaction to GM-CSF or yeast-product
+ Known to be pregnant or lactating
+ Known active haematological malignancy *(treated within last 5 years)*
+ Solid organ or bone marrow transplantation
+ Patient weight >125kg

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Good Clinical Practice (GCP)

+ International, ethical and scientific quality standard to which all research involving human participants is conducted
+ Comprised of 13 core principles & applies to all clinical investigations that could affect safety and well-being of human participants, providing international assurance that:
  - Data and reported results of clinical investigations are credible and accurate
  - Rights, safety and confidentiality of participants in clinical research are respected and protected
- You are encouraged to obtain GCP certification, such as that available through NIHR: https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm

Principles of Good Clinical Practice (GCP)

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approval/favourable opinion.

Principles of Good Clinical Practice (GCP)

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice(GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Randomisation

- Randomisation should be performed soon after confirming eligibility and prior to anticipated start of randomised treatment
- Randomisation performed using a web-based system in OpenClinica
- Record each randomisation on screening/randomisation log and print randomisation form from the OpenClinica system
- Ensure the participant's trial ID is recorded in their medical records

Randomisation Users – Access to OpenClinica

- OpenClinica is a browser-based electronic data capture system (EDC) accessed via the link https://imperial.openclinica.io/OpenClinica with email address and password to log-in
- **Please sign the combined training log / access request form** to complete your training and request a user account
  - ❖Completing this training and signing training log means randomisation only users do not then need to be on Delegation Log, complete full GCP training, complete full OpenClinica training, or provide CV for SepTiC
- Site trial team will submit the log to Trial Management at septic@imperial.ac.uk for us to set-up your OpenClinica randomisation account
- You will receive confirmation of your user account and log-in details by email

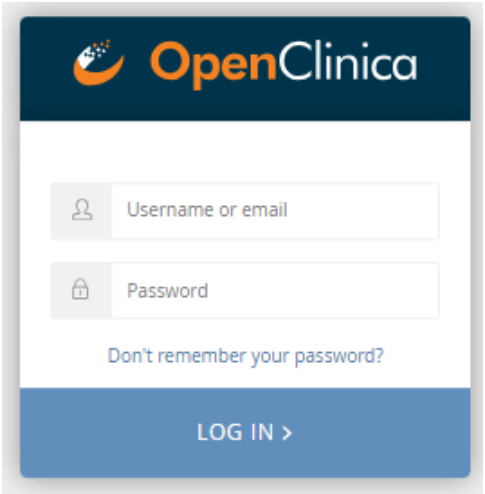
Imperial College London

SepTiC
Sepsis Trials in Critical Care

Logging in to OpenClinica for the first time

- Every time you login to the OpenClinica database, you will need to use the **Google Authenticator** app on your mobile device
- This is also known as multi factor authentication (MFA) which is another way of confirming your identity when you login
- To use the **Google Authenticator** app, you will first need to download it onto your mobile device
- Download **Google Authenticator** from the App Store (for iOS) or Google Play Store (Android)
- Go to the **OpenClinica** database and

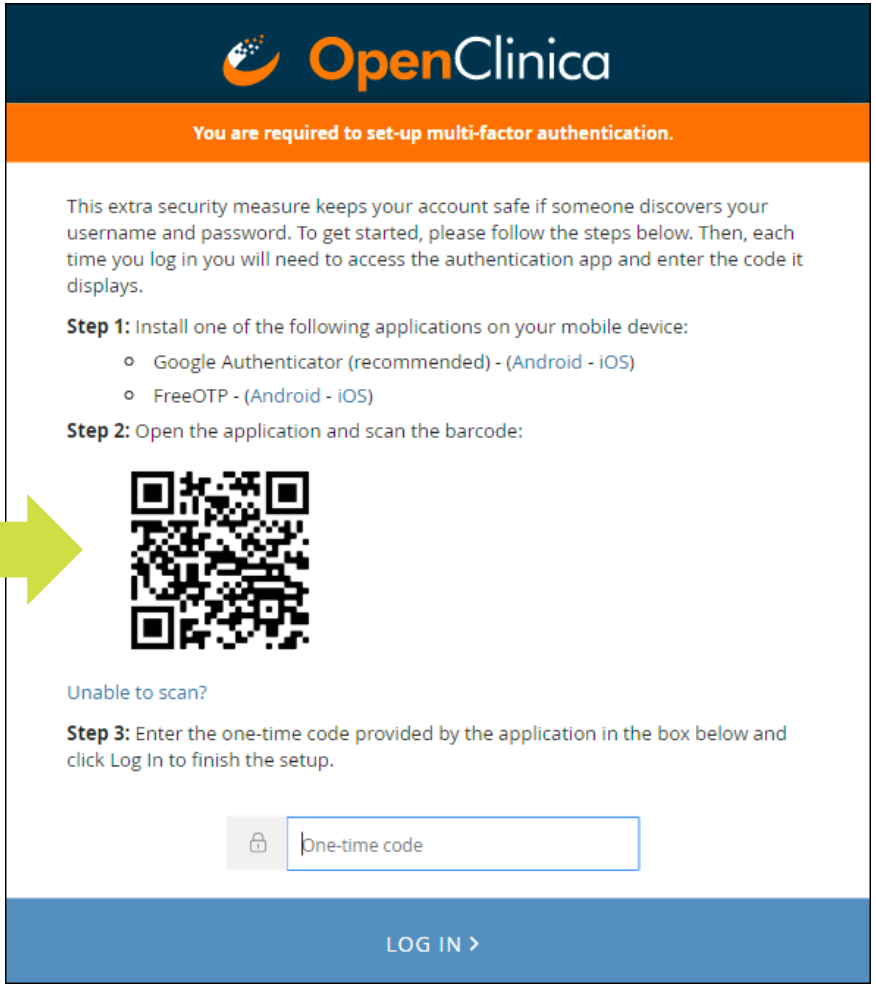
login to your account with your username and password



Imperial College London

SepTiC
Sepsis Trials in Critical Care

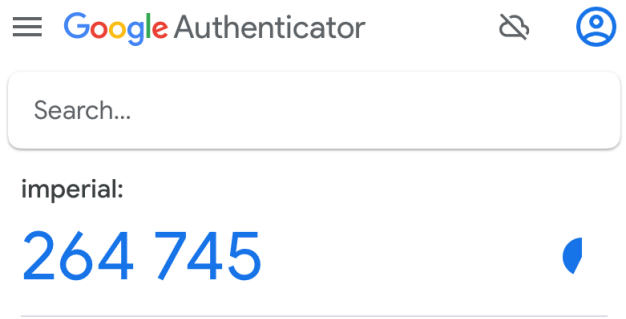
Open **Google Authenticator** on your mobile device and scan the QR code

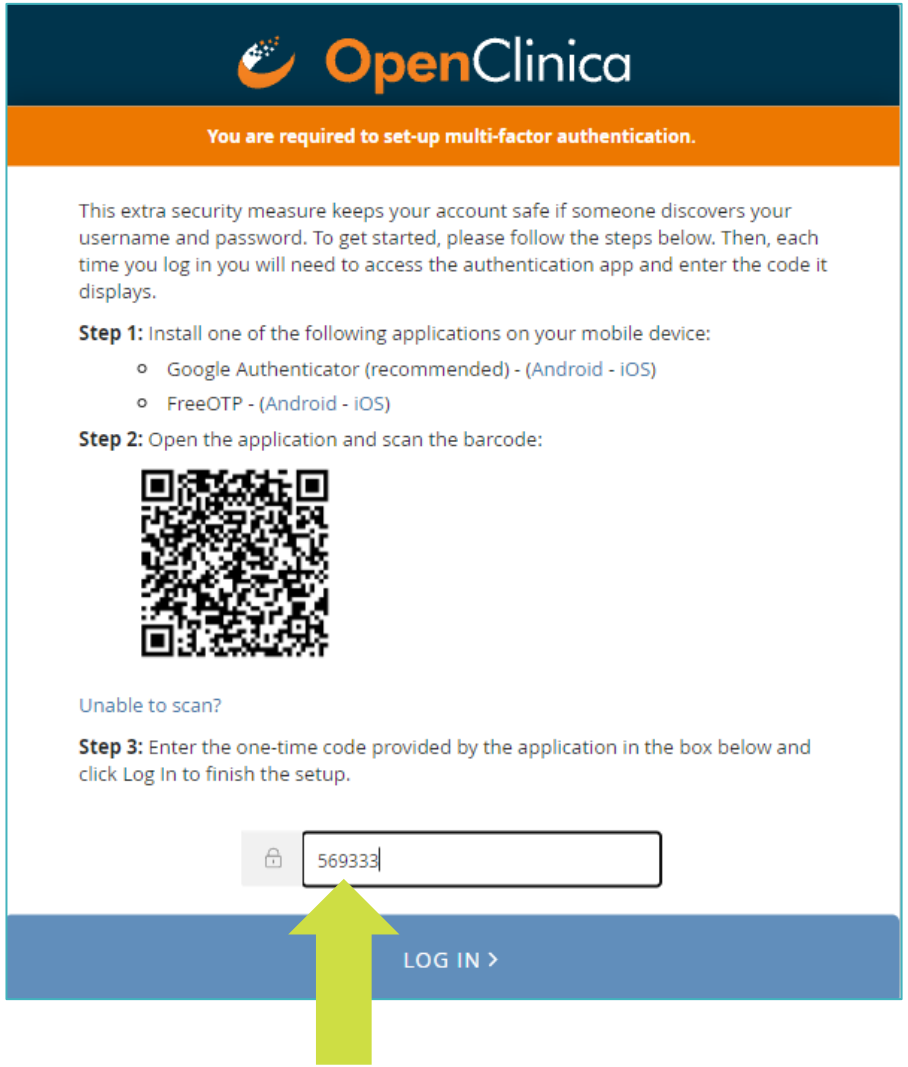


Imperial College London

SepTiC
Sepsis Trials in Critical Care

You will then receive a 6-digit code on your mobile device after scanning the QR code





Enter the 6-digit code here and click 'LOG IN'

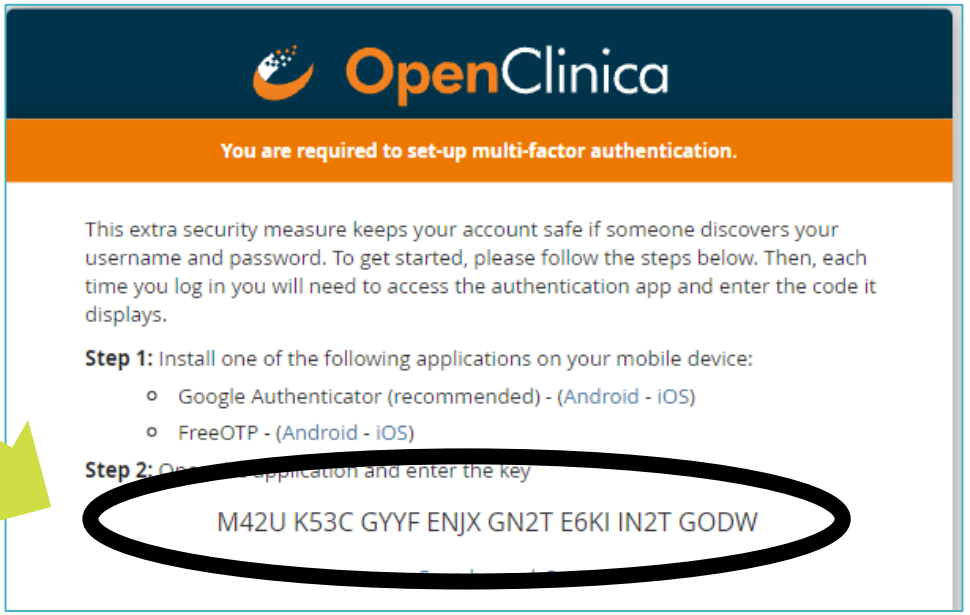
Imperial College London

SepTiC
Sepsis Trials in Critical Care

If you are unable to scan a QR code

+ Click on **"Unable to scan"** link on OpenClinica webpage after entering your username and password.

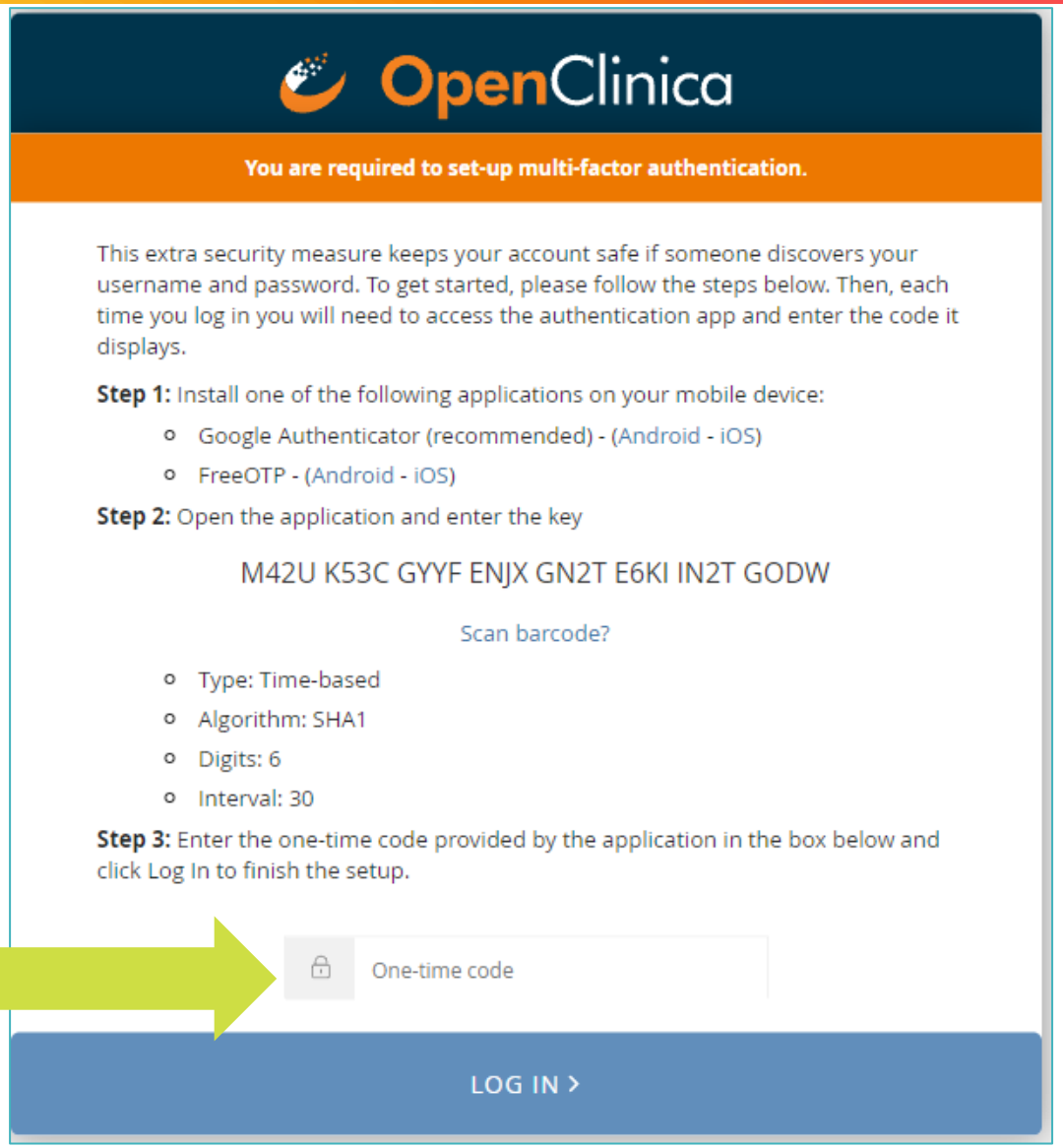
This will provide 32-key code



+ Go on to google authenticator on your mobile device and select "**Enter a setup key**" and enter the 32-key code from the previous step
+ This will generate a 6-digit code

Imperial College London

SepTiC
Sepsis Trials in Critical Care



Enter the 6 digit code here

And click here to log in

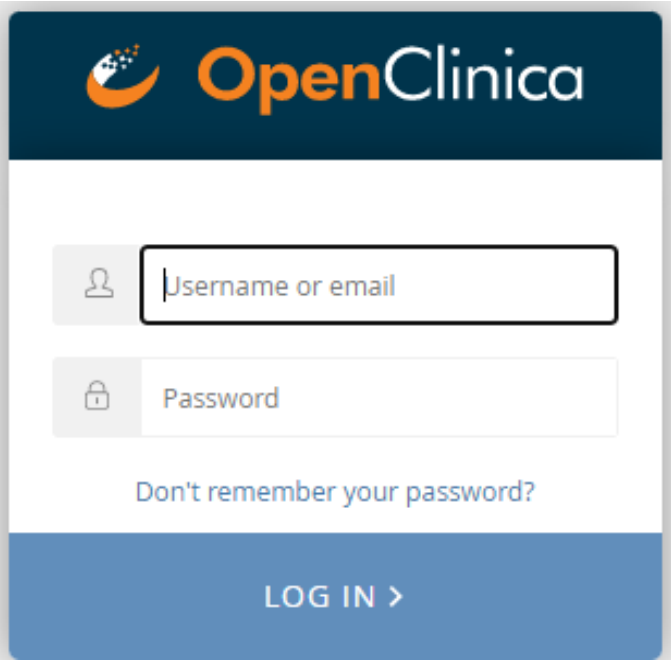
Imperial College London

SepTiC
Sepsis Trials in Critical Care

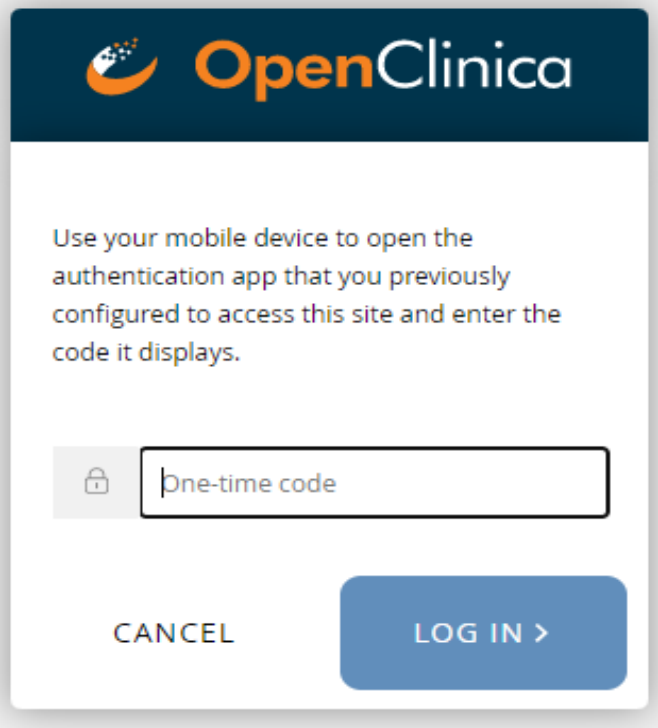
You should now be set-up for MFA

- Once this is setup and you have the account saved on Google Authenticator, you do not need to scan the QR code again
- Each time you login to OpenClinica, you will only need to use your username and password and then the 6 digit code from **Google Authenticator**

Now when you login to OpenClinica



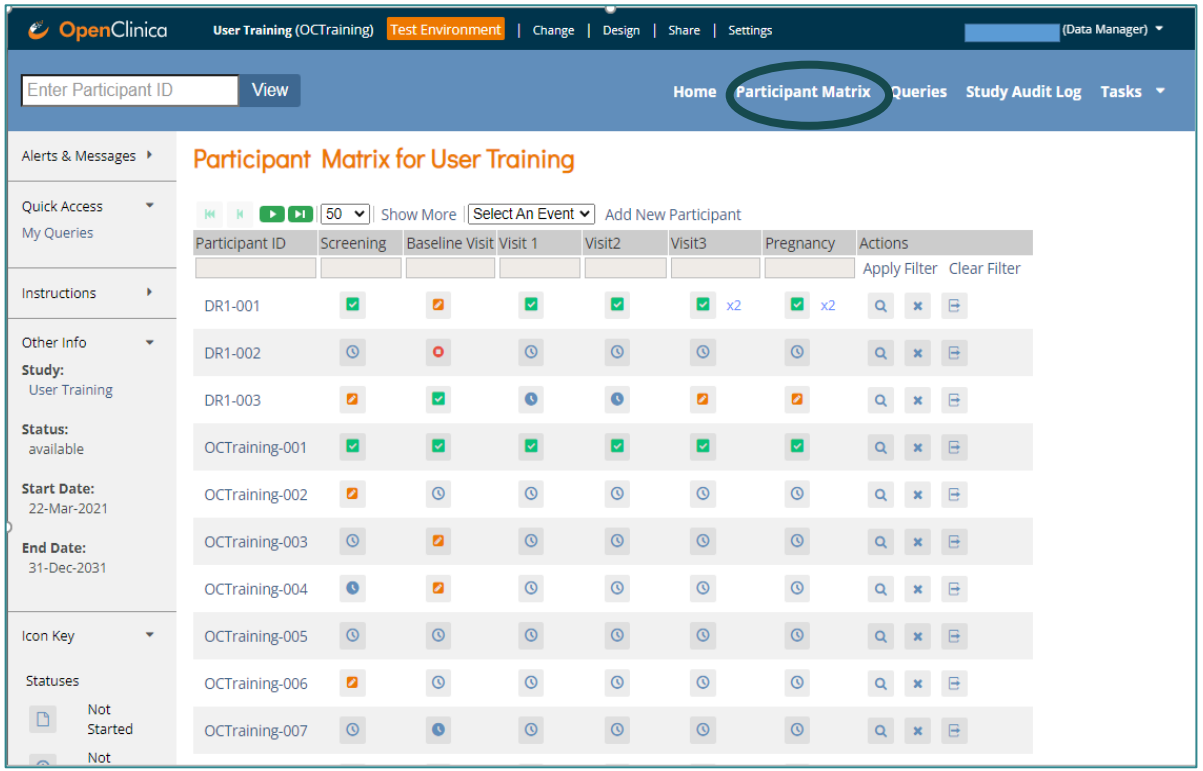
It should ask you to enter your 6-digit code from Google Authenticator



Imperial College London

SepTiC
Sepsis Trials in Critical Care

Once you have successfully logged in, navigate to the participant matrix

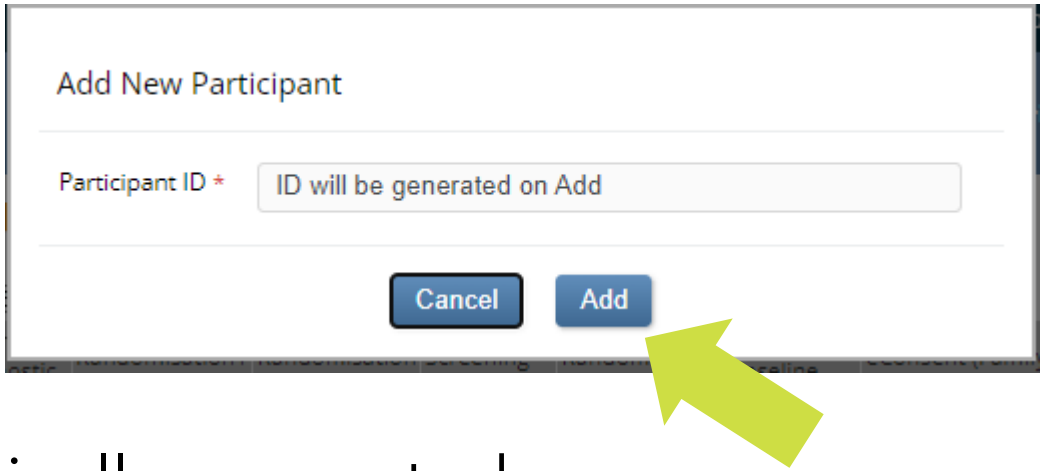


Imperial College London

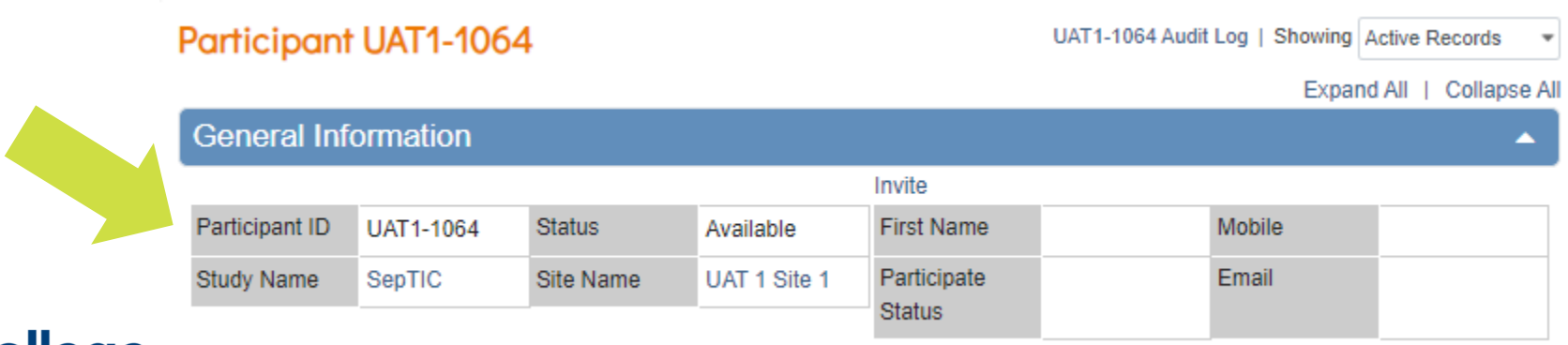
SepTiC
Sepsis Trials in Critical Care

Adding a new participant

+ Navigate to the participant matrix
+ Click 'Add New Participant'



+ The participant ID will be automatically generated

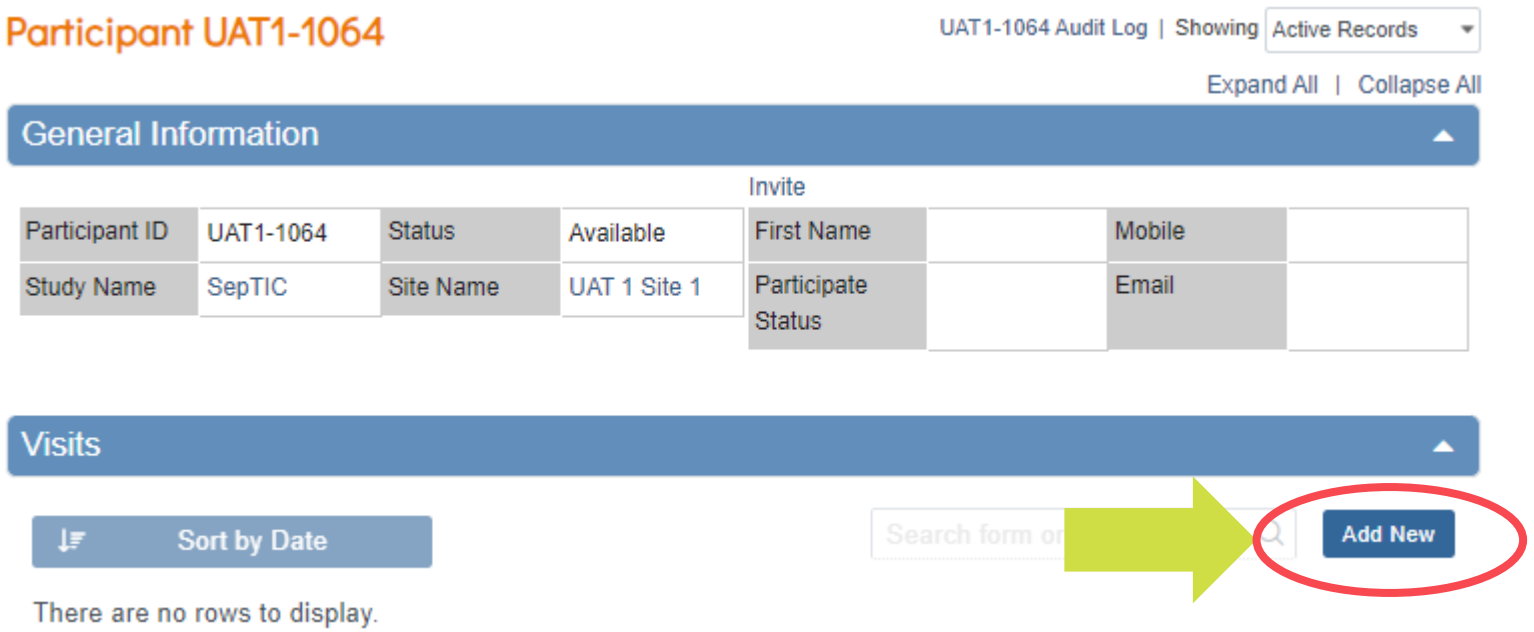


Imperial College London

SepTiC
Sepsis Trials in Critical Care

Adding a visit

- The forms on the database are organised into ‘visits’ which reflect the different timepoints of the study
- To add a visit click ‘Add New’

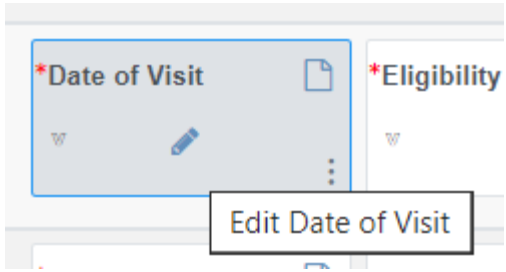


Imperial College London

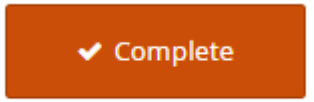
SepTiC
Sepsis Trials in Critical Care

Completing a form

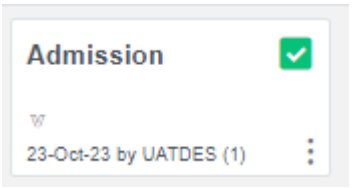
+ After adding a visit, you will need to click on the pencil icon to edit a form



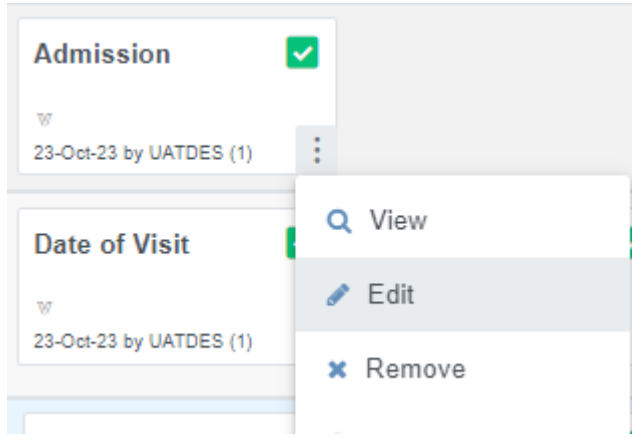
+ Clicking on the edit icon will open the form
+ Data entry is automatically saved, so even if you close a form the data will save
+ Once you have completed data entry on a form, click the orange 'Complete' button



+ Forms that are complete will have a green tick



+ If you need to edit data on a form that is complete, click the three dots, and then click 'Edit'



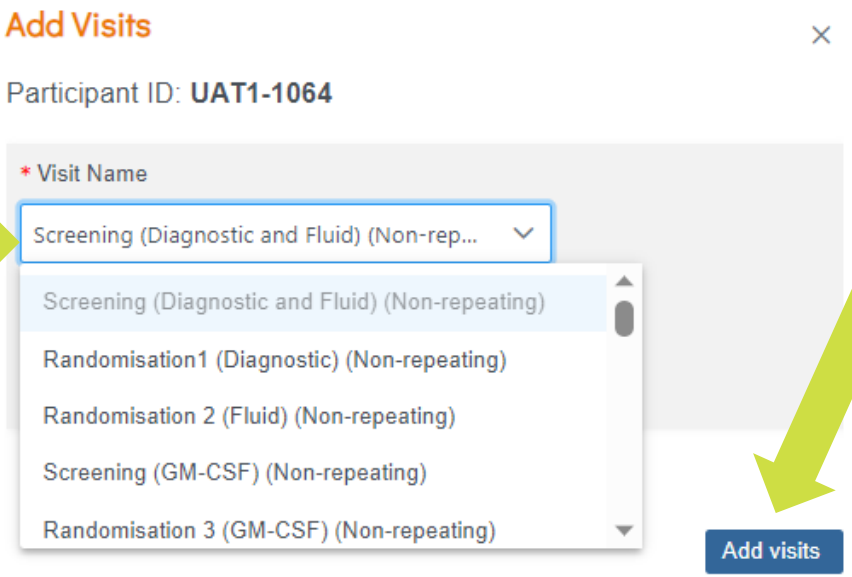
Imperial College London

SepTiC
Sepsis Trials in Critical Care

Randomising patients onto Trials 1 and 2: Diagnostic and Fluid

- The screening visit **must be** completed prior to randomisation
- This is to confirm eligibility of the patient
- The system will not allow you to randomise before completing screening
- The admission event will also need to be added to enter the patient's hospital and ICU admission details
- A drop-down list should appear with all the visits
- Select 'Screening (Diagnostic and Fluid)'

Select the correct visit



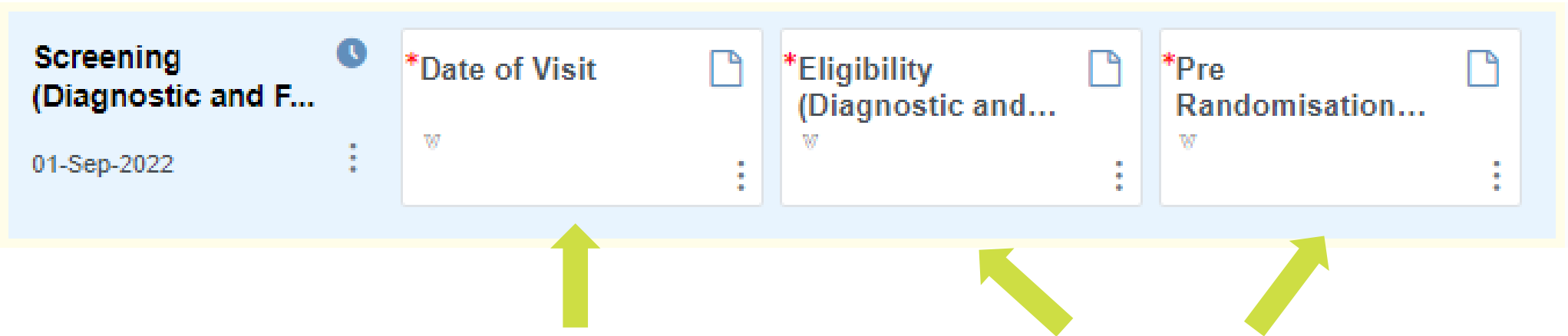
And then click 'Add visits'

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Completing the screening visit

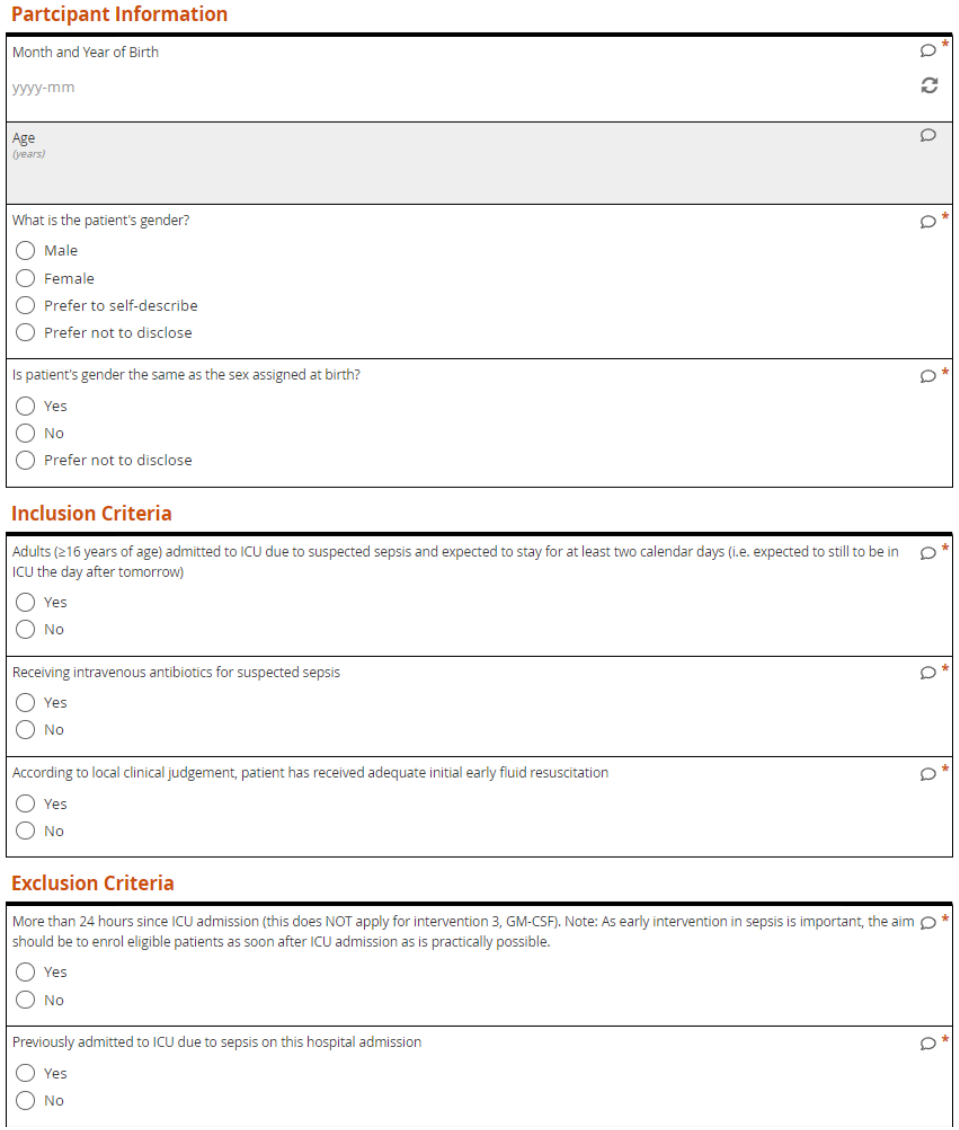
+ Once you have added the screening visit, there should be 3 forms to complete



Imperial College London

SepTiC
Sepsis Trials in Critical Care

Complete the Eligibility form



Partcipant Information

Month and Year of Birth *

yyyy-mm

Age
(years)

What is the patient's gender? *

- Male
- Female
- Prefer to self-describe
- Prefer not to disclose

Is patient's gender the same as the sex assigned at birth? *

- Yes
- No
- Prefer not to disclose

Inclusion Criteria

Adults (≥16 years of age) admitted to ICU due to suspected sepsis and expected to stay for at least two calendar days (i.e. expected to still to be in ICU the day after tomorrow) *

- Yes
- No

Receiving intravenous antibiotics for suspected sepsis *

- Yes
- No

According to local clinical judgement, patient has received adequate initial early fluid resuscitation *

- Yes
- No

Exclusion Criteria

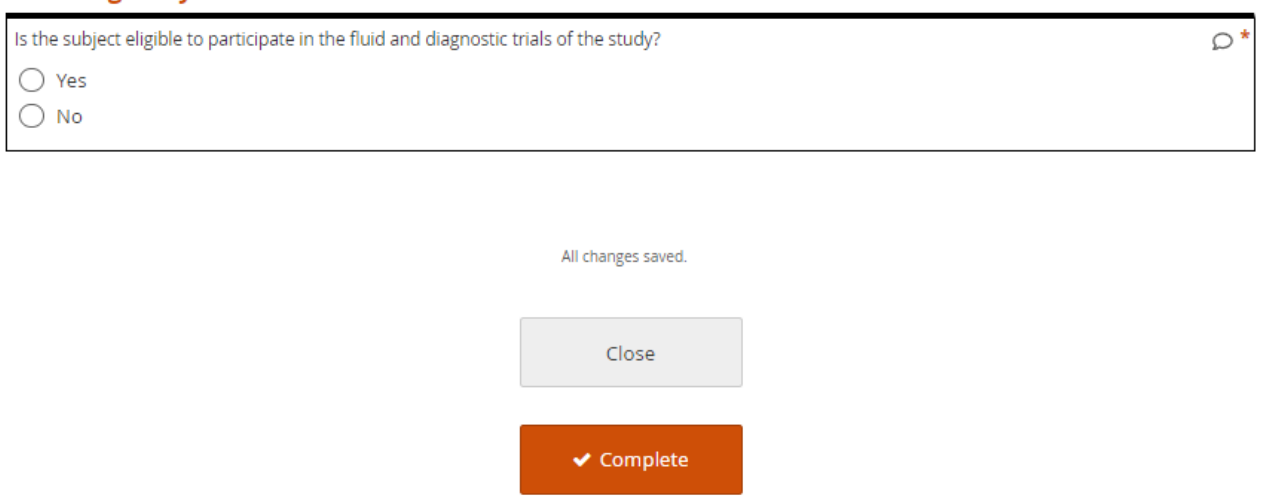
More than 24 hours since ICU admission (this does NOT apply for intervention 3, GM-CSF). Note: As early intervention in sepsis is important, the aim should be to enrol eligible patients as soon after ICU admission as is practically possible. *

- Yes
- No

Previously admitted to ICU due to sepsis on this hospital admission *

- Yes
- No

Confirm the participant is eligible for the study by selecting 'Yes' and click 'Complete'



Final Eligibility Check

Is the subject eligible to participate in the fluid and diagnostic trials of the study? *

- Yes
- No

All changes saved.

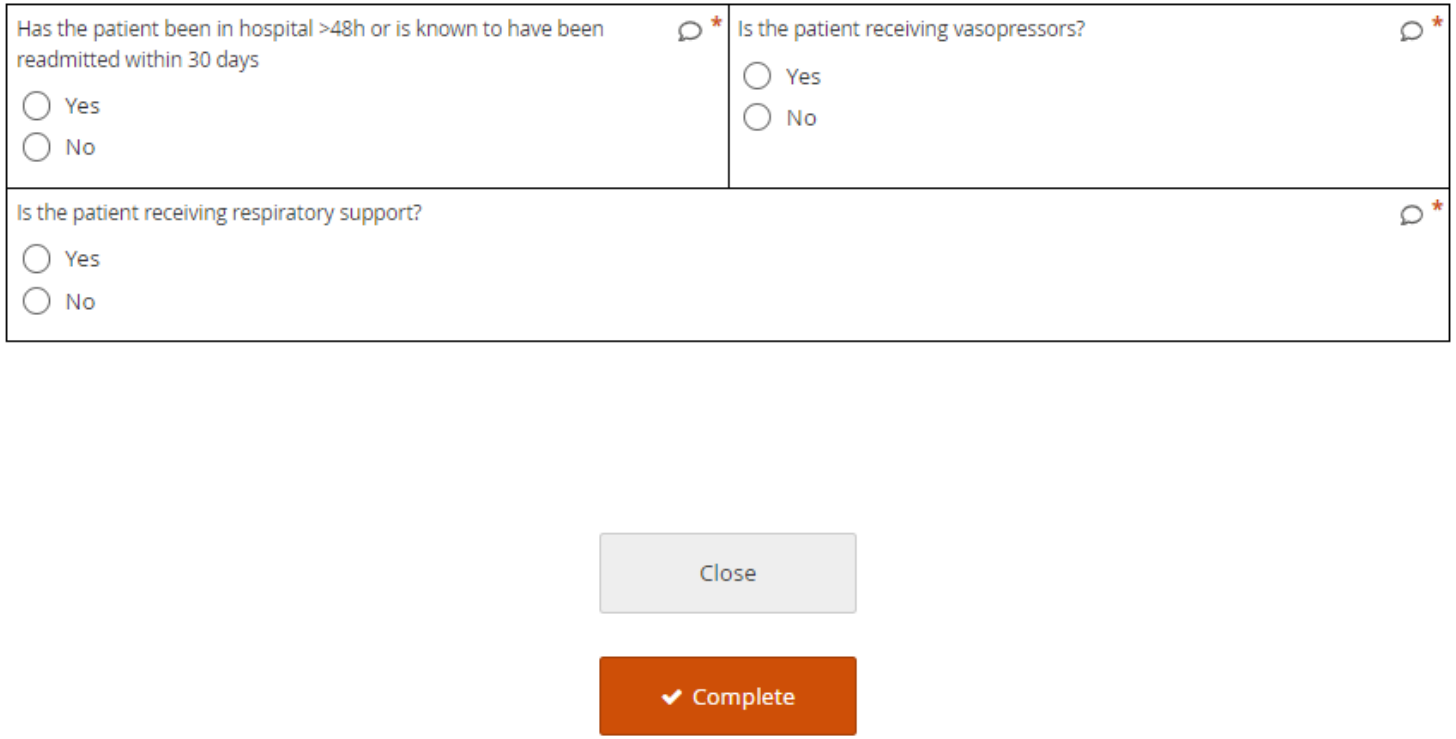
Close

✔ Complete

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Complete the Pre-randomisation Data form

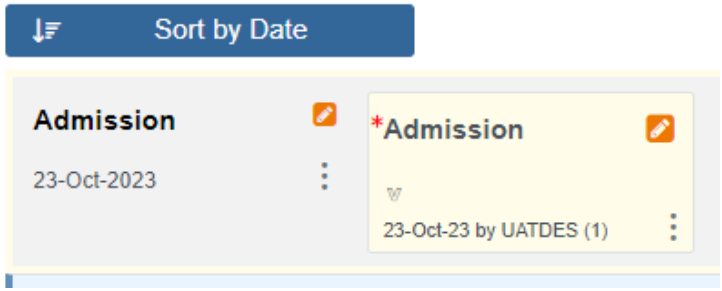


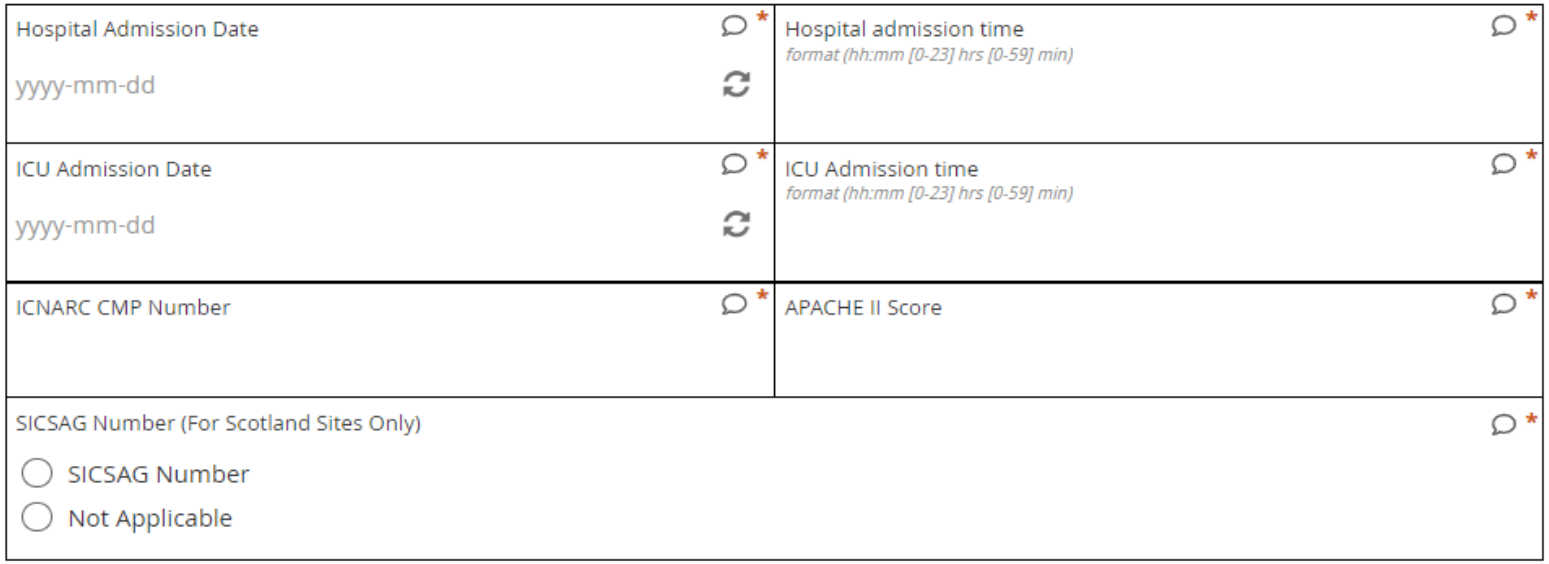
Imperial College London

SepTiC
Sepsis Trials in Critical Care

Completing the admission visit

- There is only one form to complete for the admission visit
- Add the admission visit from the drop-down menu
- Complete the form and mark as complete

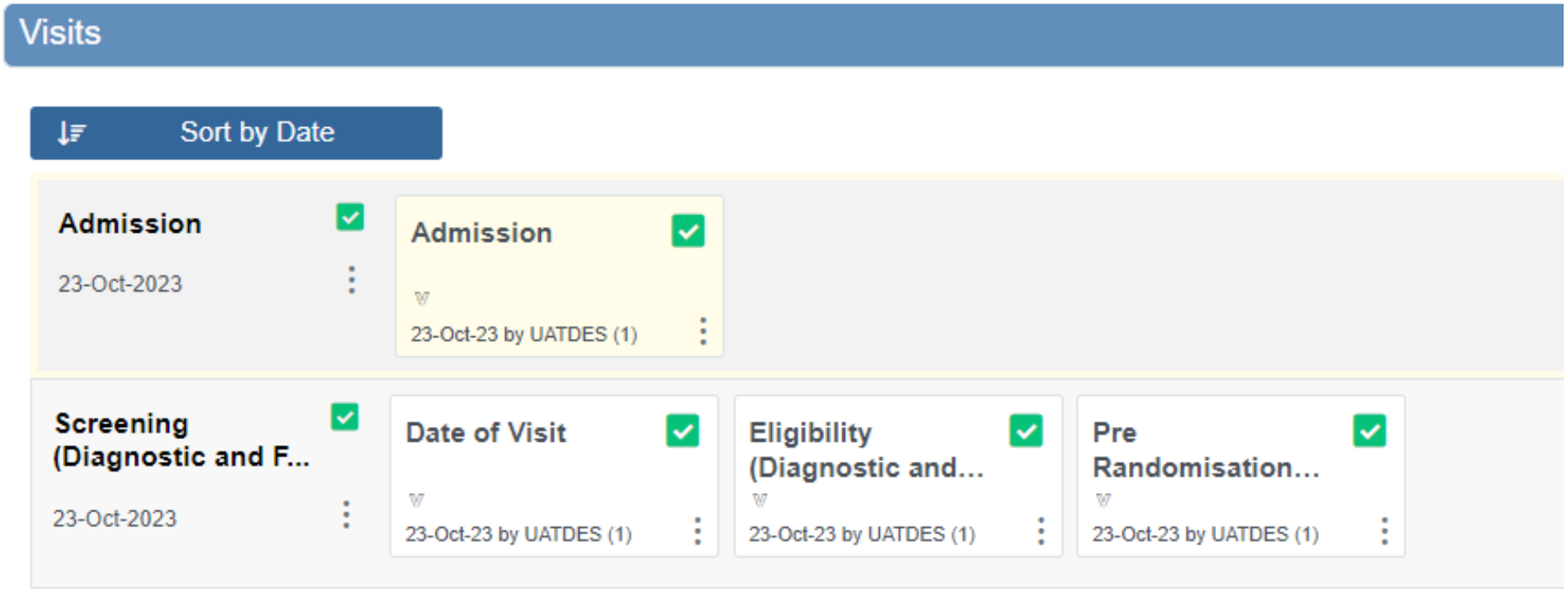




Imperial College London

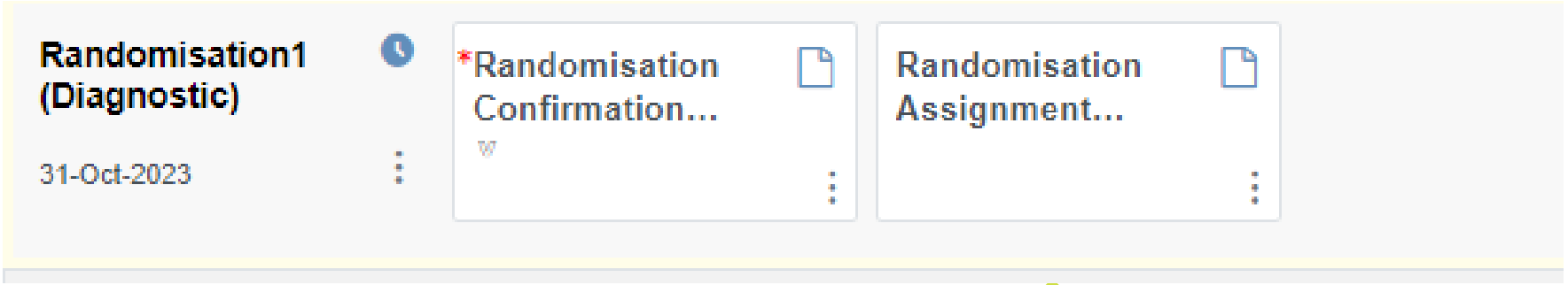
SepTiC
Sepsis Trials in Critical Care

+ You are now ready to randomise the patient once the screening and admission visits are complete



Add the randomisation visit for Trial 1: Diagnostic

+ To randomise patients onto Trial 1: Diagnostic, you will need to add the randomisation visit and complete the forms in the order below



Complete the randomisation confirmation

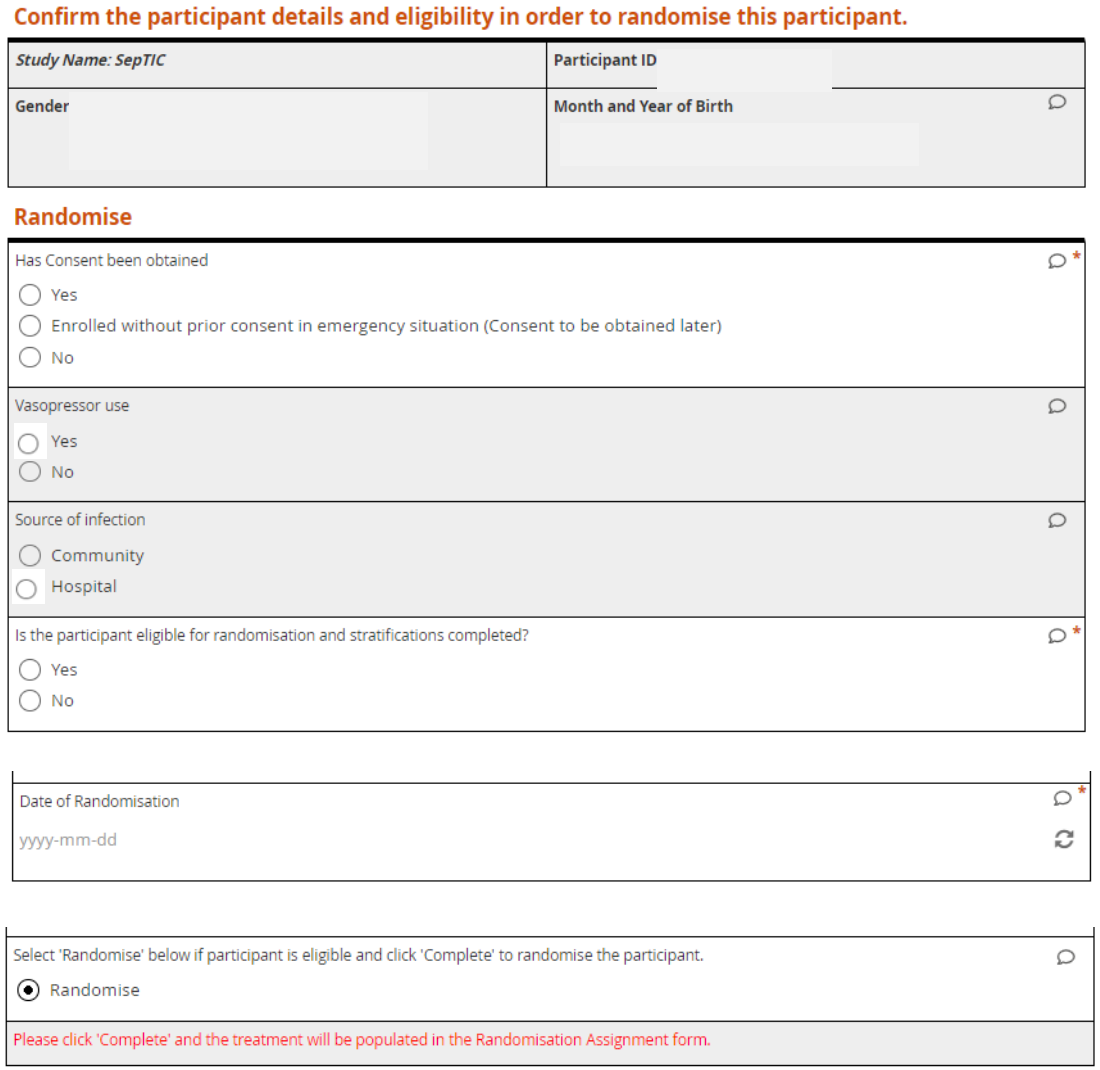
The assignment will be on this form

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Complete the diagnostic randomisation confirmation to confirmation eligibility

These questions will be automatically completed with answers from the screening visit



These questions will appear once the previous question is answered

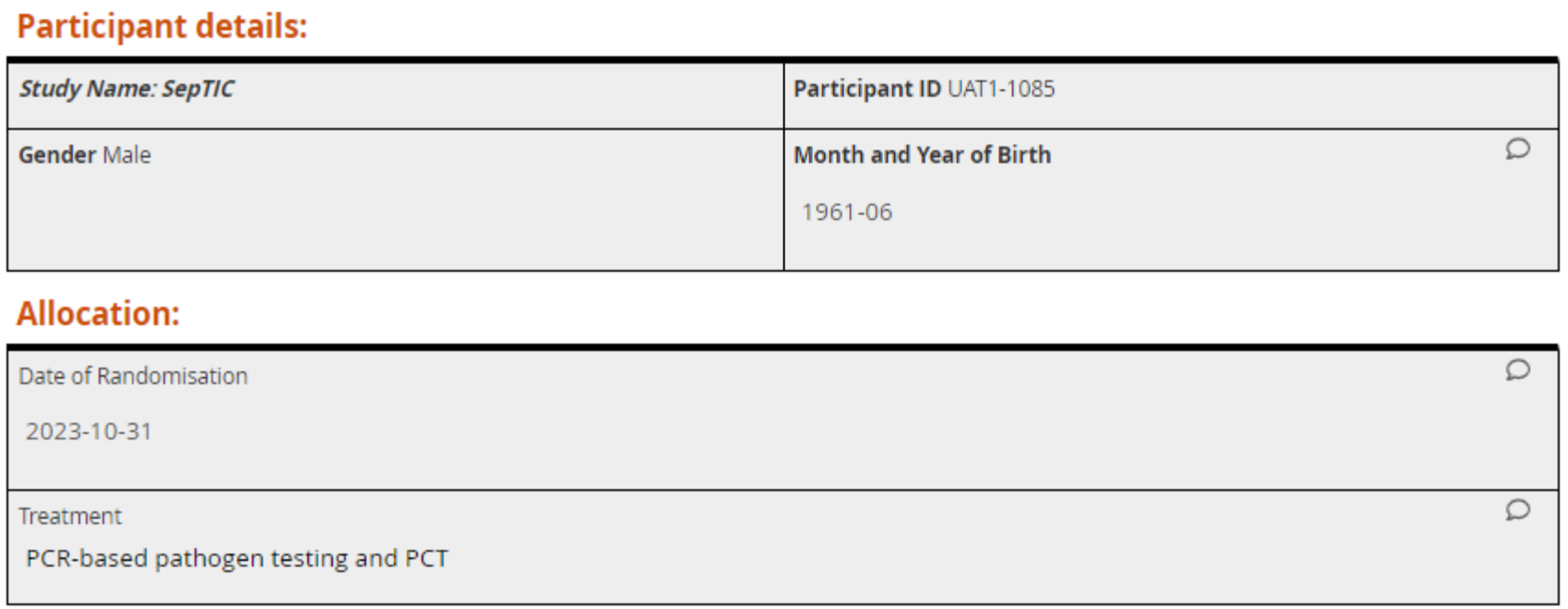
Imperial College London

SepTiC
Sepsis Trials in Critical Care

View the randomisation assignment form to see the diagnostic treatment allocation

- This form is **read-only**, no data will be entered on the form
- The participants details will appear from the eligibility form
- The allocation will be under 'Treatment'

Example:



Participant details:

Study Name: SepTIC	**Participant ID** UAT1-1085
Gender Male	**Month and Year of Birth** 1961-06

Allocation:

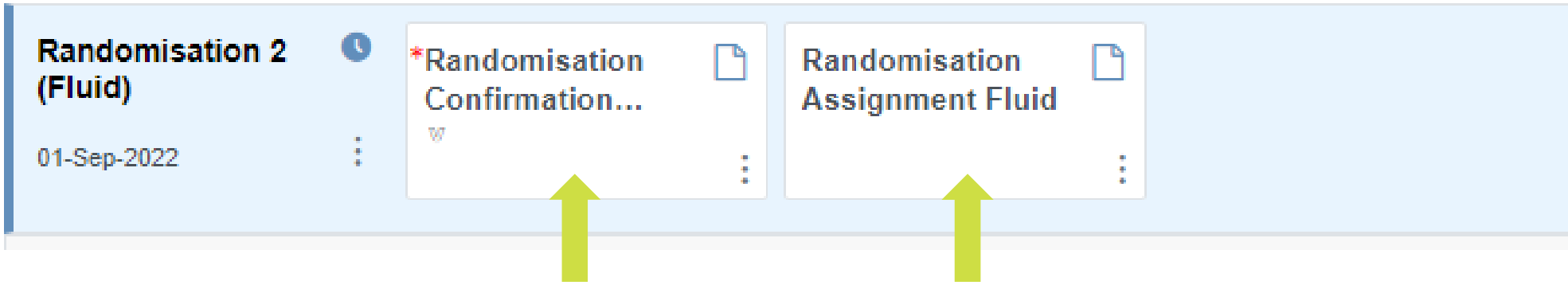
Date of Randomisation 2023-10-31
Treatment PCR-based pathogen testing and PCT

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Repeat for Trial 2: Fluid

+ To randomise patients onto the Fluid Trial, there should be 2 forms to complete

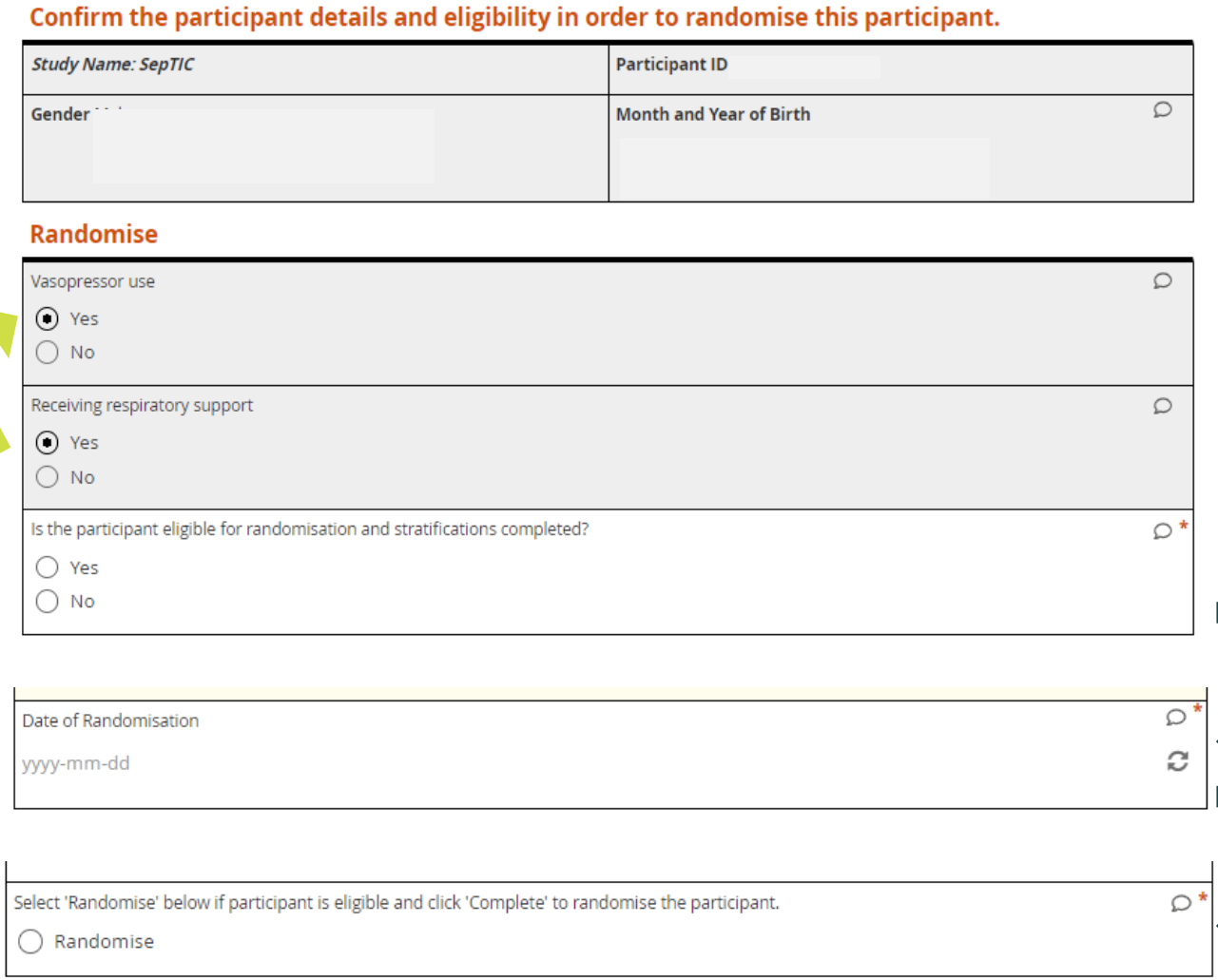


Imperial College London

SepTiC
Sepsis Trials in Critical Care

Complete the Fluid Randomisation Confirmation Form

These questions will be automatically completed with answers from the screening visit



These questions will appear once the previous question is answered

Imperial College London

SepTiC
Sepsis Trials in Critical Care

View the randomisation assignment form to see the fluid treatment allocation

- This form is **read-only**, no data will be entered on the form
- The participants details will appear from the eligibility form
- The allocation will be under 'Treatment'

Example:

Participant details:

Study Name: SepTIC	**Participant ID** UAT1-1085
Gender Male	**Month and Year of Birth** 1961-06

Allocation:

Date of Randomisation 2023-10-31
Treatment Conservative fluid therapy with de-resuscitation

Imperial College London

SepTiC Sepsis Trials in Critical Care

Randomising patients onto Trial 3 GM-CSF

+ Ensure the patient meets the additional inclusion criteria and none of the additional exclusion criteria for GM-CSF
+ To randomise patients to the GM-CSF trial, the following events/forms must be complete:

Screening (Diagnostic and Fluid)

this visit must be completed regardless of whether the patient was randomised to the Diagnostic and Fluid trials

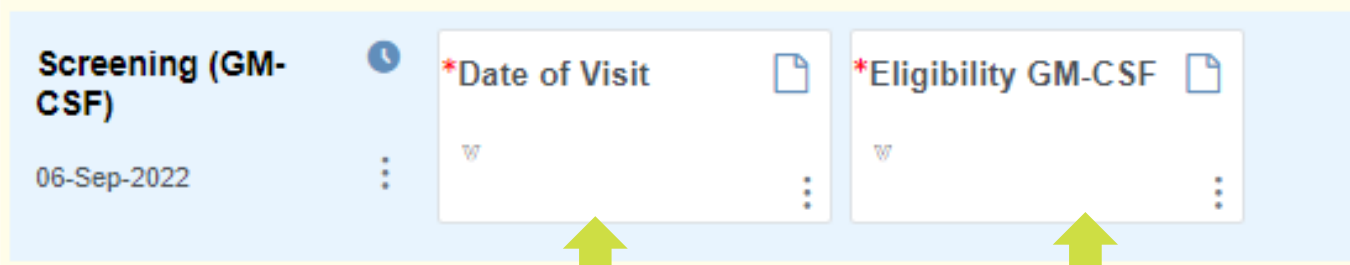
Admission

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Complete screening visit for Trial 3: GM-CSF

- The screening visit must be completed **before** randomising
- Add the 'Screening (GM-CSF)' visit and complete the forms in the order shown below



This should be todays date (date of randomisation)

Then complete eligibility form

Imperial College London

SepTiC
Sepsis Trials in Critical Care

Inclusion Criteria GM-CSF

Intubated and mechanically ventilated and expected to continue for another 24 hours or requiring two organ support (i.e. vasopressors or renal replacement therapy) *

- ◯ Yes
- ◯ No

An absolute lymphocyte count < 1.2 x10^9/L on two consecutive calendar days at least 12 hours apart, with no values >1.2 x10^9/L in between. *

- ◯ Yes
- ◯ No

Exclusion Criteria for GM-CSF

More than 120 hours (5 days) since ICU admission *

- ◯ Yes
- ◯ No

Already receiving G-CSF or GM-CSF *

- ◯ Yes
- ◯ No

A total white blood cell count >50 x10^9/L *

- ◯ Yes
- ◯ No

Known to be pregnant or breastfeeding *

- ◯ Yes
- ◯ No

Known recent (required treatment within the last 5 years) haematological malignancy *

- ◯ Yes
- ◯ No

Solid organ or bone marrow transplantation *

- ◯ Yes
- ◯ No

Patient weight >125kg *

+ Complete the GM-CSF eligibility form
+ Confirm patient eligibility on the final eligibility check before continuing

Final Eligibility Check

Eligibility results from first eligibility check, is patient eligible:-	Is the subject eligible to participate in the GM-CSF trial of the study?
	◉ Yes ◯ No

Imperial College London

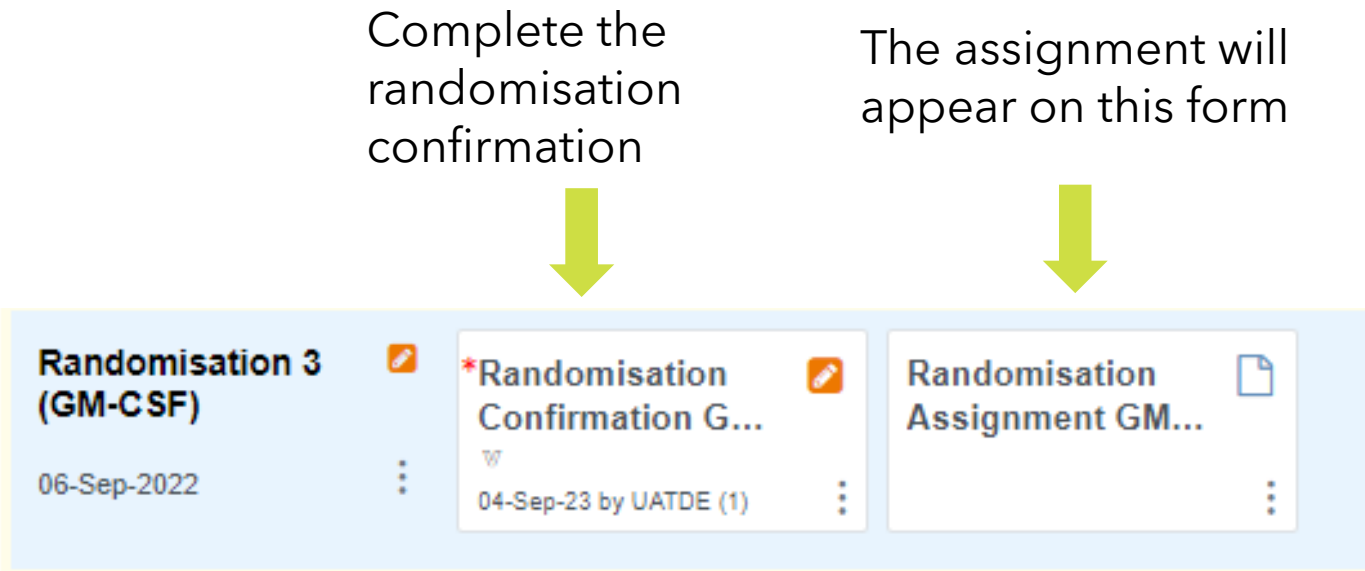
SepTiC
Sepsis Trials in Critical Care

Add the Randomisation 3 GM-CSF visit

+ Then complete the forms as shown below

Complete the randomisation confirmation

The assignment will appear on this form



Imperial College London

SepTiC
Sepsis Trials in Critical Care

Complete the GM-CSF randomisation confirmation page

Confirm the participant details and eligibility in order to randomise this participant.

Study Name: SepTIC	**Participant ID** UAT1-1085
Gender Male	**Month and Year of Birth** 1961-06

Randomise

Treatment Allocation from Randomisation 1
- ○ Standard care or Not Randomised
- ◉ PCR/procalcitonin based diagnostics

Treatment Allocation from Randomisation 2
- ○ Standard care or Not Randomised
- ◉ Conservative fluid strategy

Source of infection
- ○ Community
- ◉ Hospital

Is the participant eligible for randomisation and stratifications completed?
- ◉ Yes
- ○ No

Date of Randomisation

2023-10-31

Select 'Randomise' below if participant is eligible and click 'Complete' to randomise the participant.
- ◉ Randomise

Please click 'Complete' and the treatment will be populated in the Randomisation Assignment form.

These questions will be automatically completed from previous forms

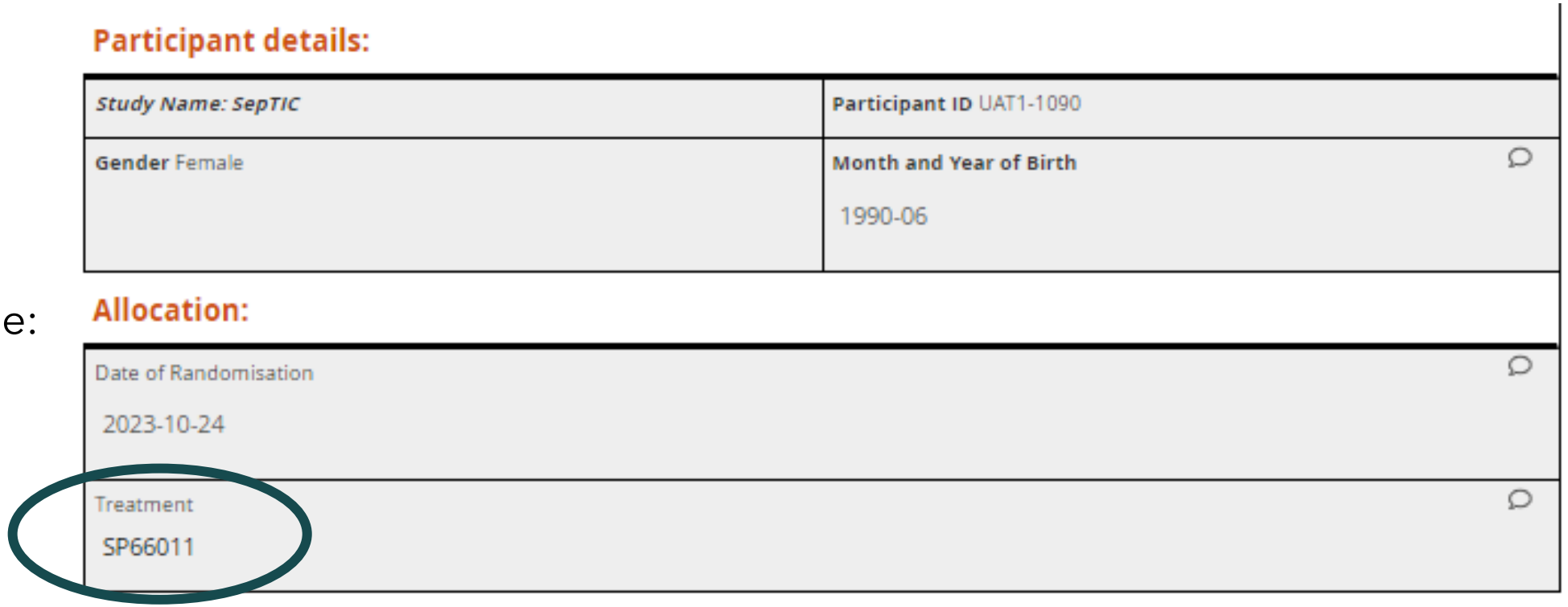
These questions will appear once the previous question is answered

Imperial College London

SepTiC
Sepsis Trials in Critical Care

The GM-CSF randomisation assignment form will have the fluid treatment allocation

Example:



Participant details:

Study Name: SepTIC	**Participant ID** UAT1-1090
Gender Female	**Month and Year of Birth** 1990-06

Allocation:

Date of Randomisation 2023-10-24
Treatment SP66011

The treatment will be the kit number that the patient has been assigned to. Make a note of the kit number.
Click 'Complete to close the form'

Imperial College London

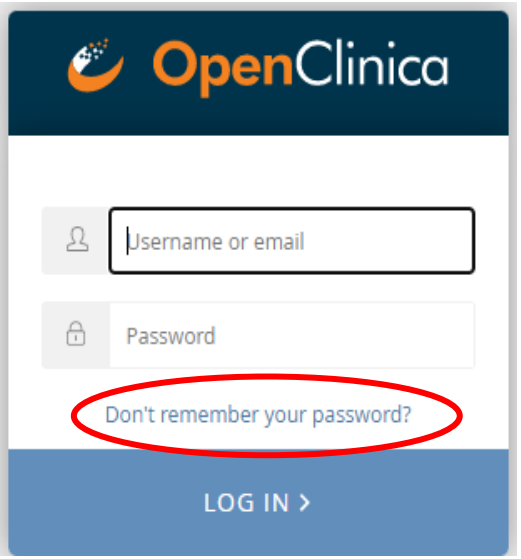
SepTiC
Sepsis Trials in Critical Care

The randomisation allocation will not appear immediately on the assignment form

- This is because there is a small lag between the assignment being generated and then appearing on the form
- Once you close any randomisation confirmation page, **refresh** the browser
- And then open the assignment form

If you have forgotten your password

- Click ‘Don’t remember your password?’
- Then you will have to enter your email address
- OpenClinica will send an automatic email to the registered email address with a link to reset the password
- On your mobile device, delete the current MFA code
- Once you click the link to reset your password, it will ask you to scan the new code
- You will then be asked to set your new password



Imperial College London

SepTiC
Sepsis Trials in Critical Care