OpenClinica eCRF Completion Guidelines

Version: **2.0**

Date: **11.06.2023**

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Contents

1. OPENCLINICA HELP

1.1 OpenClinica Support

Contact the Clinical Data Systems (CDS) Production Support for any OpenClinica technical related queries, the help desk is available:

By e-mail: cds_support@imperial.ac.uk

By phone: +44 (0)207 5942614

The team are available Monday to Friday 09:00-17:00

Links to the OpenClinica training modules can also be found on the Website**:**

https://www.imperial.ac.uk/clinical-trials-unit/clinical-data-systems/cds-openclinica/training-openclinica-40/

For help with randomisation refer to the SepTiC Randomisation Guide.

1.2 Study Specific Support

For study specific OpenClinica queries please refer to this completion manual or contact the study team below:-

septic@imperial.ac.uk or 0207 7594 9725

1.3 Study base access

Study URL: https://imperial.openclinica.io/OpenClinica

Upon successful completion of the OpenClinica role(s) based training, a user can request an OpenClinica account by completing the OpenClinica User Activation Form (UAF) accompanied by the relevant training certificate to the SepTiC email: septic@imperial.ac.uk.

The form requires approval by either the Study Manager or Chief Investigator (CI). Once the form has been completed and sent to CDS Production Support by the SepTiC team, the requested role will be created in OpenClinica.

You will receive a time sensitive email from OpenClinica inviting you to the study, which includes details of the URL and a link to setup your password. You will have 14 days to click on the link to activate your account. If the time passes and the link becomes inactive, contact the CDS Production Support team and they will send you the invitation again. Please try to complete process in a timely manner.

Once your account has been activated, to gain access to this study you will need to enter the “Username” and “Password” on the database:

Please note: your username and password should not be recorded anywhere in this document. Passwords should never be shared with other users.

It is good practice to log out once you have finished using the OpenClinica application. This is particularly important if you are not using your own computer.

After a set period of inactivity one hour, you will be automatically logged out of the system.

1.4 Password Management

If you forget or enter an incorrect password more than twice you need to click on the "Forgot Your Password?" link on the login page and answer the questions provided, the answers are based on those set up when you first logged in. For forgotten password or log in details please contact the OpenClinica/ CDS help desk Support/Helpdesk who will be able reset your password.

A new temporary password will be sent by email to the account holder, you will be expected to change this upon next login.

2. GENERAL DATA ENTRY GUIDELINES

Data entry must be completed for ALL subjects.

To adhere to **Good Clinical Practice (GCP)**:

Data entry for a completed visit should be performed within **14** business days.

Data queries should be answered within **14** business days.

Data entry must only be completed by authorized personnel who have received trial specific and OpenClinica training and are competent in eCRF completion.

Avoid using abbreviations in text fields (other than NA - **Not Applicable**, ND - **Not Done**, NK - **Not Known** and UNK - **Unknown**) and acronyms, unless they are approved medical abbreviations known to be acceptable.

Avoid using abbreviations that are ambiguous or could be interpreted differently.

Anywhere on the eCRF that **'other (specify)'** is selected, there is usually an entry in the space provided describing what 'other' means.

Subject identifiers **should not** be used anywhere on the eCRF, such as subject's name, initials, address, hospital number etc., in order to maintain the confidentiality of the subject.

2.1 Common formatting

2.1.1 Dates and Time

Enter date by choosing from the manual calendar, the format is year/month/day i.e., yyyy-mm-dd for example 13th August 1999 is 1999-08-13.

Enter time in a 24-hour clock format i.e., hh:mm e.g., 3:25pm would be entered as 15:25

2.1.2 Values

For values with decimal points, you may need to round the value up or down. To do this:

Decide which is the last number to keep.

Leave it the same if the next number is less than 5 (called rounding down) OR

Increase it by 1 if the next number is 5 or more (called rounding up)

Example 1: To round a value up or down to the nearest whole number

- 72.26 would be rounded down to 72 (as the next number is less than 5)
- 72.53 would be rounded up to 73 (as the next number is 5 or more)
- 72.81 would be rounded up to 73 (as the next number is 5 or more)

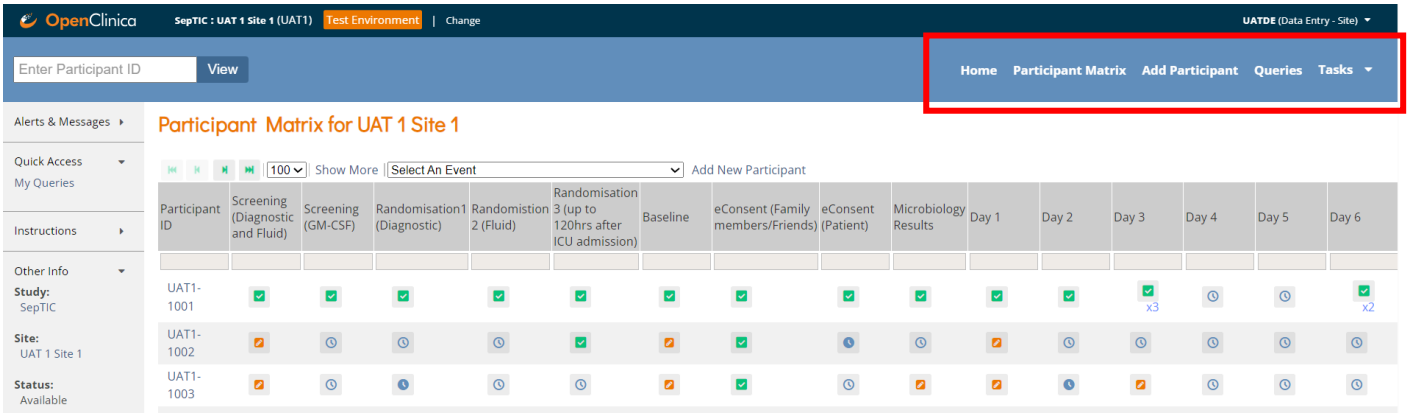
Example 2: To round a value up or down to 2 decimal points

- 72.2638 would be rounded down to 72.26 (as the next number is less than 5)
- 72.2684 would be rounded up to 72.27 (as the next number is 5 or more)

3. SUBJECT INFORMATION

3.1 Navigation Toolbar

The navigation toolbar can be found on the top right-hand corner of the OpenClinica main page:



Once logged in you will be able to see the homepage which is also the Participant Matrix. This displays all Participant added to the database at your site. The Navigation toolbar contains these links:

Home – Used to navigate back to the home page/ participant matrix.

Participant Matrix – Used to return to the participant matrix which displays the Participant's general information, Events, and Forms.

Add participant – Used to add new participant.

Queries – This shows a summary count of all queries for all participants and what the status of the query is.

Tasks:

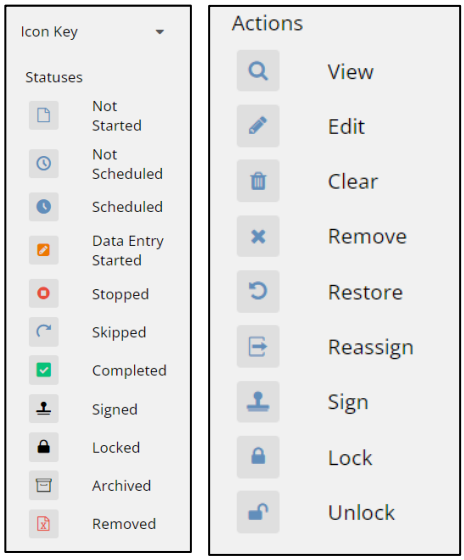
- Schedule Study event- can be used to schedule events for a given participant, without entering into that particular participant page.
- View Events- You can use this page to filter Study Events. The default view shows Study Events that apply to the current month. Participants for whom Events were scheduled but have not had data recorded as of the expected Event date will appear highlighted in yellow.

3.2 Home Page

The homepage displays the participant matrix in the centre and an icon key on the left which explains the symbols in the participant matrix.

All added participants are found under the Participant ID column and specific participants can be searched for using their ID in the top square.

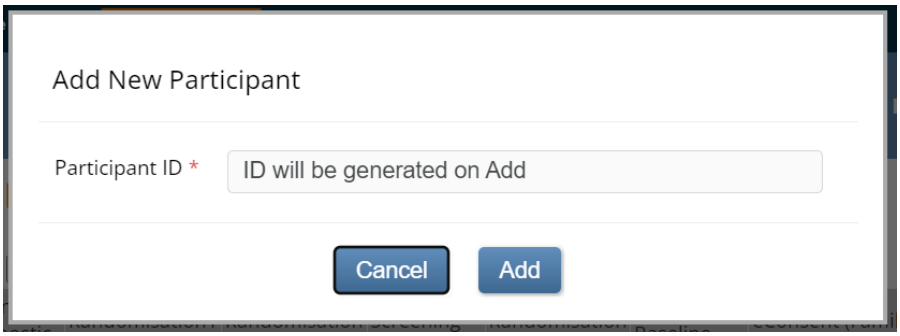
The ‘Selects an Event’ box can be used to search for individual visits. All participants that have the selected event data entered or partially entered will be shown.



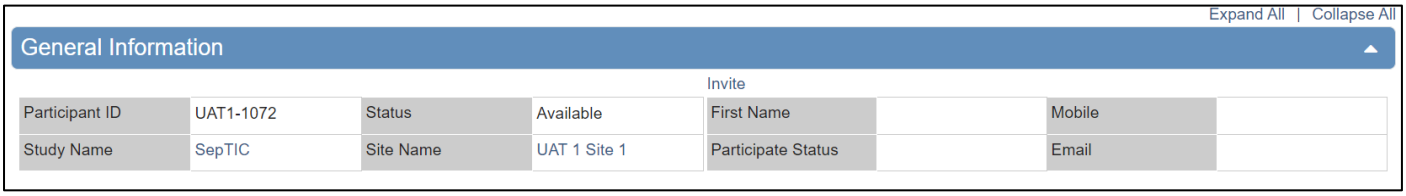
3.3 Adding a Subject in OpenClinica

To add a subject in OpenClinica select ‘Add Participant’ in the navigation toolbar.

A pop-up window will be generated, press ‘Add’ to generate a new Participant ID.



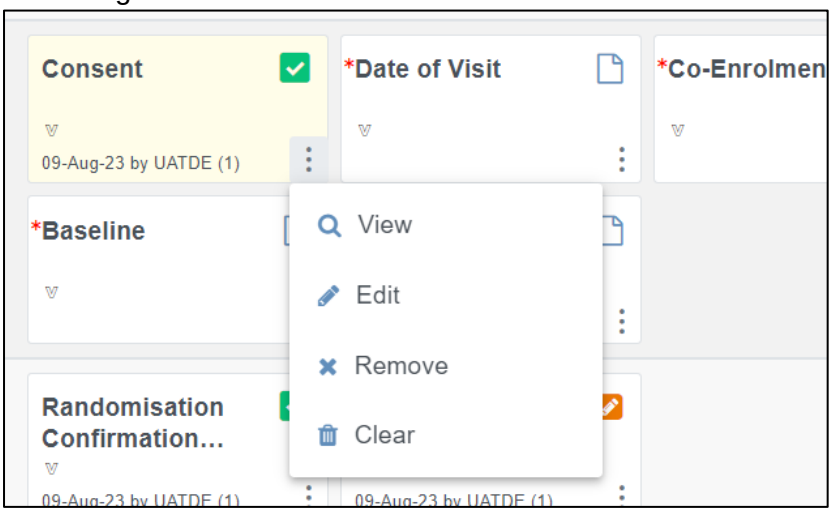
This will bring you automatically to the new participant page. The generated Participant ID can be seen in the General Information tab on the top of the page.



3.4 Resubmitting/Modifying Subject Information

You can modify a form at any time if the form has been closed **and not** saved. If the form has been saved, you can still modify the data entered however you must give a reason for this.

A saved form is one that has a green tick in the top right corner. To edit this form, find the three dots in the bottom right corner and choose 'edit' from the list.

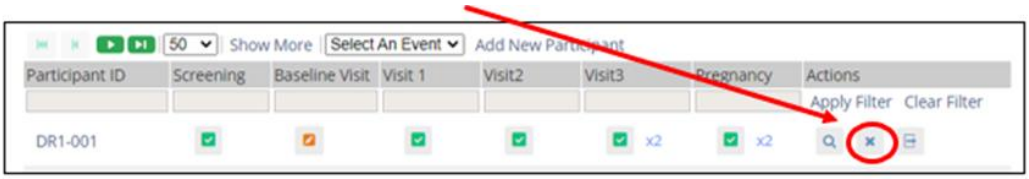


When editing a form to enter missing data/correct data, OpenClinica will ask the data entry user to enter a reason for the change. Depending on the internet browser used for data entry, this may show some auto-fill suggestions based on previous data entry. The auto-fill suggestions **should not be used** when entering a reason for change, as this saved data may be associated with other fields in the form and will change the data for those fields. Example given below: if the first option 'Updated' is selected, it will also change the dates in the form.

3.5 Removing Participant if entered in error.

If a patient has been added to the database in error e.g. patient data/screening data entered but not eligible, the PI can remove the patient from the database.

This is for PI user roles only: If you want to remove the participant from the database, open the Participant Matrix and remove the subject by selecting the (x) icon in the actions column.

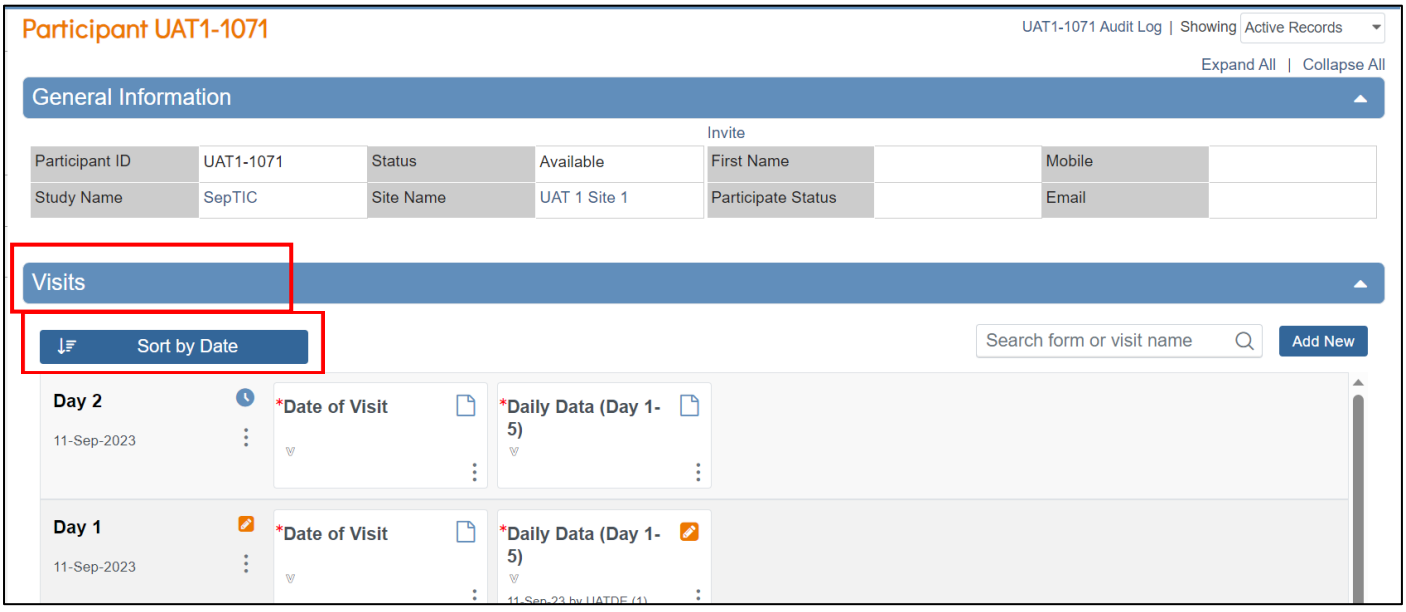


You will be redirected to the screen 'Remove Participant from Study' select 'Remove Study Participant' to confirm you want to delete the subject from the eCRF.

This action can be undone by clicking the Restore icon.

3.6 Subjects: Visit View

To view all visits that have been added to a patient's profile select the participant from the 'Participant Matrix'. On the patient page all assigned visits can be viewed under the Visits tab:



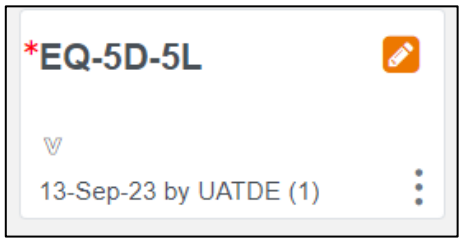
The visits will show up in **reverse-chronological** order, with the first visit: Screening (Diagnostic and Fluid) at the bottom of the page. The order in which the visits are viewed can be changed to chronological, where the first visit is at the top by selecting the 'Sort by Date'.

When the arrow on the 'Sort by Date' tab is facing up the visits will appear in a chronological order down the page.

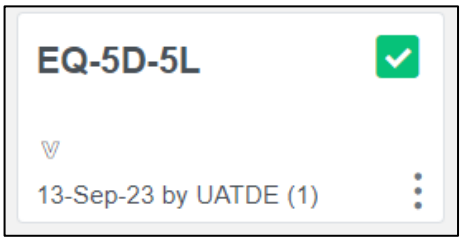
3.7 Subjects: Form View

When a visit is added to a subject's profile all the forms associated with that visit will be automatically visible. The forms have symbols in their top right corner that show the status of completeness. The date on the bottom is the day the data was entered and by who. The 'V' symbol show whether the data has been verified, and changes to black when the data has been verified.

Data entry not started



Data entry started



Data entry completed

3.8 Navigating Between Pages

For the SepTiC Trial all forms are one page with either a 'Close' or 'Complete' option.

When a form is 'Closed' the data in the form is saved however you can enter back into the form and change the data without having to enter a reason for this data change.

When the form is 'Completed' the data is saved, when the form is opened again it will be in 'Review Mode' and if you would like to change data, please refer to the Resubmitting/Modifying Subject Information

4. DATA ENTRY

4.1 Timeline For Data Entry

Visit	Forms	Timeline for site data entry
Screening (Diagnostic and Fluid)	- Date of Visit* - Eligibility * - Pre-randomisation*	Day 1 (prerandomisation)
Admission	- Admission	Day 1 (pre-randomisation)
Randomisation 1 (Diagnostic)	- Randomisation Confirmation* - Randomisation Assignment Diagnostic	Day 1 (randomisation)
Randomisation 2 (Fluid)	- Randomisation Confirmation* - Randomisation Assignment Fluid	Day 1 (randomisation)
Screening (GM-CSF)	- Date of Visit * - Eligibility GM-CSF *	Anytime up to 5 days (120 hours) after ICU admission
Randomisation 3 (GM-CSF)	- Randomisation Confirmation GM-CSF* - Randomisation Assignment GM-CSF	Anytime up to 5 days (120 hours) after ICU admission once patient meets additional inclusion / exclusion criteria found in the Eligibility GM-CSF form

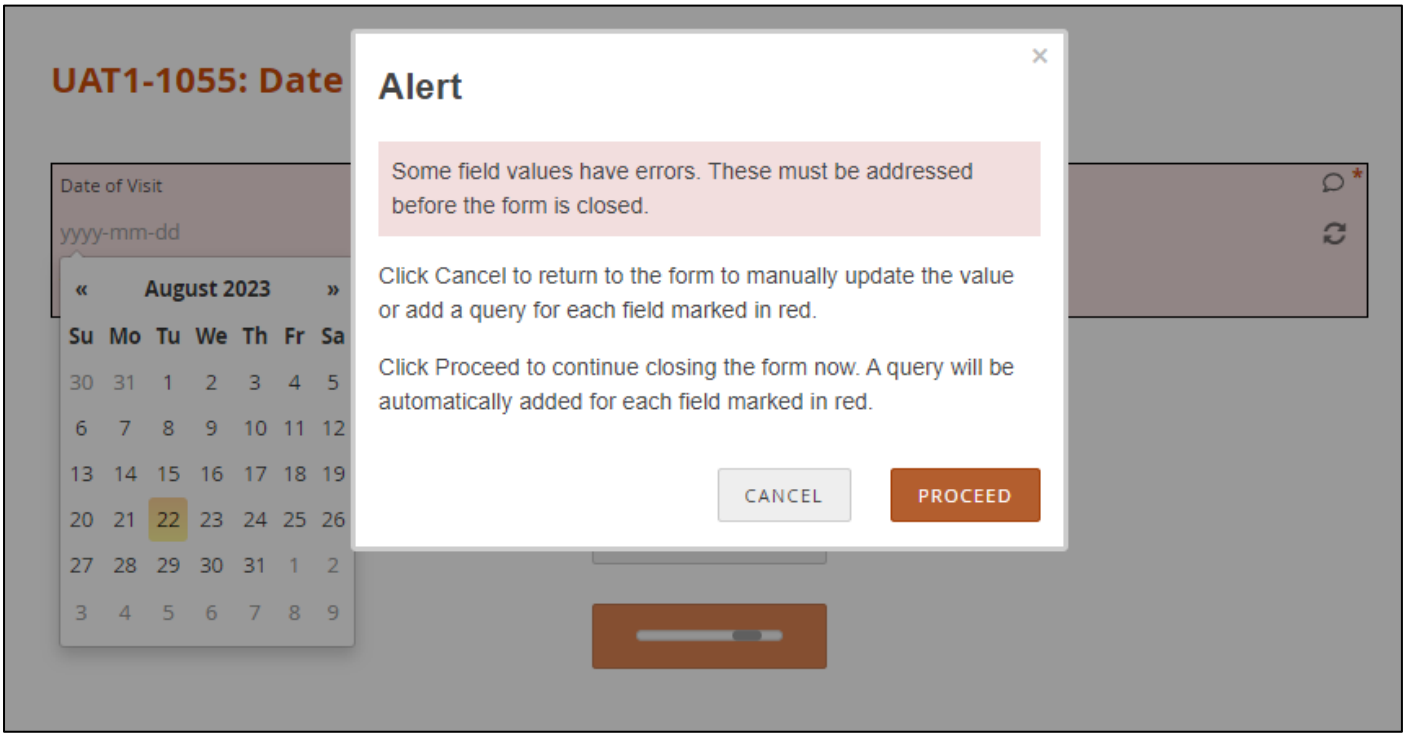
Baseline	- Consent * - Date of Visit* - Co-Enrolment * - Demography * - Diagnostic* - Baseline* - Samples*	Patient / PerLR / ProLR consent will be obtained prior or after randomisation. Retrospective patient consent will be obtained when the patient has recovered capacity to consent. All other forms to be completed on day 1 (post- randomisation)
Microbiology Results	- Microbiology results *	Day 1 (post-randomisation)
Day 1- 5	- Date of Visit - Daily Data (Day 1-5)	Every day on days 1-5
Day 6-13	- Date of Visit - Daily Data (Day 6-13)	Every day on days 6-13
Day 14-28	- Date of Visit - Daily Data (Day 14-28)	Every day on days 14-23
Follow up (Day 95)	- Date of Visit - Follow up Day 95	95 days after Screening/ Randomisation (2-week grace period, can be done up to 109 days after randomisation)
Follow up (Day 180)	- Date of Visit - EQ-5D-5L - Montreal Cognitive assessment (MoCA)	180 days after Screening/ Randomisation (can be completed up to 14 days after follow-up was due')
Follow up (Day 365)	- Date of Visit - Follow up 1 year	365 days after Screening/ Randomisation (can be completed up to 14 days after follow-up was due')

*All forms that are compulsory in OpenClinica

4.2 Specific Field Types: Mandatory Fields

All fields should be assumed to be mandatory and therefore should be filled in. If there are fields that are left empty when you attempt to close and save the form an alert message will appear highlighting which fields must have data entered.

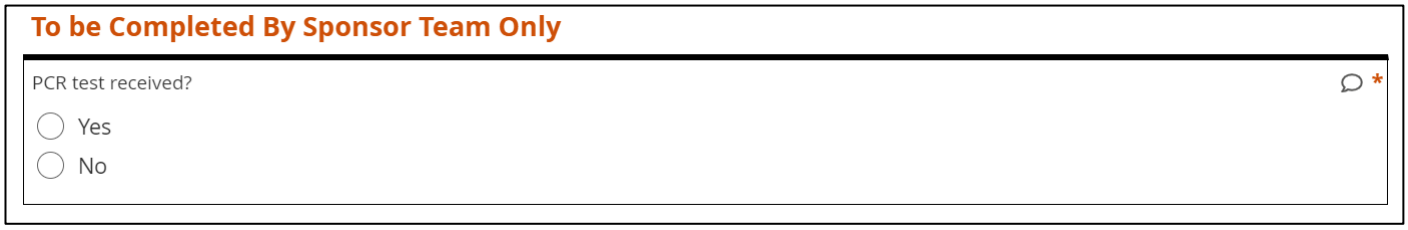
If there is no data to enter in these field, click proceed and the form will be saved with empty fields.



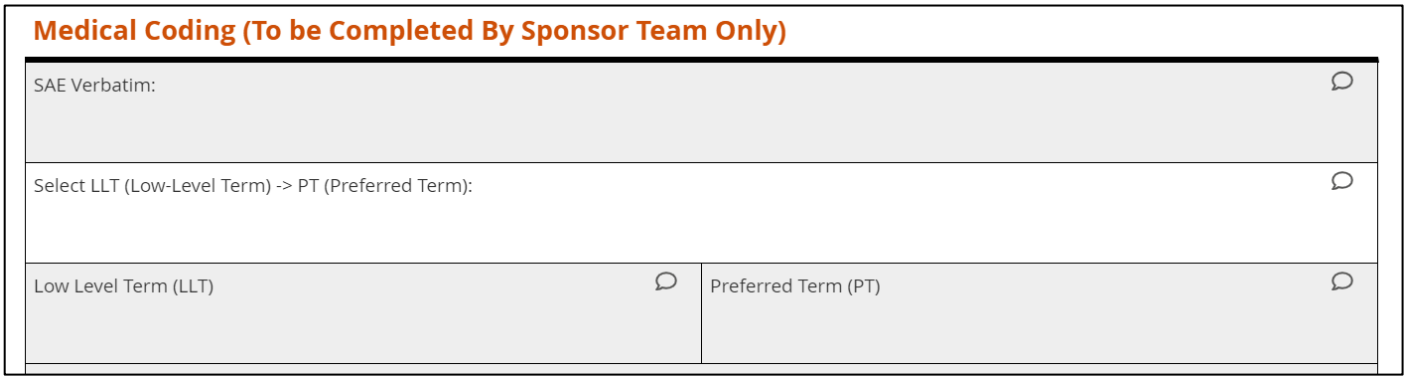
4.3 Specific Field Types: Empty State - Non-Mandatory fields

All fields should be presumed to be mandatory. There are some exceptions:

- All fields which as designated for the study team for example the PCR test section of the Baseline Diagnostic form. The title clearly states, 'To be completed by Sponsor Team Only.'

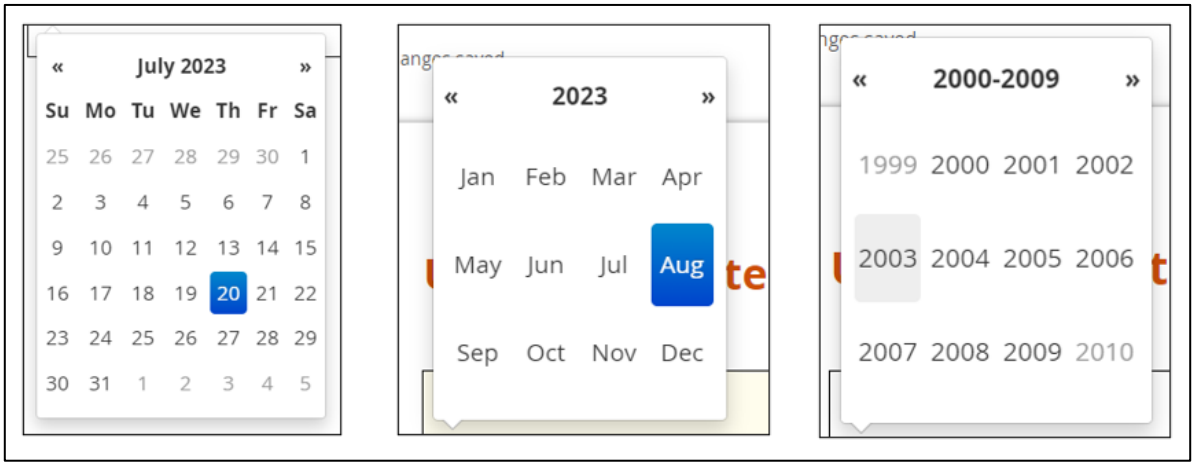


- SAE Medical Coding can only be completed by the Sponsor Team



4.4 Specific Field Types: Date Fields

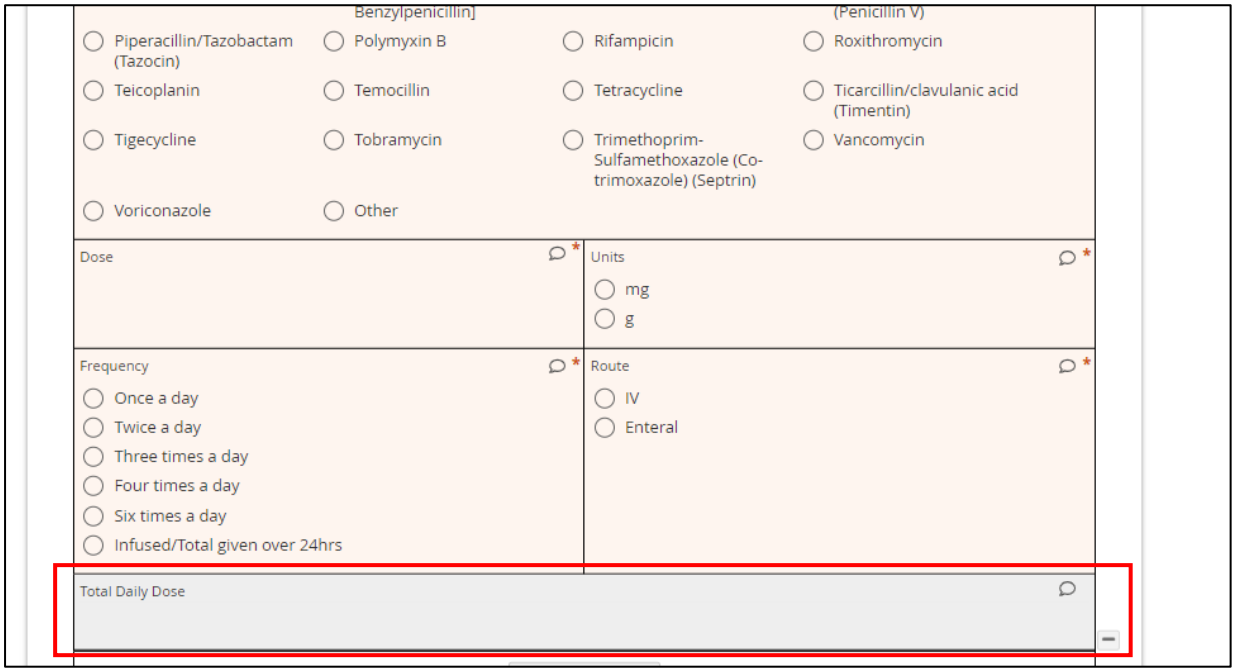
All date fields will be in the yyyy-mm-dd format. This can be either typed in or entered using the drop-down calendar, this appears automatically when you click on the date. Click on the month on top to move see all months in that year and click on the year to see all years in that decade, the arrows on the sides can be used to move between decades or months.



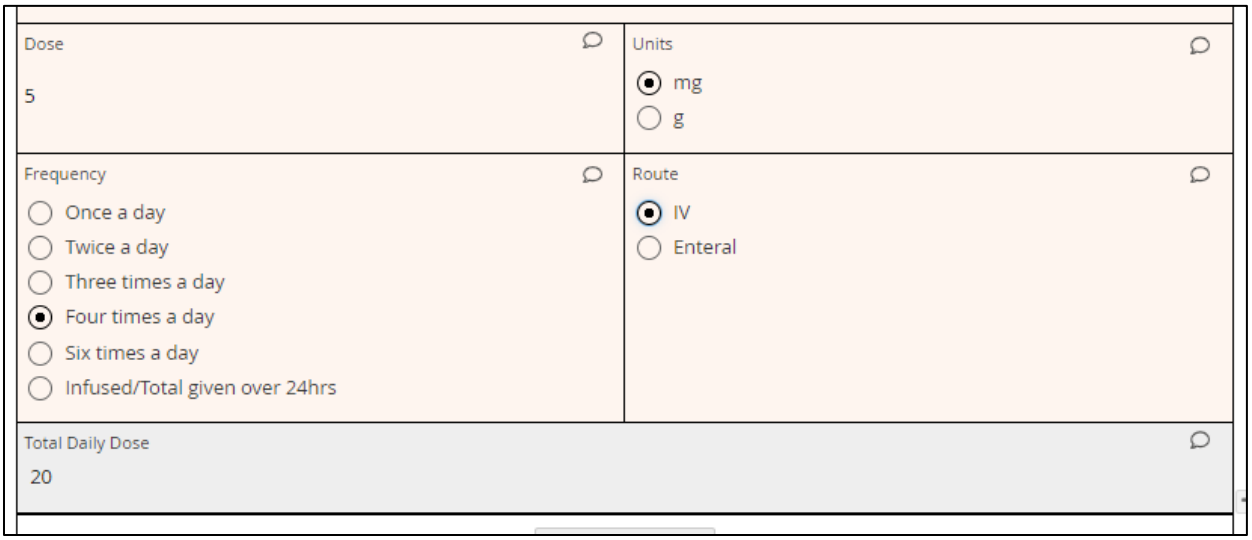
4.5 Specific Field Types: Auto Calculated

4.5.1 Antibiotic Total Daily Dose

'Total Daily Dose' of antibiotics can be found on the Daily Data Day 1-5, 6-13 and 14-28. This section is auto calculated from the dose, frequency and units entered above and does not require manual entry. The section which is auto calculated is greyed out.



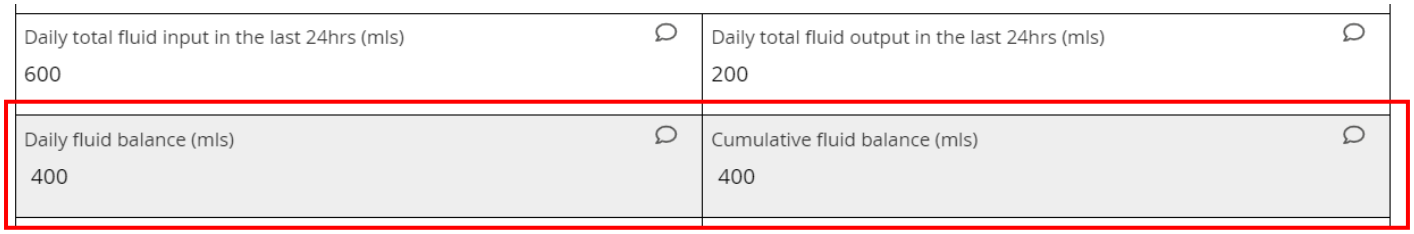
Example with values, total daily dose is auto populated.



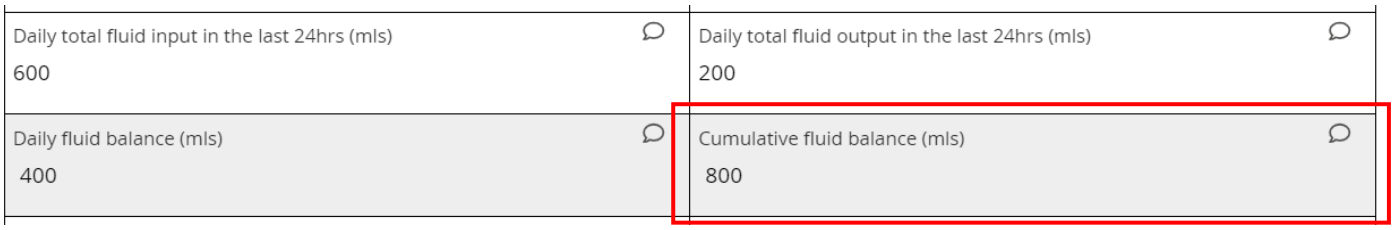
4.5.2 Daily Fluid Balance

'Daily fluid balance (mls)' and 'Cumulative fluid balance (mls)' are auto populated and can be found on the Daily Data Day 1-5. 'Daily fluid balance (mls)' is calculated from the 'Daily fluid input in the last 24h (mls) ' and 'Daily total fluid output in the last 24h (mls)', therefore for correct auto population these two values must be entered.

'Cumulative fluid balance' is a running balance from day 1. This value adds all previous Daily fluid balances together. The two auto populated sections are greyed out.



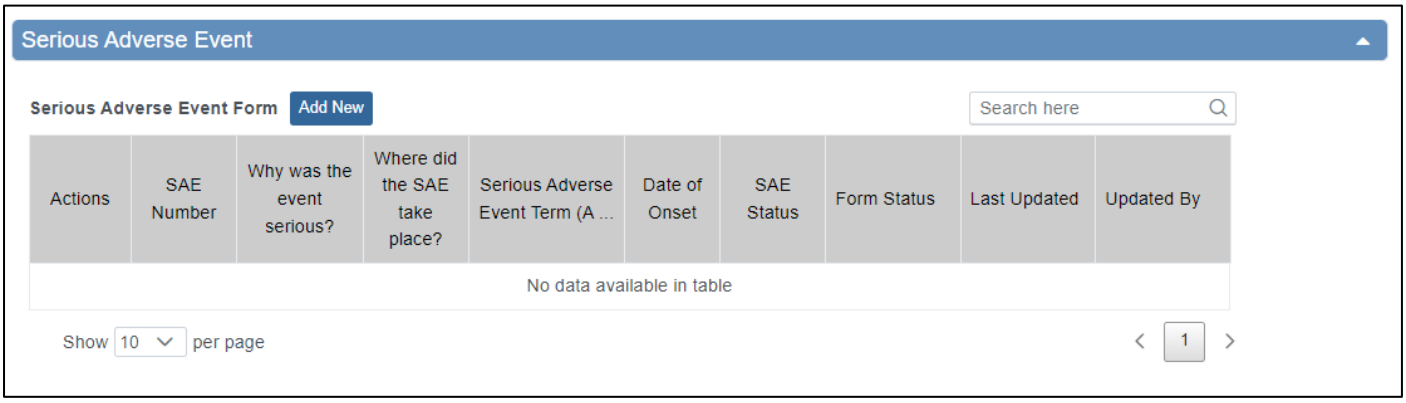
The example below shows the data entered on day 2, where the 'Daily cumulative fluid balance' has combined day 1 and 2.



4.6 Repeating Forms

Repeating Events are used for entering multiple records of data into the same form i.e., Serious Adverse Events, Protocol deviations.

When you first access a repeating form, you will see an empty summary. Click the Add New button to access the questions and create one form for entry.



Once you have completed the questions on the form, click the **Complete** button to save the data.

The saved record will then appear on the summary entries.

4.7 Adding Visits

To add a visit, navigate to the 'Add New' the visits tab when a new patient has been added. A separate box will appear where you can select which visits you would like to add. For more in depth instructions see section 7: Add Visits.

4.8 Signing Pages

After data entry of a CRF is completed, reviewed and all discrepancies are resolved, a PI (person of the site having the 'Investigator' rights in OpenClinica) must sign the CRF. When the PI signs an Event, they provide their approval of all CRF data for the CRF for the participant. CRFs are eligible for signature once the Study Events are in a "final" state i.e. (*Not Scheduled, Complete, Stopped, or Skipped)*

4.9 Manual Randomisation

Manual randomisation will be done on a case-by-case basis, if OpenClinica is down please contact the sponsor team/ monitor and we will advise you on the next steps.

5. QUERY MANAGEMENT

5.1 Answering System Queries

Once data entry has been performed and you click the '**Complete'** button, the system compares the data to the system queries associated with the page. The system creates queries automatically if you close a form that has unaddressed errors. You can also manually create queries as needed.

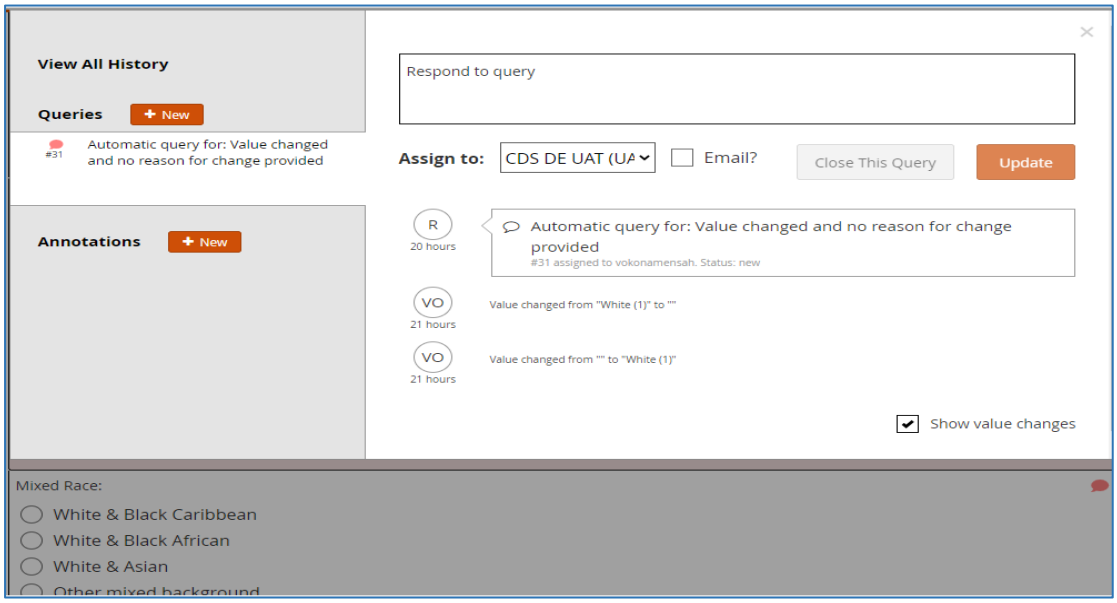
There are two options to respond to this query.

1. If the data was entered incorrectly, you can modify the data. If the updated data no longer meets the query conditions, the query will automatically close.

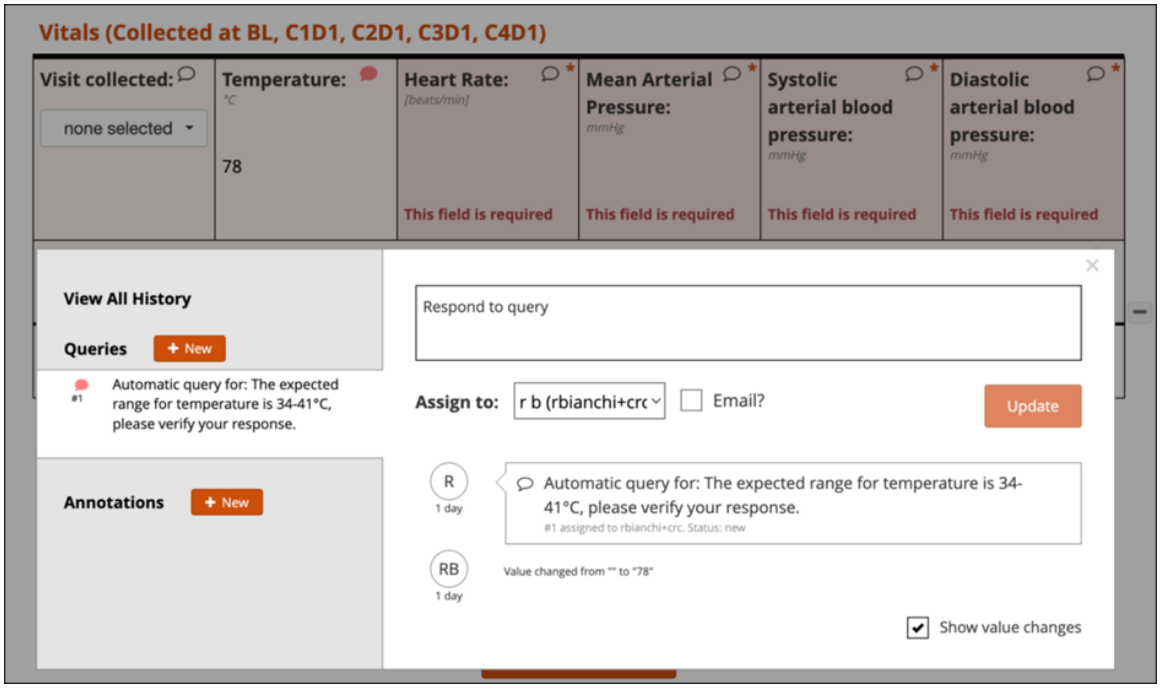
2. You can respond to the query with an explanation as to why the data is correct as entered. Query will then change to an "**Updated**" status.

To review data associated with a query You can either:

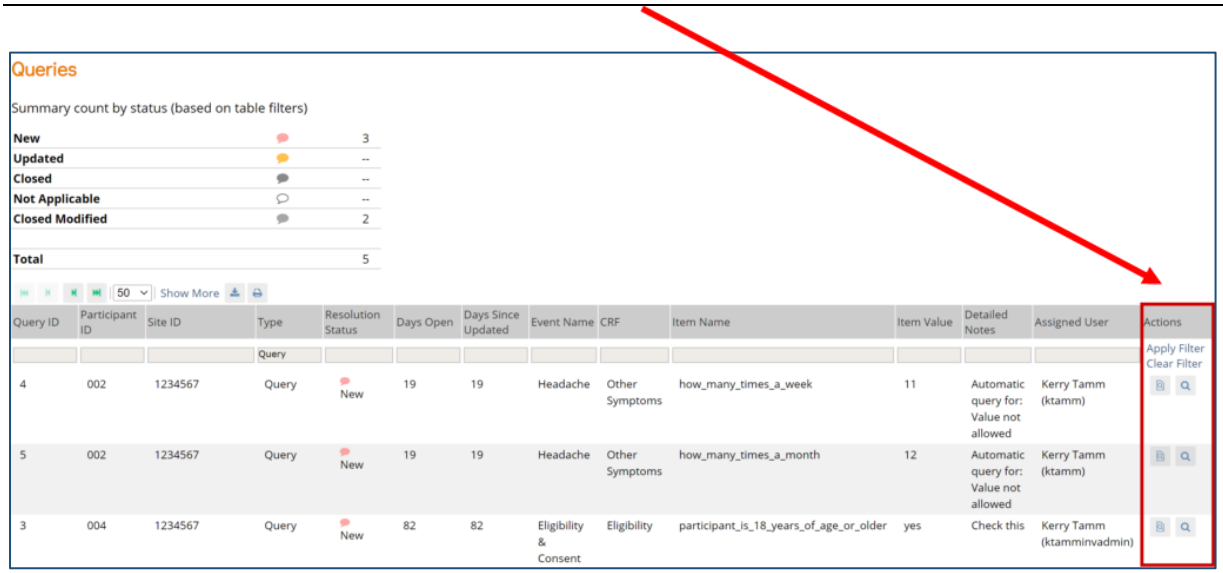
View Query Only



View Query within record



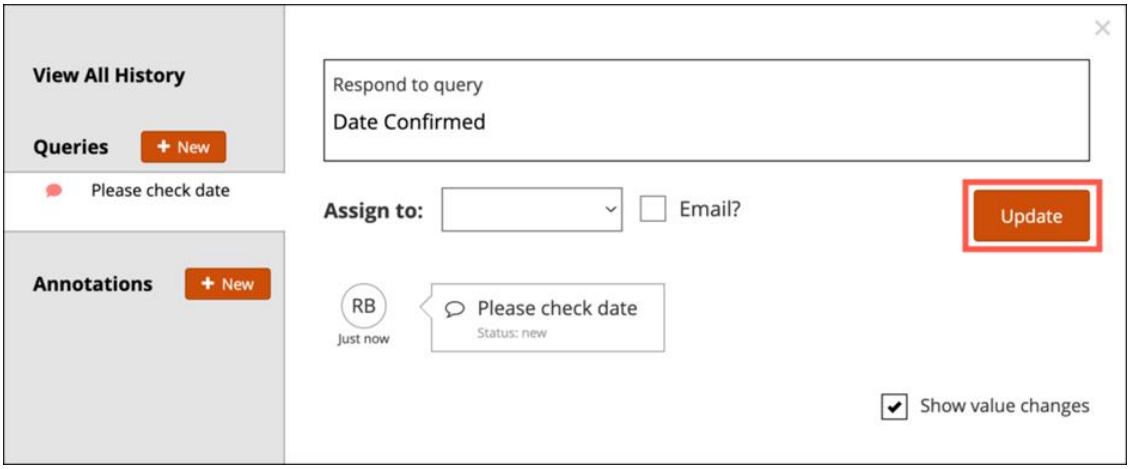
You can access these options from the **Actions** column of the **Queries** table



 Icon – indicates an Open query.

5.1.1 Answering System Queries: Modifying Data

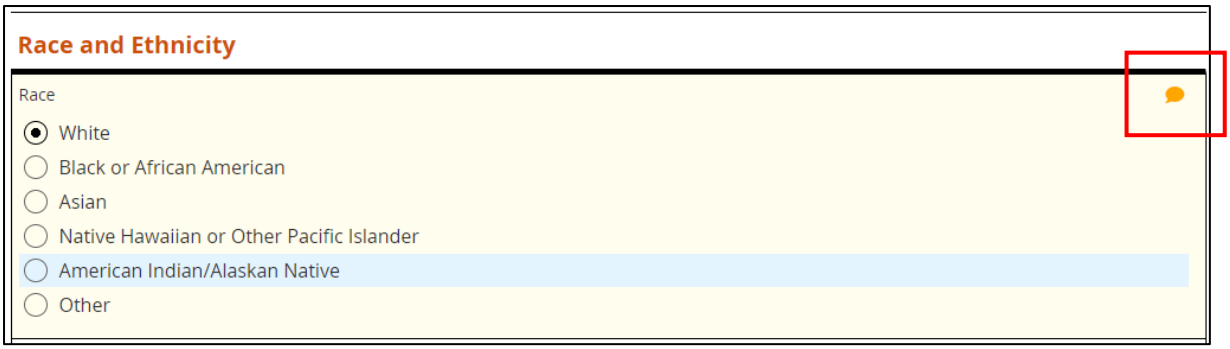
- Open a Form.
- Click the **Query Bubble** in the field you want to create a query for.
- Select the query you want to respond to and/or update.
- If you need to change information in a form, close the **Query** widget, and make changes to the Form manually. You must provide a **Reason for Change** before completing the Form (Optional).
- In the **Respond to query** field, enter text explaining the query response.
- Select a user from the drop-down list next to **Assign to**. If you want to email that user to notify them about the query, check the box next to **Email**. When a query notification email is sent, it includes the Query ID for easy access (Optional)
- Click the **Update** button to add the response and leave the query open.



5.1.2 Answering System Queries: Providing an Explanation

If the data is correct as entered, you can respond by providing more details either by responding to the query and/or updating the field, and the query status will change. Click the **'Update'** button.

Icon – indicates an Updated query.



5.1.3 Answering Queries: Other Query Types

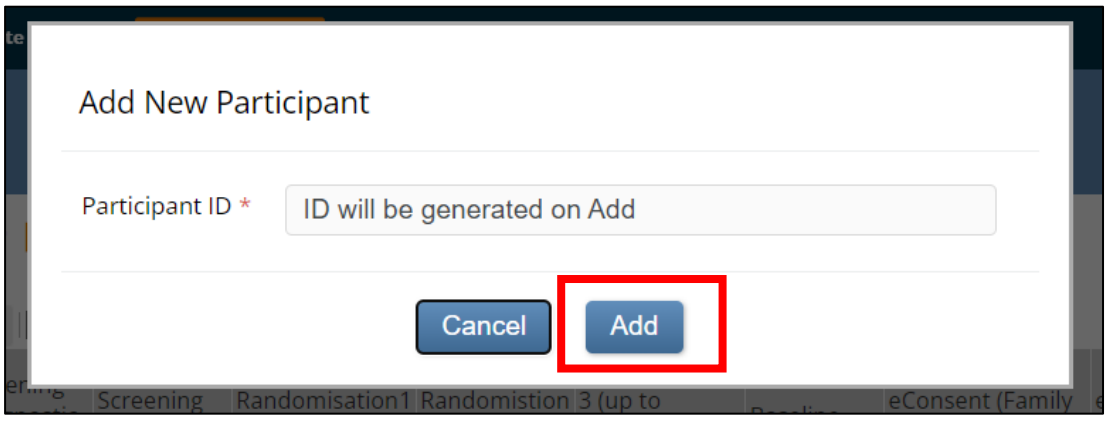
Manual Queries are entered by OpenClinica users that have permission rights, for example, a Monitor. Therefore, they do not open as an automatic query when the page is saved but may appear at any time during the conduct of the study. You have the same options to respond – to change the data or to provide an explanation. You will be required to respond to each of these queries.

6. STUDY SPECIFIC GUIDELINES

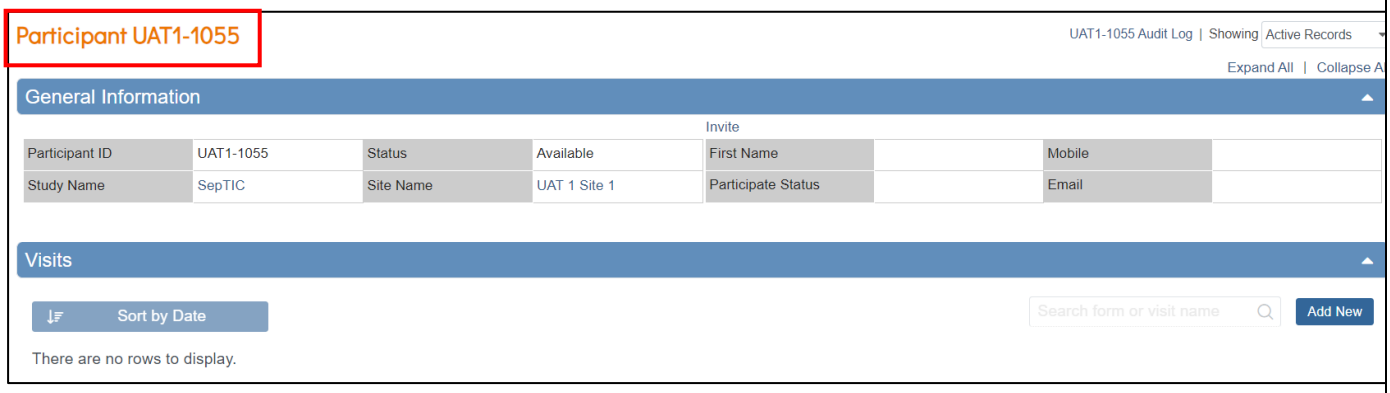
Add a New Participant

To add a new participant, navigate to the 'Add Participant' tab at the top of the home page.

This will generate a pop-up window. The participants ID will be generated once you click Add.



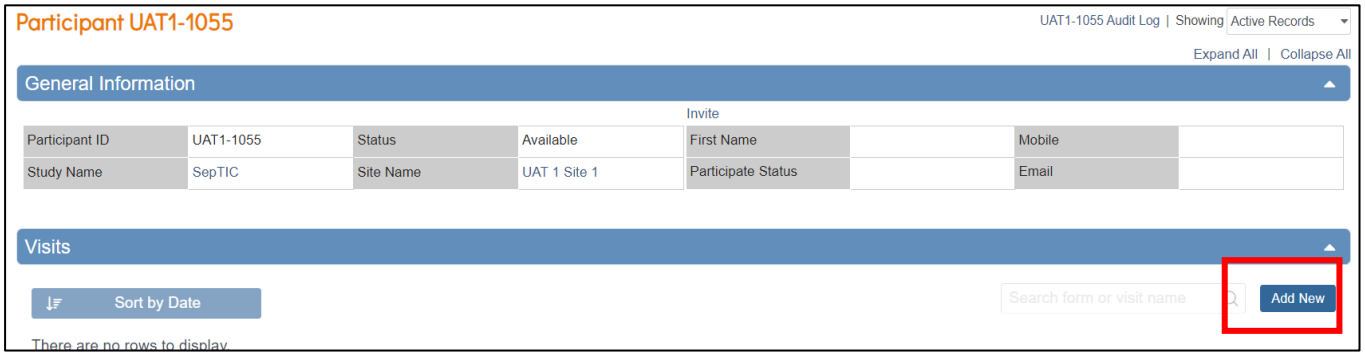
Once your participant is added you will be directly brought to the participant page:



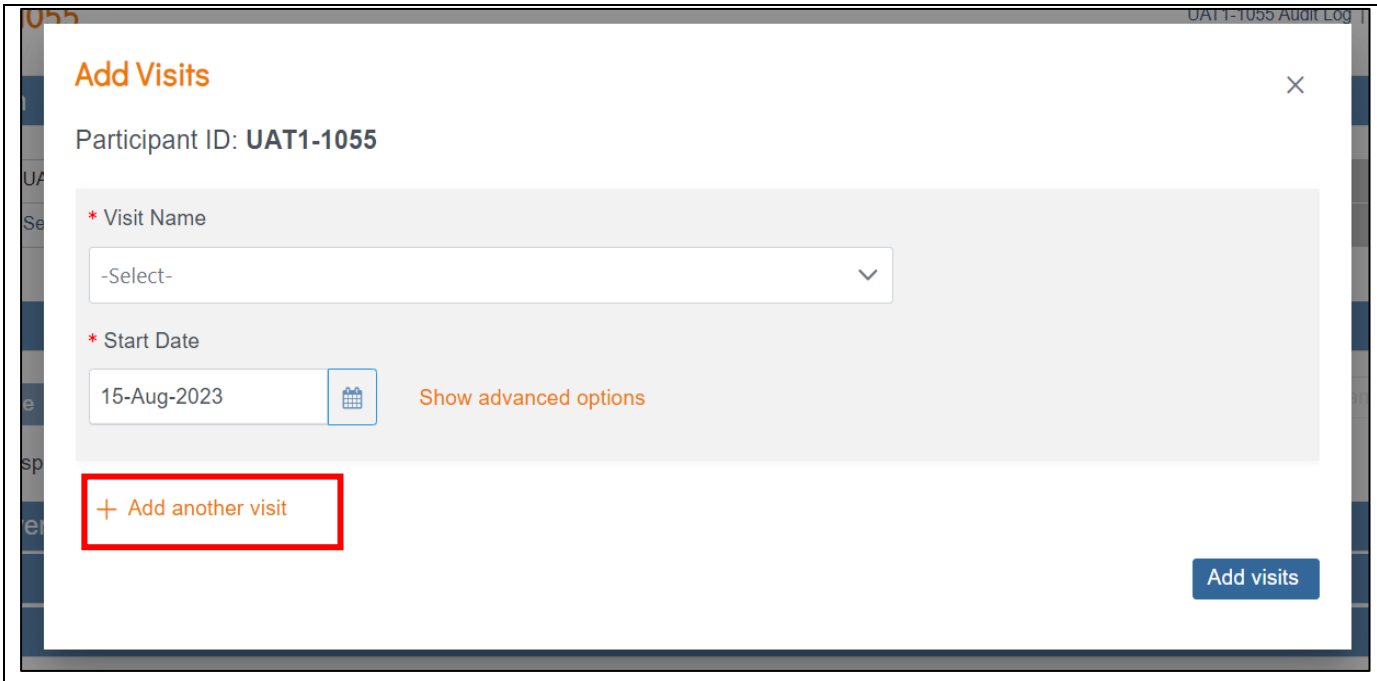
The participant page shows the patients ID at the top. This is the page where all study data for this particular patient will be added.

Add Visits

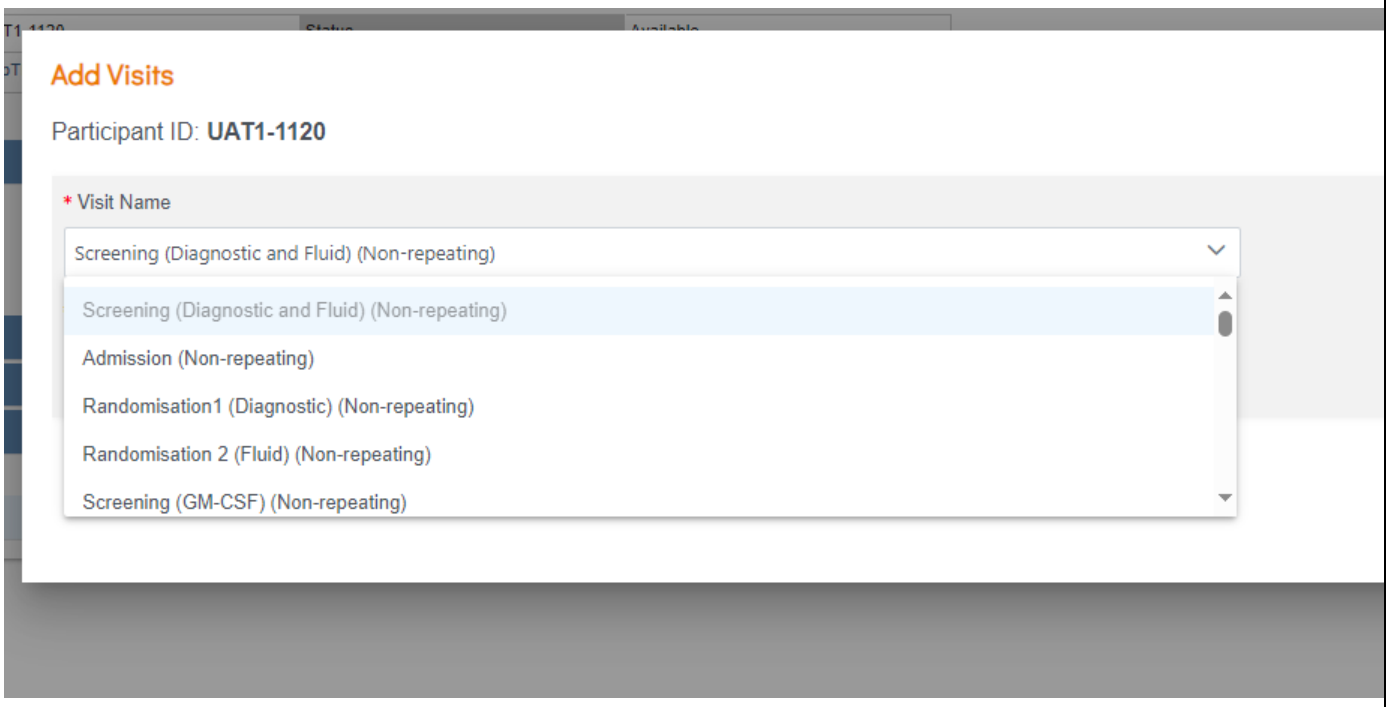
Once the patient ID has been generated, the patient visits can be added. Visits are added by clicking 'Add New' on the right-hand side of the Participant page. This generates the 'Add Visits' pop-up window.



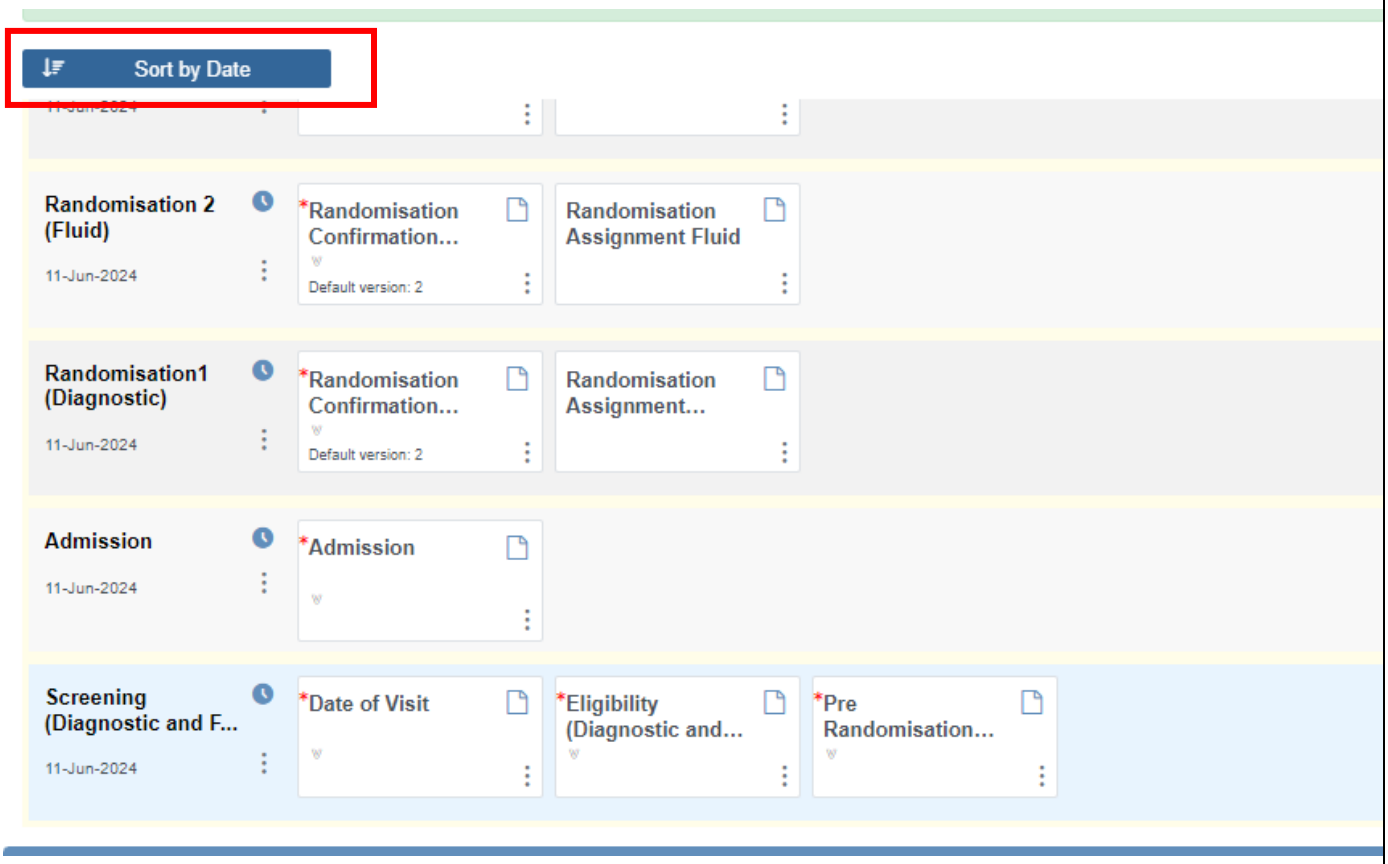
The 'Add Visits' pop up is where all visits will be added. If you navigate to '*Visit Name' and press select, the visits will appear in chronological order. The start date is the date the visits have been added onto that participants page. Multiple visits can be added at once using the '+ Add another visit' button. Visits **must** be added before the patient can be randomised or any data can be entered.



The drop-down list can be seen below, the list is chronological, and you can select which visit you want to add from this.



When the visits have been added they can be seen on the participant page, starting with the first at the bottom moving up in a chronological order. The order can be flipped with the first at the top by clicking 'Sort by Date' on the top left-hand side. This means that the first visit 'Screening (Diagnostic and Fluid)' will now be at the top of the page.



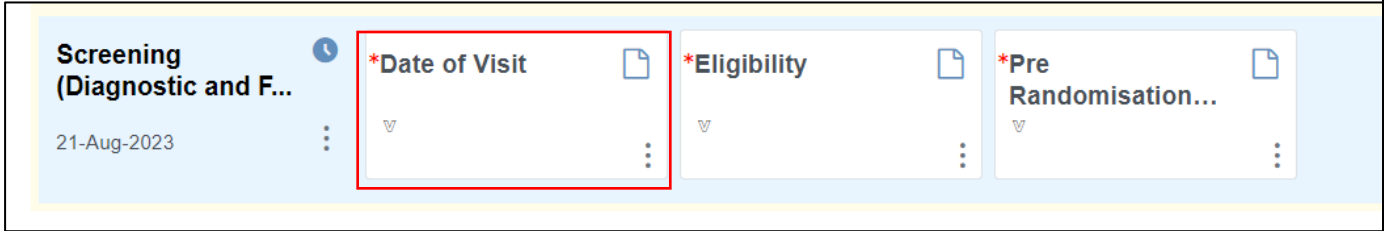
It is advised that only visits that are being completed at that moment should be added as any that are not needed can be removed however make it can be problematic for the PI and CI sign off later on.

Screening (Diagnostic and Fluid)

All patients must be screened, and the form marked as complete before randomisation. Only patients who meet all inclusion criteria and none of the exclusion criteria will be randomised.

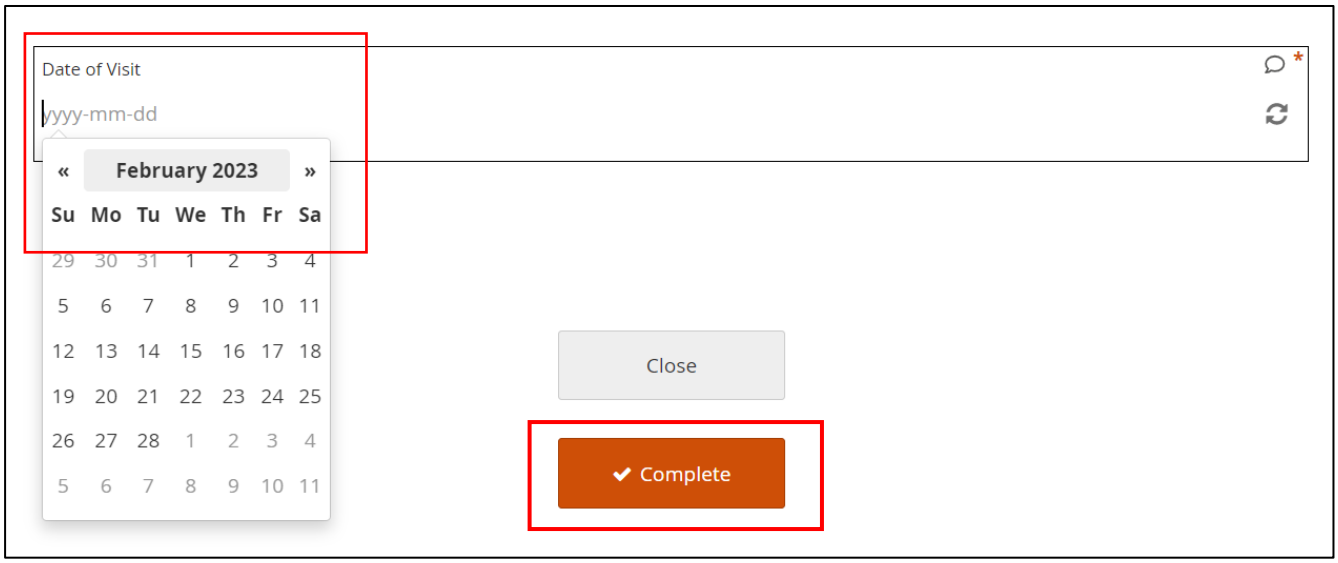
The same form is used for screening both diagnostic and fluid trials as patients should be randomised to these two trials **at the same time**.

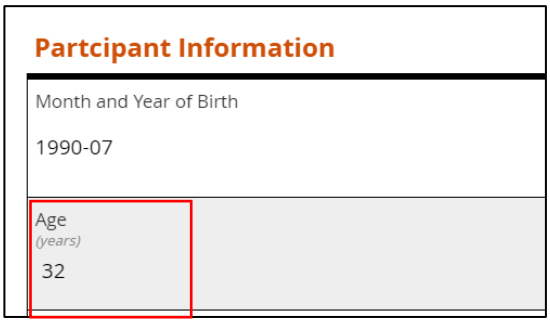
To begin screening navigate to Screening (Diagnostic and Fluid) and go to Date of Visit.



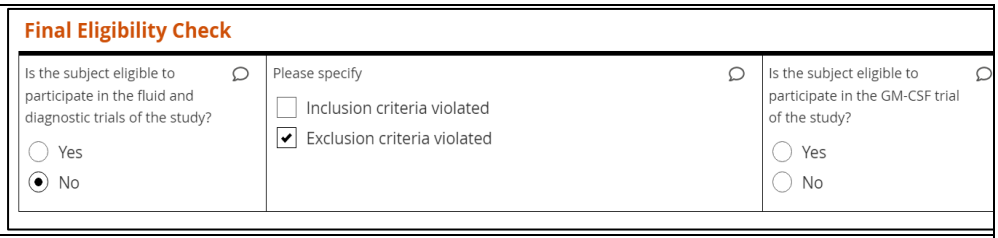
Enter the date you are completing screening and complete the form.

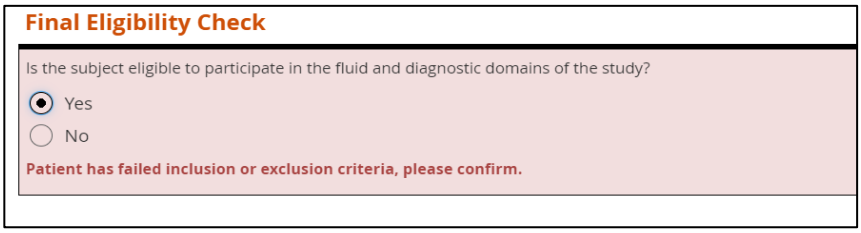
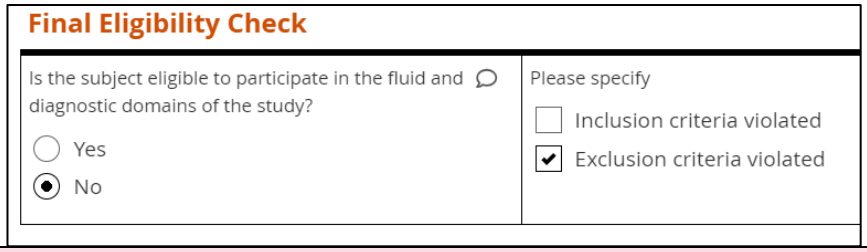
When form is completed, the information is saved.



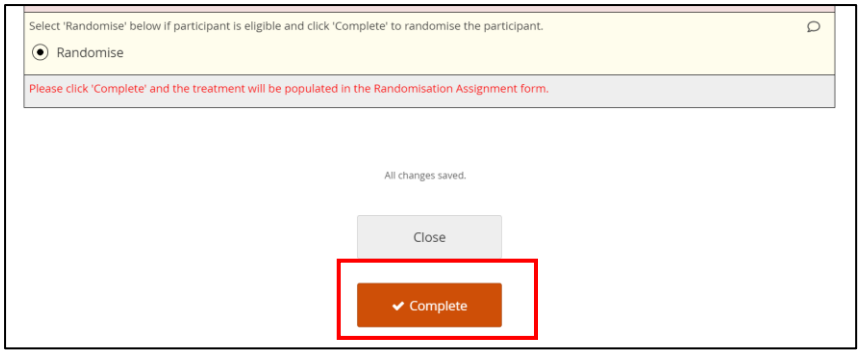
Date of Visit	
Date of Visit **yyyy-mm-dd**	- Enter the screening date. This is usually the day that randomisation is taking place. - **If this is not entered, the age will not be calculated, please make sure to enter the date of visit.**
Eligibility **All points on the eligibility form must be completed for correct randomisation**	
Participant Information	
Month and Year of Birth **yyyy-mm**	- Enter the year and month of birth of the patient. - The age will be **auto calculated** in the grey box below the month and year of birth. 
What is the patient's gender?	- Select the appropriate box corresponding to the patient's sex.

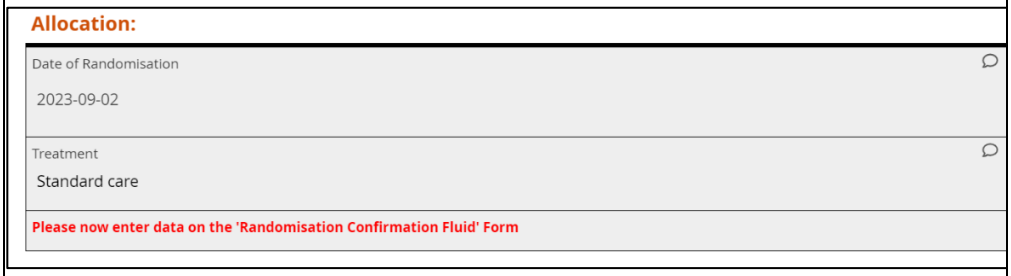
Is the patient's gender the same as the sex assigned at birth?	- Select the appropriate box.
Inclusion Criteria (**YES,** must be selected for **ALL** Inclusion Criteria for patient to be eligible for randomisation) Please make sure to fill in all of the data on the form or query will be raised	
Adults (≥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)	- At the time of randomisation, the patient must be 16 years or older. - Select yes if patient has suspected sepsis **and** is expected to remain in the ICU until the **day after tomorrow.** - The definition of suspected sepsis is: *Within the context of this study, 'suspected sepsis' is defined as 'acute organ dysfunction associated with suspected infection'. We do not mandate a specific definition for 'acute organ dysfunction' and will use local clinical decision.*
Receiving intravenous antibiotics for suspected sepsis	- The treating physician has started the patient on intravenous antibiotics for suspected sepsis
According to local clinical judgement, patient has received adequate initial early fluid resuscitation	- The treating physician has assessed the patient for signs of hypovolemia and issues have been resolved. - Initial 'rescue' phase has been completed, and the clinical team are now uncertain about the effectiveness of further fluid boluses and commencing vasopressor therapy. The patient is suitable for enrolment to SepTiC on this criterion. - The rescue phase is typically done within the first 3 hours from presentation. A volume of up to 30mL/kg would be typical of this 'rescue' phase, as described in SSC guidelines, but it is not essential that a specific volume of fluid has been given. * *For more detailed explanation please refer to the Fluid Manual*
Exclusion Criteria (**NO** must be selected for **ALL** Exclusion criteria for the patient to be eligible for randomisation)	
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.	- No more than 24 hours since admission to ICU - If the patient has been in the ICU for more than 24 hours, they may still be eligible for the GM-CSF trial. - If this first question of the exclusion criteria has been selected as yes, this makes the patient ineligible for Fluid and Diagnostic but can still be eligible for GM-CSF - An extra question will appear at the end of the form to confirm that this patient is eligible for GM-CSF

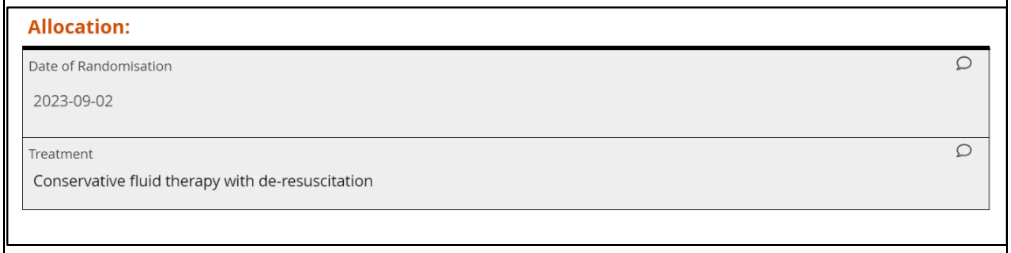
	
Previously admitted to ICU due to sepsis on this hospital admission	- If the patient has been admitted to ICU for sepsis during this same hospital admission, they are **NOT** eligible
Not expected to survive 90 days, due to pre-existing chronic (end-stage) disease	- Patient has previous medical history suggesting they are not expected to survive past day 90
Not expected to survive initial resuscitation (24 hours)	- Patient has received the initial fluid resuscitation and is not likely to survive a further 24hrs
Neutropenia (<0.5 neutrophils x109/L) due to chemotherapy/malignancy (but not due to sepsis)	- If the patient has neutropenia due to chemotherapy/cancer they are excluded, but if the neutropenia is due to sepsis they can still be included.
A source of infection that will require a prolonged course of antibiotics, for greater than 21 days (e.g., infective endocarditis, osteomyelitis, hepatic or cerebral abscess, tuberculosis)	- If the patient has an infection that requires a longer course of up to 21 days of antibiotics, then they are excluded.
Diabetic ketoacidosis (DKA) or hyperglycaemic hyperosmolar state (HHS)	- If the patient has any of the listed conditions they are excluded
Within 21 days of a spontaneous subarachnoid haemorrhage	- In the patient medical records there is a subarachnoid haemorrhage in the past 21 days
Diabetes Insipidus	- Patient has Diabetes Insipidus
Weight <40Kg	- Patient weight less that 40kg (88lbs or 6.3 stone)
Final Eligibility Check	

(Must be completed for correct randomisation)	
Is the subject eligible to participate in the fluid and diagnostic trials of the study?	- **YES,** must be selected for all inclusion criteria for patient to be eligible for randomisation, If **NO** is selected for any of the inclusion criteria, the patient is **NOT** eligible for randomisation. - **NO** must be selected for all exclusion criteria for the patient to be eligible for randomisation, If **YES** is selected for any of the exclusion criteria, the patient is not eligible for randomisation. - If yes is selected but the previous section suggested that the patient is not eligible e.g., inclusion criteria failed, a question in the exclusion criteria is a yes, a query will appear, recheck your answers when query appears.  - If patient is **not eligible**, a pop up will appear where you should specify if the inclusion or exclusion criteria has been violated 
Pre-randomisation Data **(Pre-randomisation MUST be completed AND saved for correct randomisation)**	
Has the patient been in hospital >48h or is known to have been readmitted within 30 days	- Is the hospital admission time/date more than 48 hours? - If this is second/ third etc time being admitted to hospital in the past 30 days select 'Yes'
Is the patient receiving vasopressors?	- Select yes if patient is on vasopressors at the time of randomisation
Is the patient receiving respiratory support?	- Is the patient <u>currently</u> receiving respiratory support, this includes: High Flow Nasal Oxygen (HFNO), Continuous Positive Airway Pressure (CPAP), Non-Invasive Ventilation (NIV), or Invasive Positive Pressure Ventilation (IPPV). - Respiratory support **does not** include 'Simple O_2'
Type of respiratory support	- Specify what type of respiratory support is being provided out of the three options: 1. High flow nasal cannula

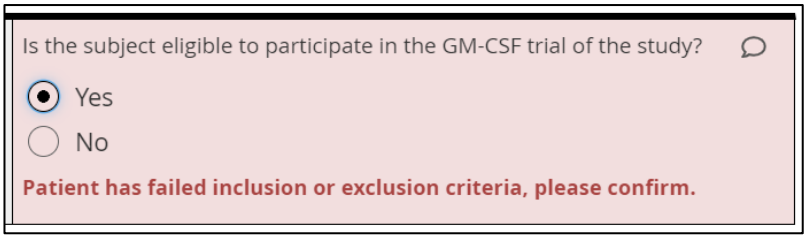
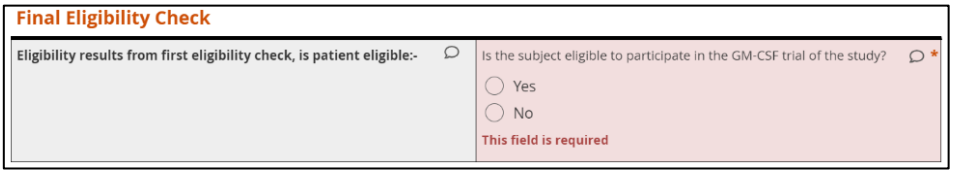
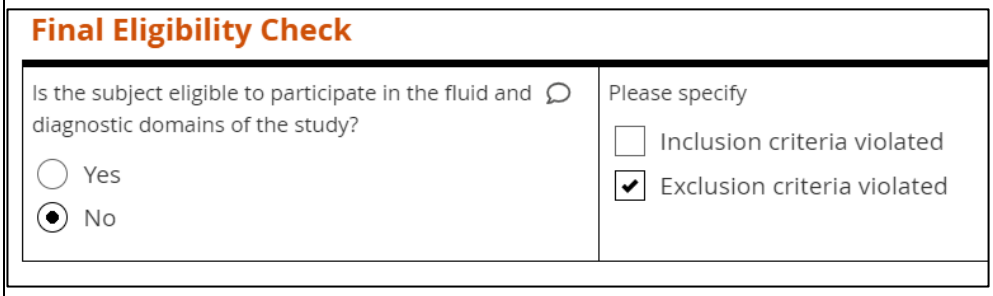
	2. Non-invasive ventilation only (HFNP or CPAP or BiPAP via a mask) 3. Invasive mechanical ventilation (CPAP through a tracheostomy or endotracheal tube, any mode of invasive mechanical ventilation via endotracheal or nasotracheal tube or tracheostomy tube, with or without positive end expiratory pressure (PEEP), High frequency Oscillation (Jet) ventilation) - Only one choice can be selected
Admission	
Hospital admission Date	- Enter the date the patient was admitted to the hospital for this current period of care. - The format is yyyy-mm-dd
Hospital admission time	- Enter the time the patient was admitted to the hospital. - The format is hh:mm
ICU admission date	- Enter the date the patient was admitted to the ICU in this hospital for this current period of care. - The format is yyyy-mm-dd
ICU admission time	- Enter the time the patient was admitted to the ICU. - The format is hh:mm
ICNARC CMP Number	- Enter the patient's specific ICNARC number, this is 8 digits
APACHE II Score	- The APACHE II score should be entered from the ICNARC database
SISAG Number (For Scotland Sites Only)	- **For Scottish Sites only** - If not a Scottish site select 'Not Applicable'
Randomisation 1 (Diagnostic) **Please see Randomisation Guidelines and Video on step-by-step instructions on randomisation, these include screenshots from database and can be found on the website: www.septictrial.co.uk/for-site-staff/**	
Randomisation Confirmation	
Confirm the participant details and eligibility in order to randomise this participant	- Participant ID, Gender and Month and Year of Birth are found at the top of the form, confirm these are correct and match the patient being randomised.
Has consent been obtained	- Has any consent been obtained? this can be:- patient, personal or professional. - If consent has not been acquired and it is not an emergency situation select 'No'

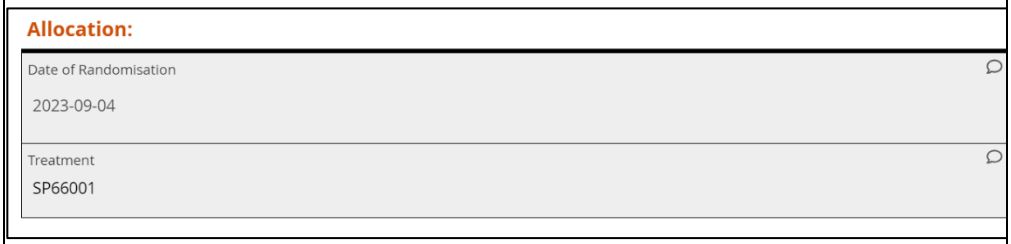
	- If this is an emergency situation and consent is to be obtained retrospectively select 'Enrolled without prior consent in emergency situation (Consent to be obtained later)
Vasopressor use	- This box is greyed out and the answer automatically generated from the pre-randomisation form. - Do not attempt to change this answer as the system will not allow it
Source of Infection	- This box is greyed out and the answer automatically generated from the pre-randomisation form. - Do not attempt to change this answer as the system will not allow it
Is the participant eligible for randomisation and stratifications completed?	- If the eligibility form, pre-randomisation, and this current form have been completed then all stratification has been completed and the patient is ready to be randomised. - When 'Yes' is selected, a 'Date of Randomisation' question will appear below.
Date of Randomisation	- Enter the date of randomisation. - Remember randomisation of the diagnostic arm must be within 24 hours of ICU admission. - The date of randomisation should be today's date. - If the date does not fit the criteria (24h from ICU admission, is in the future or not todays date) a query will flag, and you should recheck the date
Time of Randomisation	- Enter the time of randomisation. - This is not an automatic field and MUST be entered for the randomisation button below to appear. - The format is hh:mm [0-23] hrs [0-59] min
Select 'Randomise' below if participant is eligible and click 'Complete' to randomise the participant.	- When the date is complete, a 'Randomise' button will appear. - This button **MUST** be selected to correctly randomise the patient. - The form must be **COMPLETED** and not closed to correctly randomise the patient.  - When the form is completed proceed to the Randomisation Assignment Form to see the results of the randomisation

Randomisation assignment Diagnostic	
Date of Randomisation	- The date of randomisation will be shown automatically, this is taken from the Randomisation Confirmation form.
Treatment	- Treatment will be either: PCR-based pathogen testing and Procalcitonin (PCT) **OR** Standard Care - If the treatment box is empty when you initially view the form, try refreshing the page or exiting the form and selecting it again. - This is what a successful randomisation result would look like:  **Now continue to the fluid confirmation form to randomise to the fluid intervention.** **Print this page and file in the medical records.**
Randomisation 2 (Fluid)	
Randomisation Confirmation	
Confirm the Participant details and eligibility in order to randomise this participant	- Participant ID, Gender and Month and Year of Birth are found at the top of the form, confirm these are correct and match the patient being randomised.
Vasopressor use	- This box is greyed out and the answer automatically generated from the pre-randomisation form. - Do not attempt to change this answer as the system will not allow it
Receiving respiratory support	- This box is greyed out and the answer automatically generated from the pre-randomisation form. - Do not attempt to change this answer as the system will not allow it
Is the participant eligible for randomisation and stratification?	- If the eligibility form, pre-randomisation, and this current form have been filled out then all stratification has been completed and the patient is ready to be randomised. - When 'Yes' is selected, the randomisation button will appear below. - If 'No' is selected, then the participant is not eligible and will not be allowed to be randomised.
Select 'Randomise' below if participant is eligible	- This button **MUST** be selected to correctly randomise the patient.

and click 'Complete' to randomise the participant.	- The form must be **COMPLETED** and not 'closed' to correctly randomise the patient. - When the form is completed proceed to the Randomisation Assignment Form to see the results of the randomisation
Randomisation Assignment fluid	
Date of Randomisation	- The date of randomisation will be shown automatically, this is taken from the Diagnostic Randomisation Confirmation form.
Treatment	- Treatment will be either: Conservative fluid therapy with de-resuscitation **OR** Standard Care - If the treatment box is empty when you initially view the form, try refreshing the page or exiting the form and selecting again. - This is what a successful randomisation result would look like:  **Print this page and file in the medical records**
Screening (GM-CSF)	
Date of Visit	- Date the screening for GM-CSF is completed
Eligibility GM-CSF	
Inclusion Criteria for 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)	- Receiving invasive mechanical ventilation and expected to continue for the next 24hrs (CPAP through a tracheostomy or endotracheal tube, any mode of invasive mechanical ventilation via endotracheal or nasotracheal tube or tracheostomy tube, with or without positive end expiratory pressure (PEEP), High frequency Oscillation (Jet) ventilation **OR** - Receiving two modes of organ support such as RRT and Vasopressors
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.	- When 'Yes' selected the Value and Date boxes will appear below - The first lymphocyte count can be taken prior to ICU admission as long as the second count is the following day.
Value 1	- Enter the absolute lymphocyte count. - If the value is above 1.2 x109/L a query will flag asking to confirm and re-check the value

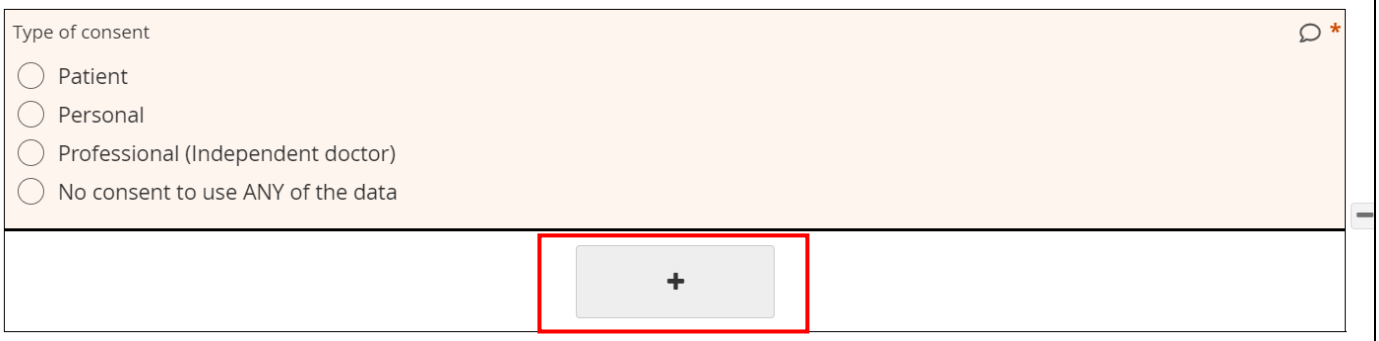
Date	- The format is yyyy-mm-dd
Value 2	- Enter the absolute lymphocyte count. - If the value is above 1.2 x109/L a query will flag asking to confirm and re-check the value
Date	- The second lymphocyte count must be a minimum of 12 hours after the first, or one calendar day after the first, if the date is wrong a query will flag and the date must be rechecked. - The format is yyyy-mm-dd
Exclusion criteria for GM-CSF	
More than 120 hours (5 days) since ICU admission	- The patient remains in ICU and is within 120hrs/5days since this ICU admission
Already receiving G-CSF or GM-CSF	- If the patient is already receiving G-CSF or GM-CSF products
A total white blood cell count >50 x10^9/L	- If the patient has a total white blood cell count of more than 50 x 10^9/L
Known to be pregnant or breastfeeding	- If the patient is known to be pregnant or breastfeeding/lactating *(confirmed via highly sensitive urine pregnancy test' sensitivity of 25 IU/L or better)*
Known recent (required treatment within the last 5 years) haematological malignancy	- The patient has received treatment within the last 5 years for haematological malignancy
Solid organ or bone marrow transplantation	- The patient has received a solid organ or bone marrow transplant
Patient weight >125kg	- The patient is more than 125kg in weight or 276lb or 19.7 stone
Known anaphylaxis or allergy to GM-CSF or yeast-derived products	- The patient has a known anaphylaxis allergy to GM-CSF or yeast-derived products – if this is documented in the medical records or if the site team are informed/aware of the allergy.
Final Eligibility Check	
Is the subject eligible to participate in the GM-CSF trial of the study?	- **YES,** must be selected for all inclusion criteria for patient to be eligible for randomisation, If **NO** is selected for any of the inclusion criteria, the patient is **NOT** eligible for randomisation. - **NO** must be selected for all exclusion criteria for the patient to be eligible for randomisation, If **YES** is selected for any of the exclusion criteria, the patient is not eligible got randomisation.

	- If yes is selected but the previous section suggested that the patient is not eligible e.g., inclusion criteria failed, a question in the exclusion is a yes, a query will appear, recheck your answers when query appears.   - If the patient was already found eligible for the GM-CSF arm in the initial eligibility form due to being over 24 hours since ICU admission, the answer will appear in the box on the left. - If patient is **not eligible**, a 'please specify' option will appear where you should specify if the inclusion or exclusion criteria has been violated.  **When this form is completed, remember to close the form by pressing 'Complete' this will save all the answers and will allow you to randomise properly.**
Randomisation 3 (GM-CSF)	
Randomisation Confirmation GM-CSF	
Confirm the Participant details and eligibility in order to randomise this participant	- Participant ID, Gender and Month and Year of Birth are found at the top of the form, confirm these are correct and match the patient being randomised.
Treatment Allocation from Randomisation 1	- Patients' allocation for Diagnostic Arm
Treatment Allocation from Randomisation 2	- Patients' allocation for Fluid Arm
Source of infection	- Source of Infection from previous form

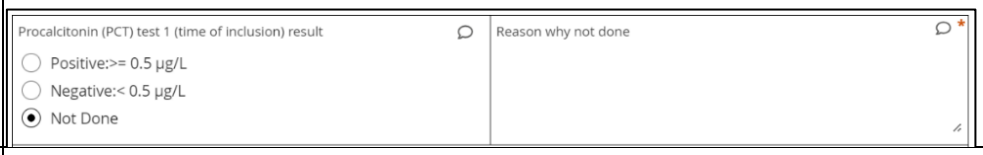
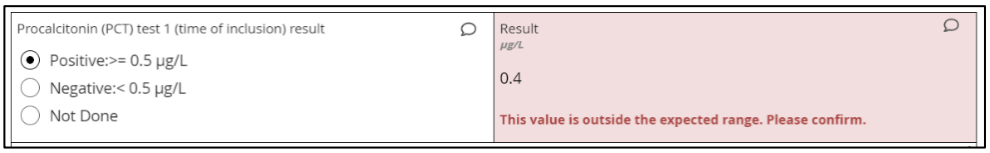
Is the participant eligible for randomisation and stratifications completed?	- Select 'Yes', if form 'Eligibility GM-CSF' has been completed and the patient is eligible – this will prompt the 'Date of Randomisation' to appear. - Select 'No' if patient is not eligible- this will not allow you to randomise the patient.
Date of Randomisation	- Enter the date of randomisation. - Remember randomisation of the GM-CSF arm must be within 120 hours of ICU admission. - The date of randomisation should be today's date. - If the date does not fit the criteria (120h from ICU admission, is in the future or not todays date) a query will flag, and you should recheck the date
Select 'Randomise' below if participant is eligible and click 'Complete' to randomise the participant.	- This button **MUST** be selected to correctly randomise the patient. - The form must be **COMPLETED** and not 'closed' to correctly randomise the patient. - When the form is completed proceed to Randomisation Assignment Form to see the results of the randomisation
Randomisation Assignment GM-CSF	
Date of Randomisation	- The date of randomisation will be shown automatically, this is taken from the Diagnostic Randomisation Confirmation form.
Treatment	- The allocated kit code will be in the Treatment Box - The allocated kit code should be 7 digits and should correspond to a kit you can find in the ICU. - If the treatment box is empty when you initially view the form, try refreshing the page or exiting the form and entering it again. - This is what a successful randomisation result would look like:  - **Print this page and file in the medical records**
Baseline	
Consent	
Type of Consent	- Choose the type of consent from the list: - Patient - Personal (PerLR) - Professional/Independent doctor (ProLR) - No consent to use ANY of the data

Date of Consent	- Date of the consent on the form identified above

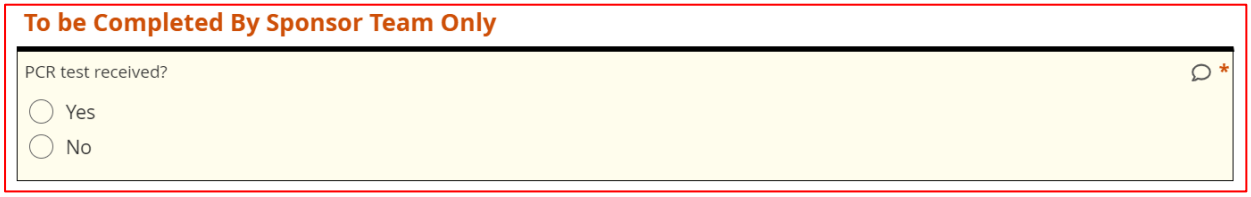
All consents must be included, to add more consents use the '+' symbol at the bottom.



Are there any restrictions to the consent	- Are there any restrictions to the consent given by the family member / next of kin or the patient. Please select any restrictions if specified by the family member/next of kin.
Date of Visit	
Visit date	- Choose the date the baseline is completed. - Baseline should be completed **on the same day** as randomisation. - If the patient is randomised to Diagnostic and Fluid initially and to GM-CSF a few days later, baseline data should be entered from the initial Diagnostic and Fluid randomisation. - For example: Randomisation Diagnostic and Fluid – 01/08/2023 Randomisation GM-CSF – 03/08/2023 Baseline Data – 01/08/2023
Co-enrolment	
Was the patient co-enrolled in any other clinical research studies	- Select yes or no depending on whether the patient is enrolled in any studies **PRIOR** to randomisation to SepTiC.
Study name/ Acronym	- Please provide the study name or acronym
Participant ID for the study co-enrolled	- Please provide the Participant ID of the patient in the co-enrolled study.
Trial Intervention (if known)	- Please provide the trial intervention the patient received if known
Date of enrolment in the study co-enrolled	- Please provide the Date the patient was enrolled in the study.
If the patient is enrolled to more than one study, press the plus button and enter the details of the other studies	
Demography	

Ethnicity	- Select the appropriate box corresponding to the patient's ethnicity. - If none of the options are suitable please use the 'Please Specify' option to capture the ethnicity.
Diagnostic This form should be completed for all patients including those who have not been randomised to the diagnostic intervention. Although it is not mandatory for those who have been randomised to standard of care, the information can be added if available.	
Procalcitonin (PCT) test 1 (time of inclusion) result	- Select the appropriate choice: • Positive:>= 0.5 µg/L • Negative:< 0.5 µg/L • Not done. - If the test was not done, please provide a reason in the 'Reason not done' box on the right, e.g.: patient randomised to standard care. 
Result	- Enter the result in µg/L - - If the value does not 'match' the previously chosen result a query text will appear, please check the value. 
Date of Procalcitonin (PCT) test 1	- The first Procalcitonin (PCT) test may be obtained prior to randomisation but not prior to ICU admission. Enter this date
Procalcitonin (PCT) test 2 (18-36 hrs later) result	- Select the appropriate choice: • Positive:>= 0.5 µg/L • Negative:< 0.5 µg/L • Not done- if not done enter reason why
Result	- Enter the result in µg/L - If the value does not 'match' the previously chosen result a query text will appear, please check the value, for example if the positive >0.5 is selected but then a value of <0.5 is added, a query will fire.
Date of Procalcitonin (PCT) test 2	- Enter the date the second Procalcitonin (PCT) test. - The second Procalcitonin (PCT) test **must** be done within 2 days (18-36 hours) of the first Procalcitonin (PCT) test.

If the patient was randomised to PCR Diagnostic a 'To be completed by Sponsor Team Only' section will appear, the study team will enter the results of the PCR test in this section.

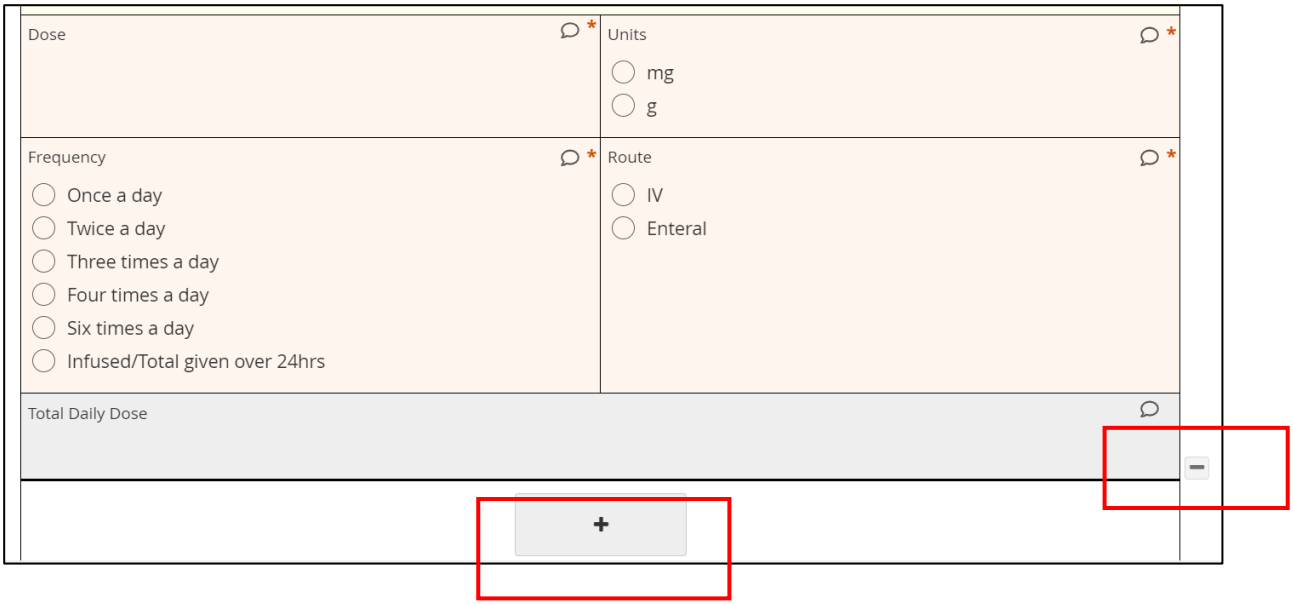


Baseline	
Results closest prior to inclusion	
Weight	- Enter the patient's weight in kilograms (kg) - Weight may be measured, documented in the medical records, obtained from the patients relative or estimated by clinicians. - If the last recorded weight is thought to be significantly inaccurate to the patient's current weight, provide the best estimate of the weight
Temperature	- Enter the patient's temperature in degrees Celsius (°C) - This result should be the last recorded temperature taken prior to randomisation
MAP	- Enter the patients mean arterial pressure in mmHg
Heart Rate	- Enter the patient's Heart Rate in bpm
Respiratory Rate	- Enter the patient's respiratory rate in bpm
$PaCO_2$	- Enter the patient's $PaCO_2$ in kPa
Site of infection	- This is the site of infection as determined by the treating clinician. - The site of infection must be documented. - Select one: - Lung - Abdomen - Urine - Primary bacteraemia - Neurological - Soft tissue/line - Other (Please specify if other)
Total fluid given in previous 24hrs (mls)	- Total volume of all fluid in 24h prior to inclusion - Please include all IV and enteral intake, including nutrition, IV fluids, drug volumes and blood transfusions.

Was the patient receiving RRT at the time of randomisation?	- Was the patient on Renal Replacement Therapy at the time of randomisation
Positive Blood cultures in the 72hrs before or after enrolment	- Have positive blood cultures been detected in the 3 days before or 3 after enrolment. - If at the time of entering baseline no results have come back, leave this box empty, close the form, and return to the form when the results are available. - If 'Yes' is selected, answer the following questions on which organisms have been detected. - If 'No' is selected move to the following question on sterile sites.
Organism	- You can pick **either/and** Bacteria and Fungi
Bacteria	- **Multiple** organisms in the drop-down list - If the organism detected is not found in the drop-down list, please enter the details in the 'Other' box
Fungi	- **Multiple** organisms in the drop-down list - If the organism detected is not found in the drop-down list, please enter the details in the 'Other' box
Positive cultures from a normally sterile site (abdominal/pleural/synovial fluid, CSF or abscess material)?	- Have positive blood cultures been detected in a normally sterile site prior to inclusion? - Select 'Yes' or 'No' - If 'Yes' is selected, answer the following questions on which organisms have been detected. - If 'No' is selected move to the 'Antibiotic Details' section of the form.
Site	- Enter the 'sterile' site that the sample has been taken from
Organism	- You can pick **either/and** Bacteria and Fungi
Bacteria	- **Multiple** organisms in the drop-down list - If the organism detected is not found in the drop-down list, please enter the details in the 'Other' box
Fungi	- **Multiple** organisms in the drop-down list - If the organism detected is not found in the drop-down list, please enter the details in the 'Other' box
Antibiotic Details	

Antibiotic details	- Select the antibiotics the patient is receiving for the suspected sepsis. - Multiple antibiotics can be selected. - The dose is not included at this time. - If the antibiotic is not included on the list, enter the antibiotic in the 'other' box. - Do not include any long-term prophylactic antibiotics

- Select one antibiotic at a time, if there have been multiple changes in antibiotics use the '+' sign found below the 'Total Daily dose' box to add another entry.
- If you have added another entry by accident, you can delete the extra antibiotic section by clicking the minus symbol on the right-hand side (shown above)

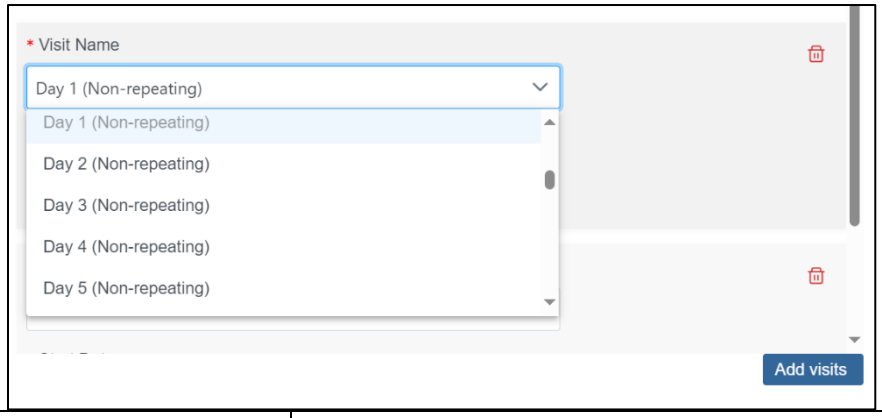


Dose	- Can be either with or without a decimal point
Units	- The dose of the antibiotic in grams or milligrams
Frequency	- Select how often the antibiotics are administered
Route	- Select whether the antibiotics are administered via IV or enterally
Total Daily Dose	- The dose is auto populated and cannot be changed
Laboratory Results **Closest lab result to time of inclusion** **If the sample was not done select 'Not Done'**	
Haemoglobin (Hb)	- Enter the haemoglobin recorded in the medical record closest to the time of inclusion in g/dL
White blood Count (WBC)	- Enter the white blood cell count recorded in the medical record closest to the time of inclusion in 10^9/L

Neutrophils (NEUT)	- Enter the neutrophils recorded in the medical record closest to the time of inclusion in 10^9/L
Lymphocytes (LYM)	- Enter the lymphocytes recorded in the medical record closest to the time of inclusion in 10^9/L
Platelets (PLAT)	- Enter the platelets recorded in the medical record closest to the time of inclusion in 10^9/L
Lactate	- Enter the lactate recorded in the medical record closest to the time of inclusion in mmol/L
Albumin (ALB)	- Enter the albumin recorded in the medical record closest to the time of inclusion in g/L
Creatinine (CREAT)	- Enter the serum creatinine recorded in the medical record closest to the time of inclusion in umol/L - Values obtained from a blood gas analyser are accepted
Bilirubin (BILI)	- Enter the bilirubin recorded in the medical record closest to the time of inclusion in umol/L
C Reactive Protein (CRP)	- Enter the CRP recorded in the medical record closest to the time of inclusion in mg/L
Bicarbonate (BICARB)	- Enter the bicarbonate recorded in the medical record closest to the time of inclusion in mmol/L
Sodium (NA)	- Enter the sodium recorded in the medical record closest to the time of inclusion in mmol/L
Samples **Refer to the Sample Manual for more specific instruction on sample collection**	
Diagnostic samples taken	- If the patient was randomised to PCR-based pathogen testing in the diagnostic arm of the study this sample should be taken on the same day as randomisation - Select 'Yes' if the sample was taken and enter the date and sample ID found on the tube label. - EDTA tube 10ml
Serum samples taken	- SST tube - Select 'Yes' if the sample was taken and enter the date and sample ID found on the tube label.
	- EDTA tube 5ml

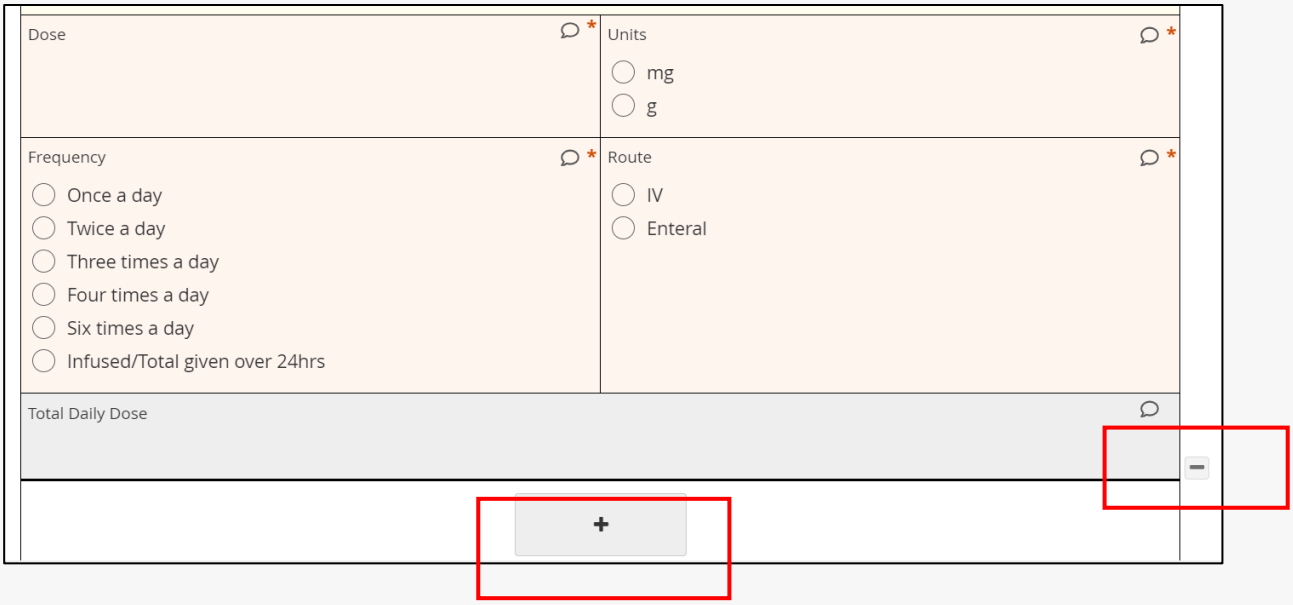
Baseline DNA sample taken	- Select 'Yes' if the sample was taken and enter the date and sample ID found on the tube label.
Baseline PAX gene tube taken	- Pax gene tube - Select 'Yes' if the sample was taken and enter the date and sample ID found on the tube label.
If the patient is not yet randomised to GM-CSF select not applicable and when closing the form 'Close' the form and do not 'Complete' it, this will allow you enter the GM-CSF specific samples if the patient is later randomised	
PAX gene tube taken at randomisation to the GMCSF trial	- Pax gene tube - Select 'Yes' if the sample was taken and enter the date and sample ID found on the tube label.
PAX gene tube taken on day 3 post randomisation into the GMCSF trial	- Pax gene tube - Select 'Yes' if the sample was taken and enter the date and sample ID found on the tube label.
PAX gene tube taken on day 5 post randomisation into the GMCSF trial	- Pax gene tube - Select 'Yes' if the sample was taken and enter the date and sample ID found on the tube label.
Microbiology	
After randomisation has the patient experienced another episode of infection? (defined as a new course of antibiotics (including anti-fungal therapy) 24hrs after stopping previous antibiotics, for the treatment of a new infection and excluding prophylaxis).	- Has an infection been detected other than one detected at randomisation? - Has the patient been prescribed a new course of antibiotics 24hrs after stopping the previous antibiotics - Excluding prophylactic antibiotics
Date	- The date the other infection was detected
Location of infection	- Location of the new infection
Clostridium Difficile infection? (PCR or toxin)	- Has Clostridium Difficile been detected in the site of the new infection
Date Clostridium Difficile sample taken	- If Clostridium Difficile has been detected, what date was the sample taken
Daily data 1-5 **This visit must be added and completed for each day the patient is in ICU. If the patient is discharged to the ward, this form should also be completed.**	

Forms for Day 1- Day 5 are all the same and have to be added individually:



Date of Visit	- The date corresponding to that particular daily data form. - For example, if the patient was randomised on 01-09-2023, then the Day 1 should be 01-09-2023, Day 2 is 02-09-2023, Day 3 is 03-09-2023. - This is **NOT** the date the eCRF is being completed
Are there any changes to antibiotics since Baseline (Including stopping and changes of dose)	- 'Yes', if there has been a change in the course of antibiotics since baseline - If 'yes', select the antibiotic that has changed below. - Select 'No' if there has been no change in antibiotics since baseline. - Select 'All Antibiotics stopped' if **ALL** antibiotics have been stopped - the patient is no longer receiving antibiotics
Name of antibiotic	- Select the antibiotic that has changed. - Select one antibiotic and fill out the dosage information for that antibiotic below. - If the antibiotics are not on the list, select 'other' and enter the name.

- Select one antibiotic at a time, if there have been multiple changes in antibiotics use the '+' sign found below the 'Total Daily dose' box to add another entry.
- If you have added another entry by accident, you can delete the extra antibiotic section by clicking the minus symbol on the right-hand side (shown above)

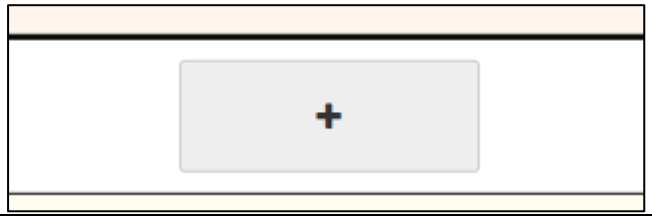


Dose	- Can be either with or without a decimal point
Units	- The dose of the antibiotic in grams or milligrams
Frequency	- Select how often the antibiotics are administered
Route	- Select whether the antibiotics are administered via IV or enterally
Total Daily Dose	- The dose is auto populated and cannot be changed
Any blood cultures taken on this day?	- If cultures have been collected on this day, select 'yes'
Organism	- If cultures have been collected on this day, select 'yes' and identify whether bacteria, fungi or virus have been detected. - If blood cultures were done there are no results, leave this field empty and return to it when results are - If blood cultures were taken, yet no growth was shown select the 'No Growth' option
IMP Given	- Select 'Yes' if the patient has been randomised to the GM-CSF intervention and the IMP has been administered. - Select 'N/A - Not randomised to GM-CSF' if the patient has not been randomised to the GM-CSF intervention. - Select 'No' if the patient has been randomised to the GM-CSF intervention but the IMP has not been given, please explain the reason in 'Please explain' box.
Daily total fluid input in the last 24hrs (mls)	- Total volume input on that day including IV and enteral intake, nutrition, drug volumes and transfusions.

Daily total fluid output in the last 24hrs (mls)	- Total volume output including urine, RRT, and drain outputs.
Daily fluid balance (mls)	- Auto calculated.
Cumulative fluid balance (mls)	- Auto calculated- daily fluid balance over the past few days
Peripheral oedema present in 2 or more sites?	- The presence of excess interstitial fluid in the tissue of the extremities, which causes palpable swelling is present in **two or more** sites
Is the patient cardiovascularly stable (noradrenaline <0.2 and not increasing)	- Select 'Yes' if the noradrenaline dose on each day was less than 0.2 mcg/kg/min and not increasing
Signs of Hypovolaemia	- Are there signs of Hypovolaemia including, if 'Yes' select all that apply in the multi-select boxes below:- - Skin mottling beyond the kneecap - Blood pressure not maintained despite up-titration of vasoactive drugs. - Serum lactate greater than or equal to 3 - Urine output <0.35ml/kg/k on day 1 only
Diuretics given	Question will only appear if the patient has been randomised to standard care for the fluid intervention arm.
Furosemide infusion given	Question will only appear if the patient randomised to conservative fluid therapy with de-resuscitation
Daily data 6-13 **This visit must be added and completed for each day the patient is in ICU. If the patient is discharged to the ward, this visit must be completed.**	
Date of Visit	- The date corresponding to that particular daily data form. - For example, if the patient was randomised on 01-09-2023, then the Day 1 should be 01-09-23, Day 2 is 02-09-2023, Day 3 is 03-09-2023. - This is **NOT** the date the eCRF is being completed
Are there any changes to antibiotics since previous day (Including stopping and changes of dose)	- 'Yes', if there has been a change in the course of antibiotics since baseline. - If 'yes', select the antibiotic that has changed below. - Select 'No' if there has been no change in antibiotics since baseline. - Select 'All Antibiotics stopped' if **ALL** antibiotics have been stopped/the patient is no longer receiving antibiotics

Select one antibiotic at a time, if there have been multiple changes in antibiotics use the '+' sign found below the 'Total Daily dose' box to add another entry.	
Dose	- Can be either with or without a decimal point
Units	- The dose of the antibiotic in grams or milligrams
Frequency	- Select how often the antibiotics are administered
Route	- Select whether the antibiotics are administered via IV or enterally
Total Daily Dose	- The dose is auto populated and cannot be changed
Any blood cultures taken on this day?	- If cultures have been collected on this day, select 'yes'
Organism	- If cultures have been collected on this day, select 'yes' and identify whether bacteria, fungi or virus have been detected. - If blood cultures were done and there are no results, leave this field empty and return to it when results are available. - If blood cultures were taken, yet no growth was shown select the 'No Growth' option.
IMP Given	- Select 'Yes' if IMP was given. - If dose was missed, please select 'No' and explain the reason for this in the free text box below - If the patient has already finished their 8 day course of IMP, please include this text or something similar: 'The patient has already finished their course of IMP'
Daily data 14-28 **This visit must be added and completed for each day the patient is in ICU. If the patient is discharged to the ward, this visit must be completed.**	
Date of Visit	- The date corresponding to that particular daily data form. - For example, if the patient was randomised on 01-09-2023, then the Day 1 should be 01-09-2023, Day 2 is 02-09-2023, Day 3 is 03-09-2023. - This is **NOT** the date the eCRF is being completed
Are there any changes to antibiotics since previous day (Including stopping and changes of dose)	- Yes', if there has been a change in the course of antibiotics since baseline e.g., new antibiotic, change in dose, change in frequency, change in route. - Select 'No' if there has been no change in antibiotics since baseline. - Select 'All Antibiotics stopped' if **ALL** antibiotics have been stopped - the patient is no longer receiving antibiotics
Select one antibiotic at a time, if there have been multiple changes in antibiotics use the '+' sign found below the 'Total Daily dose' box to add another entry.	
Dose	- Can be either with or without a decimal point

Units	- The dose of the antibiotic in grams or milligrams
Frequency	- Select how often the antibiotics are administered
Route	- Select whether the antibiotics are administered via IV or enterally
Total Daily Dose	- The dose is auto populated and cannot be changed
Any blood cultures taken on this day?	- If cultures have been collected on this day, select 'yes'
Organism	- If cultures have been collected on this day, select 'yes' and identify whether bacteria, fungi or virus have been detected. - Multiple organisms can be selected from the list. - If blood cultures were taken, yet no growth was shown select the 'No Growth' option.
Follow up (Day 95) **(Data taken from patient's medical records)**	
The follow up (Day 95) visit must be added and completed for ALL patients. Refer to the follow-up calculator to see when this visit is due for each patient. **The primary outcome of the study is 90-day mortality combined with clinical state over time. Please ensure this form is completed as close to Day 95 as possible.**	
Date of visit	
Date of Visit	Enter the date the data is being entered.
Follow-Up Day 95	
Has the patient been discharged alive from Hospital before the end of day 95?	Day 95 is calculated from the patient's initial randomisation into the study, up until the end of the calendar day on day 95. Select **one** option: -Yes -No – Died in Hospital *If selected, complete the date of death. Then save and close.* -No – Still in Hospital *If selected, the questions below (from respiratory support) will appear.*
	If 'Yes' is selected above the following questions will appear
Date of discharge	Enter the date the patient was discharged from hospital after randomisation. If the patient was re-admitted, enter the date the patient was **first** discharged from hospital.
Was respiratory support started for the patient during the ICU stay	Select 'Yes' if respiratory support was started at any point during initial ICU stay from randomisation until discharge. As a reminder respiratory support includes: - High flow nasal cannula, non-invasive ventilation or invasive mechanical ventilation.
If 'Yes' to respiratory support **Date Started**	Enter the date respiratory support was first started during initial ICU stay.

If 'Yes' to respiratory support **Has it been Weaned off**	Select from the options below: -Yes -No -Died on support
If 'Yes' to previous question **Date Weaned off**	Enter the date respiratory support was weaned off during ICU stay.
Was vasopressors/inotropes started for the patient during the ICU stay	Select 'Yes' if vasopressors/inotropes were started at any point during ICU stay from randomisation until discharge.
If 'Yes' to vasopressors/inotropes **Date Started**	Enter the date vasopressors/inotropes were first started during initial ICU stay.
If 'Yes' to vasopressors/inotropes **Have they been Weaned off**	Select from the options below: -Yes -No -Died on support
If 'Yes' to previous question **Date Weaned off**	Enter the date vasopressors/inotropes were weaned off during ICU stay.
Was the patient been readmitted to hospital prior to day 95?	Select 'Yes' if patient was readmitted to any acute hospital prior to Day 95. - Do not include non-acute hospitals, nursing homes or rehabilitation units. If 'Yes', then enter each hospital re-admission up to and including Day 95. To add more admissions, click the + icon. 
If 'Yes' to hospital readmission **Hospital Admission Number**	Auto-populated field, this box is read-only. Each hospital re-admission will be automatically numbered beginning from 1.
If 'Yes' to hospital readmission **Admission Start Date**	Enter the date the patient was re-admitted to hospital up to and including Day 95.
If 'Yes' to hospital readmission **Admission Stop Date**	Enter the date the patient was discharged during this hospital re-admission. Date can be up to and including Day 95.
Has the patient been readmitted to the ICU prior to day 95?	Select 'Yes' if patient was readmitted to **any** ICU prior to Day 95. ICU' is defined as any department overseen by an Intensive Care Clinician. If 'Yes' then enter each ICU re-admission up to and including Day 95. To add more admissions, click the + icon.
If 'Yes' to ICU readmission **Hospital Admission Number**	Auto-populated field, this box is read-only. Each ICU re-admission will be automatically numbered beginning from 1.
If 'Yes' to ICU readmission **Admission Start Date**	Enter the date the patient was re-admitted to ICU up to and including Day 95.
If 'Yes' to ICU readmission **Admission Stop Date**	Enter the date the patient was discharged during this ICU re-admission. Date can be up to and including Day 95.
Is the patient alive at the end of day 95?	Select 'Yes' if patient was alive at Day 95. Select 'No' if the patient died on or prior to Day 95. If the patient was discharged from hospital prior to day 95 and then proceeded to pass away, please confirm the day that they passed away,

	you can move straight to the Day 365 form and enter the date the patient passed away.
Date confirmed	Enter the date the patient was confirmed alive at Day 95. This must be completed as close to Day 95 as possible, within a 14 day time window.

Follow up (Day 180)

This visit should be completed within 14 Days of Follow Up (Day 180).

Please verify whether the patient is alive at D180, if the patient has passed away please do not raise this visit and complete the D365 form.

Date of Visit Follow Up (Day 180)	
Date of Visit	- The date the questionnaire was completed.

EQ-5D-5L

The EQ-5D-5L Health Questionnaire is a standardised instrument, developed by Euro Qol, for use as a measure of health outcome.

The questionnaire can be administered over the telephone using the **EQ-5D-5L Script for Telephone Interview**. It is recommended that the interviewer have a copy of the script in front of them as they administer over the telephone and when face to face in the hospital.

Patients can be excluded from the EQ-5D-5L if they are unable to speak English.

If the patient is incapacitated due to their medical condition and is unable to complete the questionnaire, a proxy can be interviewed using the same script. Proxies are defined as a family caregiver such as a spouse, sibling, or offspring or if unavailable a friend.

This Questionnaire should be completed within 14 Days after the follow up (Day 180) is due. If the questionnaire is not completed during this time (if the patient/proxy is not available) please exclude the questionnaire, do not complete if after the 14 day time window.

MOBILITY	Select the option that the patient has described/selected
SELF-CARE	Select the option that the patient has described/selected
USUAL ACTIVITIES	Select the option that the patient has described/selected
PAIN/ DISCOMFORT	Select the option that the patient has described/selected
ANXIETY/ DEPRESSION	Select the option that the patient has described/selected
We would like to know how good or bad your health is TODAY. Please indicate on the scale (0-100) to indicate how your health is TODAY.	Enter the number that the patient has stated

MONTREAL COGNITIVE ASSESSMENT/MoCA-BLIND

Only site staff who have been trained and hold a training certificate should complete the MoCA-BLIND assessment. This assessment can be carried out over the telephone.
The MoCA-BLIND assessment should be printed off and completed by the assessor whilst on the telephone with the patient and the answers subsequently transcribed onto the database.

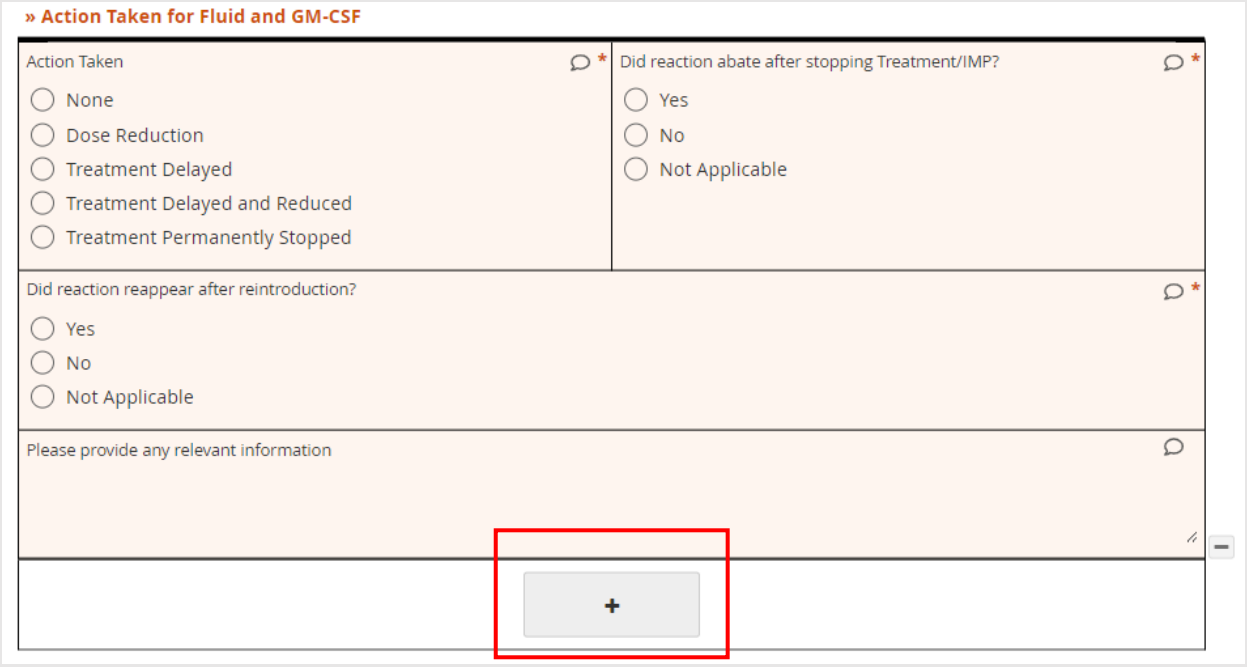
This Questionnaire should be completed within 14 Days after the follow up (Day 180) is due. If the questionnaire is not completed during this time (if the patient/proxy is not available) please exclude the questionnaire, do not complete if after the 14 day time window.

Memory – was this completed	Select the correct option (Yes / No / Not Done)
Attention – Read list of digits	Select the score given for this question (0/1/2) or select 'Not Done'
Attention – Read list of letters	Select the score given for this question (0/1) or select 'Not Done'

Attention – Serial 7 subtraction	Select the score given for this question (0/1/2/3) or select 'Not Done'
Language - Repeat	Select the score given for this question (0/1/2) or select 'Not Done'
Language - Fluency	Select the score given for this question (0/1) or select 'Not Done'
Abstraction	Select the score given for this question (0/1/2) or select 'Not Done'
Delayed recall - With no cue	Select the score given for this question (0/1/2/3/4/5) or select 'Not Done'
Orientation	Select the score given for this question (0/1/2/3/4/5/6) or select 'Not Done'
Total score	**Read-only field.** The total score is automatically calculated by the system according to the scores given in previous questions.
Follow up (Day 365) **(Data taken from patient's medical records)**	
The follow up (Day 365) must be added and completed for **all** patients. Please ensure this form is completed as close to Day 365 as possible.	
Date of visit	
Date of Visit	The date the questionnaire was completed.
Follow up (1 year)	
Is the patient alive 1 year after randomisation?	The 1-year follow-up information should be taken from the patient's medical records. No patient contact is required. If the patient was discharged to another hospital, site staff should endeavour to collect this information through contacting the other hospital.
If 'Yes' to previous question: **Date confirmed**	Enter the date patient was confirmed alive, 1 year following randomisation. This date should be as close to Day 365 post randomisation as possible but should not be prior to this date.
If 'No' to previous question: **Date of death**	Enter the date of death from the death certificate/patients' medical records.
Serious Adverse Event	
Type of report	Select whether this is a First, Interim or Final type of report
Was the trial treatment given at full protocol does prior to event?	Select 'Yes' if the IMP was given to the patient as per protocol. Select 'Yes' if Conservative fluid therapy was followed as per protocol if the patient was randomised to this arm. Select 'No' if the protocol was not followed and provide details in the box that appears below the question, this should include how
Why was the event serious?	Choose the most serious outcome of the SAE
Where did the SAE take place?	Select where the SAE took place, if none of the options apply, please select other and enter the location
Briefly describe SAE	Include relevant symptoms, body site, lab tests and treatments received for management of the SAE
Details of SAE	
Serious Adverse Event Term	Provide a few word summary of the SAE
Date of Notification	The date the site was notified of the SAE
Date of Onset	The date the SAE began
Ongoing	'Yes', the SAE is ongoing. 'No' the SAE has ended. - If 'No' selected enter the date SAE ended
Severity	Select the severity of the SAE
SAE Status	Current status of the SAE at the time of data entry
This section shows which interventions to which the patient was randomised.	

Action Taken for Fluid and GM-CSF

The diagnostic arm does not involve any direct treatment/ IMP therefore the 'Action Taken' section should be completed for the Fluid and GM-CSF intervention. To make multiple entries use the '+' symbol:

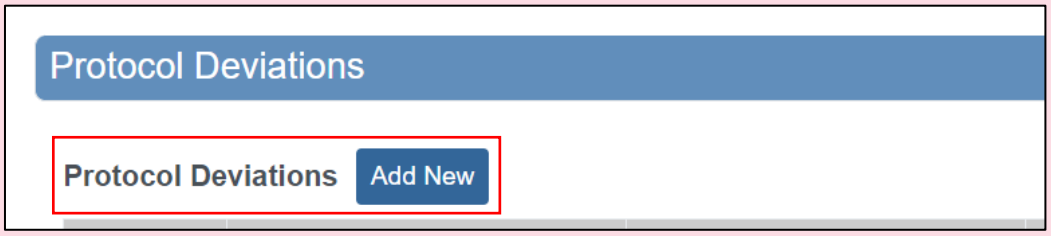


Action Taken	Select the appropriate action relating to either the fluid or GM-CSF arm
Did reaction abate after stopping Treatment/IMP?	Select 'Yes' if the reaction subsided after stopping treatment/ IMP Select 'No' if the reaction did not subside after stopping the treatment/IMP Select 'Not Applicable' if there was no change in dose or the treatment/IMP continued as per protocol
Did reaction reappear after reintroduction?	Select 'Yes' if the reaction reappeared after re-introduction of the treatment/ IMP Select 'No' if there was no reaction after the treatment/IMP was re-introduced. Select 'Not Applicable' if there was no change in dose or the treatment/IMP continued as per protocol
Please provide any relevant information	Relevant information would include: the dose after reduction, how much of a delay there was in re-introducing the treatment etc
Causal relationship section to be completed by PI only	
Causal Relationship to Event Diagnostic	Select the causal relationship relevant to the diagnostic arm.
Causal Relationship to Event Fluid	Select the causal relationship relevant to the fluid arm.
RSI Version used to assess (IB/SmPC)	Enter the version of the IB that was used to assess the SAE.

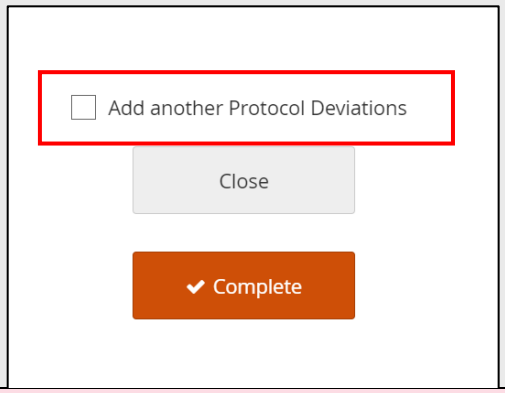
Causal Relationship to Event GM-CSF	Select the causal relationship relevant to the GM-CSF arm.
Other Treatments at Time of Event	
Are there other important medication given at time of event including treatment of SAE?	Document any relevant concomitant medication, radiotherapy, surgery, or palliative care if necessary. Do not include therapy given for the management of the SAE. Select 'Yes' if important medication given at time of event. When selected further questions on details of medication will appear Select 'No' if no important medication given at time of event.
If 'Yes' to above - Treatment	Give the generic drug/treatment name given in the last 30 days.
Dosage	What dose of the drug was given
Units	Choose the units from the drop-down list
Frequency	Choose the frequency of administration from the drop-down list
Route of Administration	Select the route of administration from the drop-down list
Start Date	Enter the date the drug/treatment was started
Ongoing	Select 'Yes' if at the time of the SAE the patient was receiving the drug/treatment. Select 'No' if the last dose of the drug/treatment was given prior to the onset of the SAE
End Date	If 'No' selected in prior question enter the date the last dose of the drug/treatment was given
Action Taken	Select the appropriate action relating to the drug/treatment
Use the '+' symbol to add another entry – all relevant concomitant medication, radiotherapy, surgery, or palliative care should be added.	
Any Other Relevant Information (Such as the participant's medical history, drug or alcohol abuse, family history, findings from special investigations etc including treatment of SAE)	Include any relevant findings
Was this event expected in view of the patient's clinical history?	Select 'Yes' if expected. Select 'No' if not expected.
Medical Coding To be Completed by Sponsor Team Only- Do not enter data	
SAE Verbatim	Not applicable to sites
Select LLT (Low-Level Term) -> PT (Preferred Term)	Not applicable to sites
Low Level Term (LLT)	Not applicable to sites
Preferred Term (PT)	Not applicable to sites
Enter the PT (Preferred Term) from above to complete the MedDRA hierarchy	Not applicable to sites
Preferred Term (PT)	Not applicable to sites
Low Level Term (LLT)	Not applicable to sites
High Level Term (HLT)	Not applicable to sites
High Level Group Term (HLGT)	Not applicable to sites
System Organ Class (SOC)	Not applicable to sites

Protocol Deviation

This form should be added and completed for **all** protocol deviations/violations. All protocol deviations can be submitted under the protocol deviation tab:



Date Deviation/Violation Reported	Enter the date the protocol deviation/violation has been reported
Definition of Protocol Deviation/Violation	Briefly define the deviation/ violation
Protocol Deviation or Violation	Select whether this was a protocol deviation or violation: Deviation: a protocol deviation occurs when a process or criteria has not been actioned in line with the approved protocol. Violation: a protocol violation occurs when there is a consistent variation in practice from the defined protocol. Non-compliance with the inclusion and exclusion criteria is always classed as a significant protocol violation.
How was Deviation / Violation Identified?	Select how the deviation/violation was identified, if none apply, select 'other' and specify in the 'Please specify' box
Classification of Protocol Deviation/Violation	Select one of the classifications. Only one can be selected
Description of Deviation/Violation	Describe in detail the deviation/violation
Date of Deviation/Violation Occurred	Enter the date the deviation/violation occurred
Response to Deviation / Violation (e.g., CAPA)	Enter any Corrective Action Preventive Action that have been taken/ implemented as a response to this deviation/violation
Is this a potential serious breach?	Select 'Yes' or 'No'
Was Deviation/Violation reported to CA (Competent Authority) as a serious breach?	Not applicable to sites
If multiple deviations are being entered at once, you can add another form automatically by selecting 'Add another Protocol Deviation' above the close form button.	



End of Study

This form should be added for any patients who withdraw/ partially withdraw from the study prior to the 1-year follow-up, this should be documented in the patient notes and on this eCRF.

Otherwise, this form should be added and completed for **all** patients **after** the 1-year follow-up is complete.

Did the subject complete the study as planned?	Select 'Yes' if the patient has completed the follow-up as per protocol or if the patient died on or before follow-up (Day 365). If 'Yes' there is no further data to complete, the form can be saved and closed. Select 'No' if the patient has withdrawn from all or part of the study.
If 'No' is selected, the following questions will appear:	
Date of withdrawal	Enter the date patient withdrew from the study
Type of withdrawal	Choose one of the following options, whichever is most applicable: - Withdrawal from study treatment only - Withdrawal from study follow up only - Withdrawal from all study treatment and follow up
Primary reason for Withdrawal	Choose one of the following options: -Adverse Event -Consent Withdrawn -Subject did not meet Inclusion/Exclusion Criteria -Lost to follow-up -Sponsor Decision -Investigator Decision -Other *(if none of the options listed above)*
Please specify	If 'Other' is selected for previous question, enter the reason for withdrawal
Consent	If a patient has withdrawn consent from the study, site staff should clarify with the patient if they are happy to be contacted/ continue to consent to data linkage/follow-up. Select one of the following from the list below: -Withdrawal of consent to be contacted for any purposes related to the study - Consent given for data linkage only - Consent given for follow up only - Lost to follow up - Other - Not Applicable (only select this option if the patient has **not** withdrawn any consent)
Other	If 'Other' is selected for previous question, enter the reason for withdrawal

7. CRF COMPLETION QUERIES

If you have any questions, please contact your trial management team.

8. VERSION HISTORY

Version Number	Date	Author	Description
V1.0	14.11.23	Paulina Kuswik	New Manual
V2.0	11.06.24	Paulina Kuswik	Reviewed and updated manual to include changes made in 'SepTiC OpenClinica Update 1'

AMENDMENTS

Section	Amendment