



ADAPT-Sepsis TRIAL

BiomArker-guided Duration of Antibiotic treatment in hospitalised PaTients with Suspected Sepsis

CRF COMPLETION GUIDELINES



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General Instructions for CRF Completion

- All dates should be recorded in the format DD-MM-YYYY format.
- When completing incomplete dates, provide as much information as possible. If Date is not known, enter the first of the month. If month is not known, enter January e.g. 01/Jan/2017.
- Enter all times in the 24-hour format.
- Tick 'Yes' or 'No' where applicable. Do not leave any Yes/No questions blank.
- When entering numerical values, ensure the correct unit is used.
- Where available, enter numerical values to two decimal places. If decimal values are required but not known, enter 0 e.g. 92.00 kg.
- All CRFs must be completed, signed and dated by an appropriately trained member of staff who is listed on the Site Signature and Delegation Log with the relevant trial responsibilities.

General Instructions for Remote Data Entry CRF Completion



- When using the Remote Data Entry System (RDE), CRFs are accessed by navigating to the 'Data Entry' tab and selecting either 'Daily Data Tracking', 'Scheduled Events' or 'Unscheduled Events' (Figure 1).
- To navigate to a particular participant, type the participant trial number in the 'Search by TNO' field and press enter. When accessing either the 'Scheduled Events' or 'Unscheduled Event's page, you can also use the arrows at the bottom of the window to cycle through the participants (Figure 1).
- Click the plus symbol ( Open) to begin a new form or the edit symbol ( Open) to edit an existing form.
- Daily Data Tracking includes the *Daily Data – Intervention Form* and the *Daily Data Follow-up Form*. Daily Data collection is triggered by updating the 'Daily Data Tracking' tab.
- Scheduled Events include the *Randomisation Form*, *Baseline Form* and *28 Day Follow-up Form*.
- Unscheduled Events include the *Daily data – Intervention*, *Daily Data- Follow-up*, *Antibiotics Form*, *Discharge Form*, *Readmission Form*, *Withdrawal Form*, *Notification of Death Form* and *Protocol Deviation Form & File Note*.
- At the end of each form on the RDE system there is a 'Form Completion' section which must be completed before saving the form. Here, the individual who completed the form should select their name from the drop down list, enter the date signed and complete 'Form Status' to categorise the information within the form (Figure 2). Once data is entered into the form, one of three statuses must be selected:
 - If the form has been completed, all of the fields have been entered and there is no outstanding data, mark the form as 'Clean'.
 - If the form has been completed but some data is unattainable, leave these fields blank and mark the form as 'Clean with unattainable missing data'.
 - If trial office identify any information in a CRF that they would like to query, the form will be marked with 'Data Query'.

Figure 1: Accessing Scheduled Events Forms

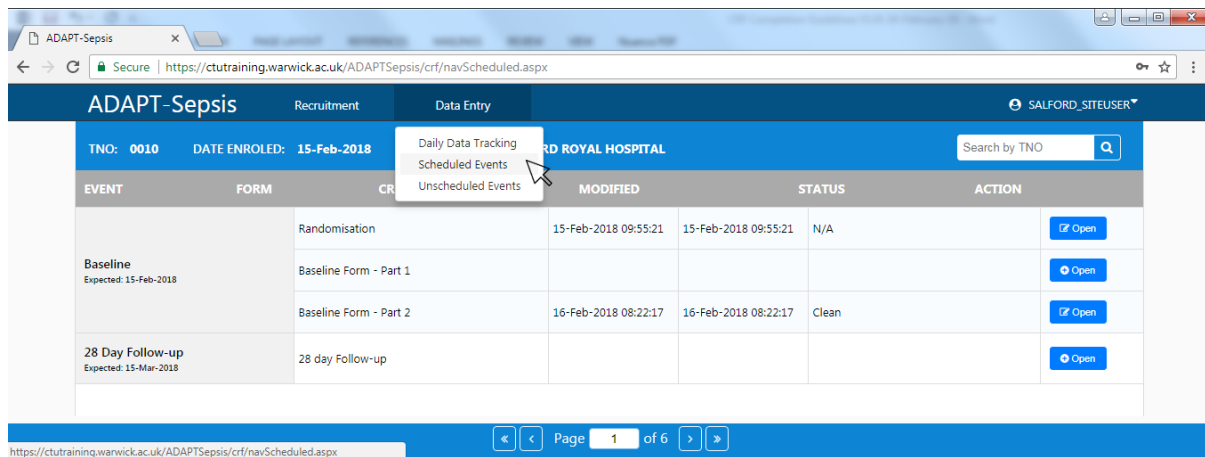


Figure 2: Form Completion Section

The screenshot shows the 'FORM COMPLETION' section of the web application. It contains three input fields: 'Form completed by' (a dropdown menu), 'Date signed' (a text input field), and 'Form status' (a dropdown menu). Below the input fields are two buttons: 'Save' and 'Cancel'.

General Instructions for Paper CRF Completion

- If completing a paper CRF, participant initials and trial number should be recorded at the top of each page.
- Paper CRFs should be completed in black ball point pen in clear legible handwriting. The *Eligibility Form* and *Serious Adverse Event Forms* must always be completed using a paper CRF. Other CRFs may be completed on paper forms in the event that the database is unavailable for a prolonged period of time. This information will later be transcribed onto the database, copies made of the paper CRFs and originals forwarded to trial office.

1. Eligibility Form

- The *Eligibility Form* should be completed on a paper CRF and sent via post to WCTU within 4 weeks of completion. This information will not be entered onto ADAPT-Sepsis Database system via Remote Data Entry (RDE).
- This form acts as a checklist to confirm eligibility and should be completed prior to randomisation.
- The information documented on the *Eligibility Form* **MUST** be agreed and signed off by a treating clinician on delegation log.
- Participant Trial Number will not be known until the participant has been successfully randomised. When the trial number is given at randomisation, please enter the number at the top of the CRF before you send it to the trial office.

A. Participant Inclusion Checklist

- The relevant answers should be ticked for each participant. In order for a patient to be eligible, all answers in this section must fall in the unshaded boxes (Yes). If any answers fall in a shaded box (No), the patient will not be eligible for the study and should not be randomised.

B. Participant Exclusion Checklist

- The relevant answers should be ticked for each participant. In order for a patient to be eligible, all answers in this section must fall in the unshaded boxes (No). If any answers fall in a shaded box (Yes), the patient will not be eligible for the study and should not be randomised.
- Further examples to provide additional guidance for completing exclusion criteria **2.** and **3.:**
 - Bone marrow transplant
 - Chemotherapy induced neutropenia (<500 neutrophils per ml)
 - Infections for which long-term (>21 days) antibiotic treatment is strongly recommended (e.g., infective endocarditis, osteoarticular infections, anterior mediastinitis after cardiac surgery, hepatic or cerebral abscesses, chronic prostatitis, or infection with *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, or *Toxoplasma gondii*)
- Patients receiving or due to receive/re-establish antibiotics for bacterial infection prophylaxis within 28 days are excluded from this trial.

C. Is the patient eligible for randomisation?

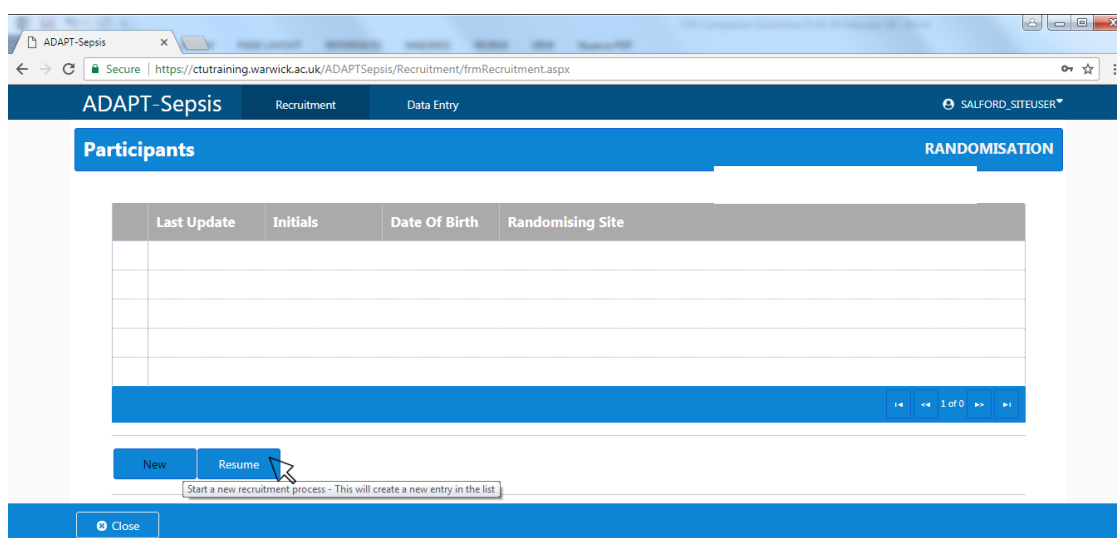
- In order for the patient to be eligible for the study, all unshaded options need to have been ticked for sections A and B (see above). If the patient is eligible, please tick 'Yes' and proceed to randomisation. If ineligible, please do not enter the patient into the trial.

2. Randomisation Form

- Prior to randomisation, the *Eligibility Form* should be completed. A patient should only be randomised if they meet the eligibility and exclusion criteria.
- This form should be completed at T0 - the time of randomisation.
- To perform a randomisation:
 - Click on the 'Recruitment' tab of the ADAPT-Sepsis database (Figure 3).
 - Select either 'New' to start a new randomisation or 'Resume' to continue a randomisation.
 - Answer the questions as prompted to complete the randomisation (Figure 4).
- Once randomised, the *Randomisation Form* can be viewed by navigating to the 'Scheduled Events' tab under 'Data Entry' (Figure 1).

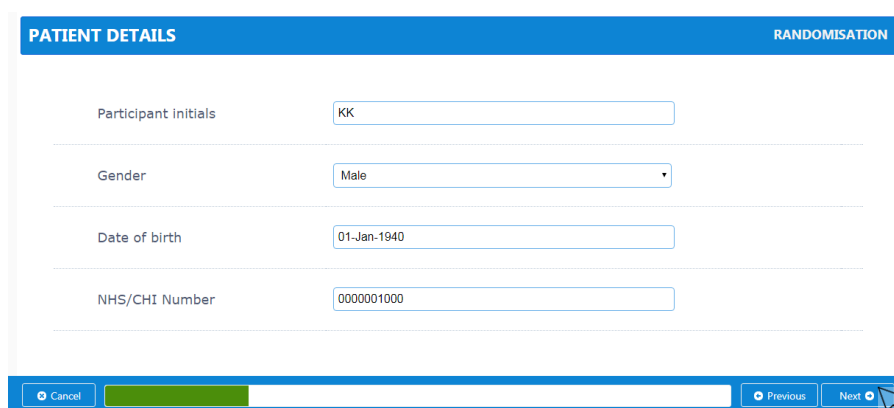
If it later becomes apparent that information provided at randomisation was incorrect, please edit the information. Once entered, some fields, will become locked to editing. If any of these locked fields are incorrect and need to be amended, please contact the ADAPT-Sepsis Trial Team at Warwick CTU to notify them of any necessary corrections to make.

Figure 3: Starting a Randomisation



The screenshot shows a web browser window with the URL <https://ctutrainin.warwick.ac.uk/ADAPTSepsis/Recruitment/frmRecruitment.aspx>. The page has a blue header with 'ADAPT-Sepsis' and navigation tabs for 'Recruitment' and 'Data Entry'. The main content area is titled 'Participants' and 'RANDOMISATION'. It features a table with columns: 'Last Update', 'Initials', 'Date Of Birth', and 'Randomising Site'. Below the table are two buttons: 'New' and 'Resume'. A tooltip over the 'Resume' button reads: 'Start a new recruitment process - This will create a new entry in the list'. A 'Close' button is at the bottom left.

Figure 3: Performing a Randomisation. Answer the questions as prompted using free text entry and drop down menus. Answer every question then press next to proceed to the next section.



The screenshot shows the 'PATIENT DETAILS' form. It has a blue header with 'PATIENT DETAILS' and 'RANDOMISATION'. The form contains four fields:

- Participant initials: KK
- Gender: Male (dropdown menu)
- Date of birth: 01-Jan-1940
- NHS/CHI Number: 0000001000

At the bottom, there are three buttons: 'Cancel', 'Previous', and 'Next'. A green progress bar is visible above the 'Previous' and 'Next' buttons.

A. Patient Details

- Write the initials of the participant's first/given name and surname/family name only.
- The following formats should be used for all dates: 06-Jun-1956.
- The patient's NHS or CHI number should be entered in the numerical field as applicable.

B. Consent

- Please confirm the types of consent acquired. See Table 1 for guidance. Further advice is available in the trial protocol.
- Please complete date consent was obtained.
- Consent version and date will be noted in the footer of the CRF on the bottom right. Please enter version number in the format 1.0.

Table 1: Types of Consent

Personal Consultee/Next of Kin	A friend or relative who has considered the wishes of the patient and if they would have any objections to taking part in this research, if they were well enough to think about this information for themselves.
Trust Nominated Consultee	A professional who has been provided with information about this research and has agreed to be contacted to consider the participation of a patient, when a Personal Consultee cannot yet be identified, or has declined to undertake this role. This individual will be independent to and have no other involvement in this study. <i>Please note – this does not apply to Scotland or Northern Ireland.</i>
Guardian or Welfare Attorney	An individual nominated by the patient who will consider the patient's wishes and if they would have any objection to taking part in this research, if they were well enough to think about this information for themselves. <i>Please note - this applies to Scotland only.</i>

C. Eligibility

- Please tick to confirm whether the participant fulfils the eligibility criteria. The patient should only be randomised if 'Yes' can be ticked.
- Please tick to confirm whether the clinician has completed the *Eligibility Form*. The patient should only be randomised if 'Yes' can be ticked.
- Please complete date eligibility confirmed.

D. Stratification Factors

- Please tick 'Yes' to confirm whether the patient has suspected septic shock or 'No' for suspected sepsis. See the Table 2 for further advice.
- Please tick to confirm whether the patient had surgery within the last 72 hours or not.
 - Definition of Surgery- A surgical procedure conducted in a hospital operating theatre whether under general, regional or local anaesthetic.

Table 2: Definition of Suspected Sepsis and Suspected Septic Shock Mervyn Singer et al. *The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)*.

	Sepsis	Septic Shock
2015 Definition:	Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria:		Sepsis and vasopressor therapy needed to elevate MAP \geq 65mm Hg and lactate $>$ 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation

E. Randomisation Details

- If completing a paper randomisation form (see *Emergency Randomisation Procedure* below), please complete this section after randomisation has been completed. This information will be prepopulated on the RDE system.
- Please enter the participant trial number once this has been allocated (see Figure 4).
- Please enter date and time of randomisation.

Figure 4: Randomisation Confirmation Page. Once a randomisation is completed, a participant trial number will be allocated. This confirmation can be printed and filed.

The screenshot shows a confirmation window titled 'PARTICIPANT TRIAL NUMBER' and 'RANDOMISATION'. It contains two fields: 'Participant Trial Number' with the value '0001' and 'Date and time of randomisation' with the value '13-Dec-2017 10:03'. At the bottom, there are 'Close' and 'Print' buttons.

Emergency Randomisation Procedure

- In the event that the ADAPT-Sepsis database is unavailable, the emergency randomisation procedures should be followed.
- A dedicated randomisation service, hosted by Warwick Clinical Trials Unit, is available 9am to 5pm, Monday to Friday.
- Please complete a paper *Randomisation Form* as per the instructions above and send via post to WCTU within 2 weeks of completion.
- Then call **02476 150402** to be guided through the randomisation.

- The randomisation team will allocate a participant trial number and you will receive a randomisation confirmation email.
- This process should only be followed if the database is unavailable.

3. Baseline Form

- When using the RDE system, the *Baseline Form* is accessed by navigating to the 'Data Entry' tab and selecting 'Scheduled Events' (Figure 1).
- Part 1 and Part 2 of the *Baseline Form* are located in separate forms on the RDE system.
- Both Part 1 and Part 2 should be signed and dated, upon completion.

Part 1

- Part 1 should be completed as soon as possible after randomisation.

A. Baseline Characteristics

- **A4-** Core body temperature should be entered in degrees centigrade, e.g. 37.0. This information should be captured from measurements taken around the time of diagnosis.
- **A5-** White cell count should be entered in the units $\times 10^9/L$. This information should be captured from measurements taken around the time of diagnosis.

B. Critical Care Admission and Origin

- **B1-** Critical care admission category refers to the reason for initial hospital admission. This may not relate to sepsis.
- **B1-** Please select one option from the drop down list for critical care admission category. If the applicable category is absent, select 'Other' and briefly specify using free text entry.
- **B2-** Origin refers to the hospital department which the patient was initially admitted via.
- **B2-** Please select one option from the drop down list for origin. If the applicable category is absent, select 'Other' and briefly specify using free text entry.

C. Initial Care Bundle, Within 12 hours of presentation and Within 24 hours of presentation

- Please tick 'Yes' or 'No' for all questions. 'Not relevant' can also be ticked for Source control.
- *"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis or septic shock ascertained through chart review.

D. Trial Specific Procedures

- **D1-** Please record the date and time the first study blood sample was collected.

E. qSOFA, SOFA and APACHE II scores

- For the purposes of the ADAPT-Sepsis trial the following SOFA and qSOFA assessments will be calculated:

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiration					
Pao ₂ /Fio ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b	
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio₂, fraction of inspired oxygen; MAP, mean arterial pressure; Pao₂, partial pressure of oxygen.

^a Adapted from Vincent et al.²⁷

^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

- #Conversion of mmHg to kPa = mmHg × 0.13332
- qSOFA should be recorded as close to the first clinical decision of suspected sepsis/septic shock as possible.
- If the participant is receiving assisted ventilation, please confirm whether this was invasive or non-invasive using the drop down menu.
- PLEASE NOTE- there is currently an error on the database which limits the values which can be entered for highest creatinine. If the score cannot be entered onto the system, please leave this blank and trial office will flag this as a data query once the issue is resolved.
- If a Glasgow Coma Score is provided, skip the remaining neurological questions.
- If it is not possible to provide a Glasgow Coma Score, tick to confirm whether the participant is sedated and whether the participant has an endotracheal tube for ventilation. If 'Yes' is ticked for this question, this should be recorded as invasive under assisted ventilation.
- Please provide either an APACHE II score or CMP number. If APACHE II scores are not calculated locally, please refer to the supplied calculation booklet.

F. Co-enrolment

- **F1-** If the participant is co-enrolled in other trials that have agreed co-enrolment with Adapt-Sepsis, please tick 'Yes' and provide the name(s) of the trials using free text entry.
- If the patient is co-enrolled in more than one clinical trial, enter each trial name separately followed by a full stop.

Part 2

- Part 2 should be completed as soon as possible after the information becomes available.

A. Infection

- **A1-** Tick to confirm whether the infection was community or hospital acquired.
 - Hospital acquired/associated infection occurs at least 48 hours after hospital admission or recent exposure to hospital care.
 - Community acquired/associated infection is anything that is not hospital acquired.
- **A2-** Select 'Yes' or 'No' for each infection site.
 - If 'Yes' is ticked for an infection site, provide additional information where applicable.
 - If 'Other' is ticked, please specify the site of infection.
- **A3-** Tick to confirm whether a causative microorganism has been identified. If 'No', skip the remainder of the form and sign of the CRF. If 'Yes', complete question 3i.
 - **A3i-** On the RDE system, press the plus symbol (+) to add a new pathogen entry (Figure 5) and use the arrow buttons to move between previously completed entries. Specify the name of each pathogen and tick to confirm what sample it was detected in. Refer to the Table 3 and enter the numerical code corresponding to the applicable pathogen(s).
 - Please note that the pathogen list (Table 3) is a comprehensive list of bacteria associated with sepsis and also includes Candidia (no. 15) species which are fungi and Influenza virus A (no.31) which is a virus, which can also be associated with sepsis.

Figure 5: Adding a pathogen thought to cause the sepsis episode

The screenshot shows a web-based form interface. At the top, there is a blue header bar with navigation and form information: a 'Back' button, 'TNO: 0001', 'DATE ENROLLED: 04-Sep-2017', and 'FORM: BASELINE FORM - PART 2'. Below the header, there is a question: 'Is there a causative microorganism identified for the infection causing sepsis?' with a dropdown menu showing 'Yes'. Underneath this is a section titled 'Record all pathogens thought to cause the sepsis episode'. This section is currently empty and contains the text 'No Records Have Been Entered' with a clock icon. At the bottom of this section, there are navigation arrows and a plus sign (+) button, which is highlighted by a mouse cursor. The 'Add' button is also visible at the bottom of the form.

Table 3: Pathogen List

Code	Pathogen	Code	Pathogen
1	Acinetobacter baumannii	36	Listeria monocytogenes
2	Acinetobacter Iwoffii	37	Microbacterium sp.
3	Aerococcus viridans	38	Micrococcus luteus
4	Aeromonas hydrophilia	39	Moraxella catarrhalis
5	Arcanobacterium haemolyticum	40	Morganella morganii
6	Bacillus cereus	41	Mycobacterium chelonae
7	Bacteroides fragilis	42	Mycoplasma bovis
8	Bartonella heselae	43	Neisseria meningitidis
9	Bartonella quintana	44	Nocardia nova
10	Bordetella pertussis	45	Pasteurella multocida
11	Brucella neotomae	46	Propionibacterium acnes
12	Burkholderia cepacia	47	Proteus mirabilis
13	Campylobacter coli	48	Proteus vulgaris
14	Campylobacter jejuni	49	Providencia stuartii
15	Candida (any species)	50	Pseudomonas aeruginosa
16	Citrobacter freundii	51	Rothia dentocariosa
17	Clostridium difficile	52	Salmonella enterica
18	Clostridium perfringens	53	Serratia marcescens
19	Corynebacterium diptheriae	54	Shigella sonnei
20	Corynebacterium jeikeium	55	Staphylococcus aureus (MRSA)
21	Corynebacterium urealyticum	56	Staphylococcus aureus (MSSA)
22	Eikenella corrodens	57	Staphylococcus epidermidis
23	Enerococcus faecalis	58	Staphylococcus haemolyticus
24	Enerococcus faecium	59	Staphylococcus lugdunensis
25	Enterobacter aerogenes	60	Staphylococcus saprophyticus
26	Enterobacter cloacae	61	Stenotrophomonas maltophilia
27	Escherichia coli	62	Streptococcus agalactiae
28	Fusobacterium nucleatum	63	Streptococcus gordonii
29	Haemophilus influenzae	64	Streptococcus mutans
30	Helicobacter pylori	65	Streptococcus pneumoniae
31	Influenza virus A	66	Streptococcus pyogenes
32	Klebsiella oxytoca	67	Veillonella dispar
33	Klebsiella pneumoniae	68	Vibrio parahaemolyticus
34	Lactobacillus acidophilus	69	Yersinia pseudotuberculosis
35	Legionella pneumophila	70	Other, specify

4. Daily Data Collection – Intervention





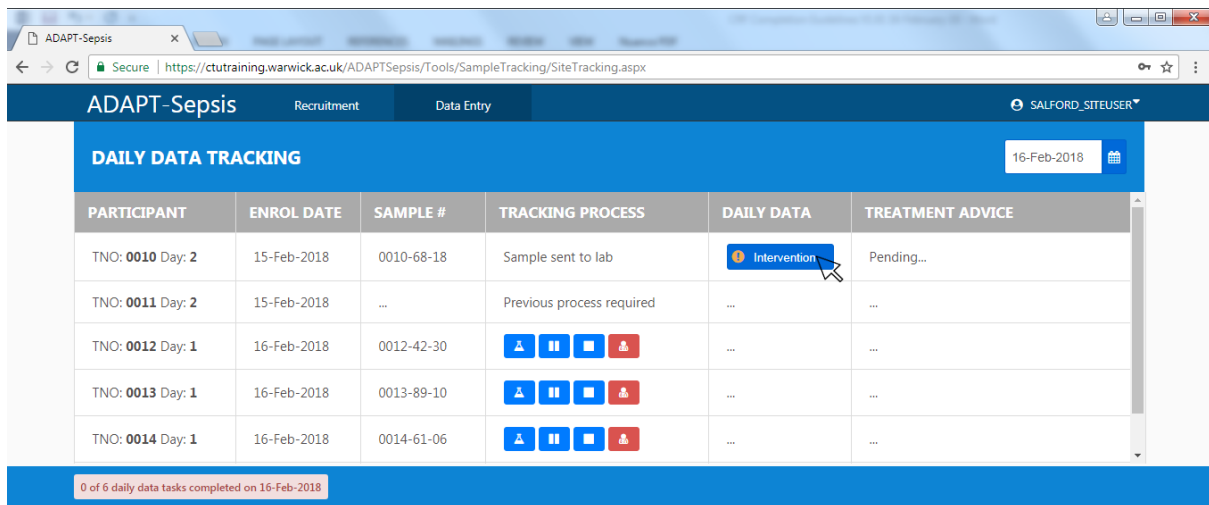
- This CRF should first be completed the **following calendar day** from baseline, a new form should be completed each calendar day whilst the participant is receiving antibiotics for suspected sepsis.
- Once the participant has stopped receiving antibiotics for suspected sepsis, please continue completing daily data follow-up forms each calendar day that they are a hospital inpatient.
- Once the participant is discharged, complete the discharge form and then the 28 day follow up form as soon as possible after the participant reaches 28 days from randomisation.
- If the participant is readmitted after they have been discharged, or their care escalation increases whilst in hospital and this is not related to an infection please complete the hospital care escalation / readmission form.
- To access the form, navigate to the 'Daily Data Tracking' section of the RDE system.
- Daily Data collection is triggered by updating the 'Daily Data Tracking' tab. This includes 4 buttons:-
 -  - 'Send the sample to lab'. Press this button to confirm that the blood sample for this participant has been sent to the lab team. Please ensure that this is completed promptly as the lab view of the database is triggered once this button is pressed.
 -  - 'Don't send the sample to lab'. Press this button if a blood sample has been missed in error to confirm that the blood sample will not be sent to lab.
 -  - 'Stop antibiotic treatment'. Press this button to confirm when a participant has stopped initial intravenous antibiotics for suspected sepsis. This will trigger the follow-up phase to commence.
 -  - 'Assign usual care without sending the sample to lab'. If the database was previously inaccessible, retrospectively press this button to confirm that the emergency sample processing system procedure was followed and the advice adhered to was 'protocol supports usual care' see emergency sample process flowcharts for more information.
- Once the 'Daily Data Tracking' process has been completed, a link entitled 'Intervention' will become available under the daily data heading (Figure 6).
- Press the button marked 'Intervention' to create the form and then press the "**Edit**" button in the bottom left to complete the form.
- Once a form has been created, the form can also be accessed by navigating to 'Unscheduled Events' (Figure 7).

Figure 6: Accessing the Daily Data Collection – Intervention Form



A. Date of Evaluation

- This section will be prepopulated on the RDE system.
- **A1-** If completing a paper CRF, please enter the day and date of evaluation. Day 1 will be the first calendar day from baseline.

B. Patient Status

- **B1-** If the participant is not a hospital inpatient, skip to section D and ensure a discharge form has been completed.
 - If 'Yes', specify whether they are a critical care inpatient (including level of unit) and whether they are deemed fit for discharge.
 - If deemed fit for discharge, provide the date and time of this assessment.

C. SOFA Score

- Complete the SOFA score at Day 3 and 7 post-randomisation. On all other days, the SOFA score section will remain greyed out and cannot be completed.
- SOFA score should be completed retrospectively for the previous calendar day e.g. Day 3 SOFA score should be entered on Day 4.
- If SOFA score date is unavailable at Day 3 or 7, this section can be completed in the first instance using assessments from the previous calendar day (Day 2 or 6 respectively). If data from the previous calendar day is also unavailable, this section can be completed using assessments from the subsequent calendar day (Day 4 or 8 respectively). If data from the subsequent calendar day is also unavailable, leave this section blank and mark as unobtainable in the 'Form Status' category (Figure 2).
- For the purposes of the ADAPT-Sepsis trial the following SOFA assessments will be calculated:

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiration					
PaO ₂ /Fio ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.

^a Adapted from Vincent et al.²⁷

^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

- #Conversion of mmHg to kPa = mmHg × 0.13332
- If the participant is receiving assisted ventilation, please tick to confirm whether this was invasive or non-invasive.
- If a Glasgow Coma Score is provided, skip the remaining neurological questions.
- If it is not possible to provide a Glasgow Coma Score, tick to confirm whether the participant is sedated and whether the participant has an endotracheal tube for ventilation. If yes is ticked for this question, this should be recorded as invasive under assisted ventilation.

D. Protocol Adherence

- **D1**- Record the date and time the blood sample for that current calendar day was taken.
- **D2**- Check box to confirm if a research blood sample was delivered to lab for the current day.
- **D2i**- If research blood sample was taken to lab record the date and time the research blood sample for the current day was delivered to the laboratory, not the time it was sampled.
- **D2ii**- If research blood sample was not taken to lab, specify the reason why using free text entry.
- **D3**- This question collects **retrospective information** regarding the previous 24 hour blood sample.
 - If advice from the previous 24 hour blood sample was not received, skip to question **D4** and complete a protocol deviation form to document the error.
 - If advice received, tick 'Yes' for the advice that was provided and 'No' for the other options. Answer question ii) according to this advice provided.
 - **D3ii**- 'If usual care advice was given for the previous 24 hour blood sample using our research protocol and the treating clinician stopped antibiotics, what influenced this decision?'
 - If antibiotic stop advice was not received, tick 'Not Applicable' and skip to question **D4**.

- If antibiotic stop advice was received and followed, tick 'Not Applicable' and skip to question **D4**.
- If antibiotic stop advice was received but not followed, tick 'Applicable' then tick 'Yes' for all applicable reasons and 'No' for the remaining options. If an applicable reason is not listed, tick 'Yes' for 'Other' and specify using free text entry.
- **D4-** If antibiotics have been stopped or changed during the last 24 hours, ensure the *Antibiotics Form* is updated.

E. Antibiotics Focus Review

- **E1-** Tick to confirm whether a documented review has been performed by 72 hours following first systemic antibiotics administered for suspected sepsis.
 - If 'No', skip part i) and proceed to Section F.
 - If 'Yes', confirm whether this included a clear plan of action.
- A documented plan of action may include any of the following:
 1. Stop antibiotics if there is no evidence of infection
 2. Switch antibiotics from intravenous to oral
 3. Change antibiotics—ideally to a narrower spectrum- or broader if required
 4. Continue and document next review date or stop date
 5. Outpatient Parenteral Antibiotic Therapy (OPAT)

F. Suspected Clinically Relevant Antibiotic Related Events

- **F1-** Tick to confirm whether the participant has experienced new suspected clinically relevant antibiotic related events in the last 24 hours. If 'Yes', tick 'Yes' below for all applicable events and 'No' for the remaining events. If the applicable event is not listed, tick 'Other' and briefly specify using free text entry.
- **F2-** Tick to confirm whether the patient has experienced proven new Clostridia Difficile diarrhoeal infection during this 24 hour period.
- **F3-** If the participant has experienced a proven new infection with a multi-drug resistant organism within the last 24 hours, specify the micro-organism name. See Table 4 for advice.

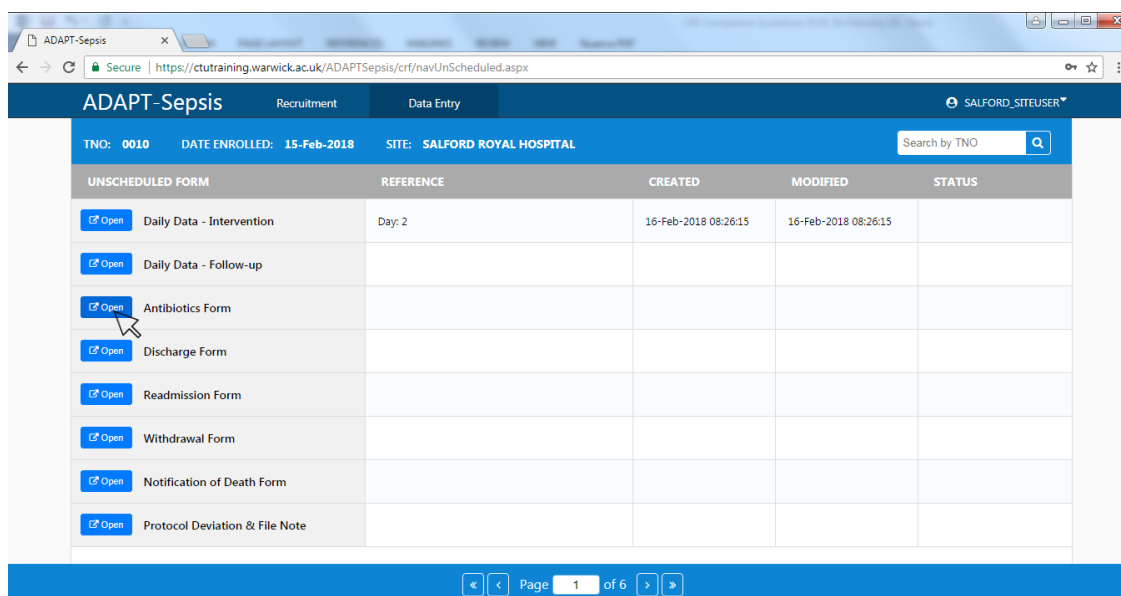
Table 4: Center for Disease Classification for Multi-Drug Resistant (MDR) bacteria

Phenotype Name	Phenotype Code	Phenotype Definition
Methicillin-resistant <i>Staphylococcus aureus</i>	MRSA_HAI	<i>Staphylococcus aureus</i> that has tested Resistant (R) to at least 1 of the following: methicillin, oxacillin, or ceftazidime
Carbapenem-resistant Enterobacteriaceae	CREall_HAI	Any <i>Escherichia coli</i> , <i>Klebsiella oxytoca</i> , <i>Klebsiella pneumoniae</i> , or <i>Enterobacter</i> spp. that has tested Resistant (R) to at least 1 of the following: imipenem, meropenem, doripenem, or ertapenem
Carbapenem-resistant <i>E.coli</i>	CREecoli_HAI	Any <i>Escherichia coli</i> that has tested Resistant (R) to at least 1 of the following: imipenem, meropenem, doripenem, or ertapenem
Carbapenem-resistant <i>Enterobacter</i> spp.	CREenterobacter_HAI	Any <i>Enterobacter</i> spp. that has tested Resistant (R) to at least 1 of the following: imipenem, meropenem, doripenem, or ertapenem
Carbapenem-resistant <i>Klebsiella pneumoniae/oxytoca</i>	CREklebsiella_HAI	Any <i>Klebsiella oxytoca</i> or <i>Klebsiella pneumoniae</i> that has tested Resistant (R) to at least 1 of the following: imipenem, meropenem, doripenem, or ertapenem
Carbapenem-non-susceptible <i>Pseudomonas aeruginosa</i>	carbNS_PA_HAI	<i>Pseudomonas aeruginosa</i> that has tested either Intermediate (I) or Resistant (R) to at least 1 of the following: imipenem, meropenem, or doripenem
Extended-spectrum cephalosporin-resistant <i>E.coli</i>	ESCecoli_HAI	Any <i>Escherichia coli</i> that has tested Resistant (R) to at least 1 of the following: cefepime, ceftazidime, ceftazidime/avibactam, or ceftazidime/avibactam.
Extended-spectrum cephalosporin-resistant <i>Klebsiella pneumoniae/oxytoca</i>	ESCKlebsiella_HAI	Any <i>Klebsiella oxytoca</i> or <i>Klebsiella pneumoniae</i> that has tested Resistant (R) to at least 1 of the following: cefepime, ceftazidime, ceftazidime/avibactam, or ceftazidime/avibactam.
Multidrug-resistant <i>Pseudomonas aeruginosa</i>	MDR_PA_HAI	<i>Pseudomonas aeruginosa</i> that has tested either Intermediate (I) or Resistant (R) to at least 1 drug in at least 3 of the following 5 categories: <ol style="list-style-type: none"> 1. Extended-spectrum cephalosporin (cefepime, ceftazidime) 2. Fluoroquinolones (ciprofloxacin, levofloxacin) 3. Aminoglycosides (amikacin, gentamicin, tobramycin) 4. Carbapenems (imipenem, meropenem, doripenem) 5. PIP/PIPTAZ (piperacillin, piperacillin/tazobactam)
Carbapenem-non-susceptible <i>Acinetobacter</i> spp.	carbNS_Acine_HAI	Any <i>Acinetobacter</i> spp. that has tested either Intermediate (I) or Resistant (R) to at least 1 of the following: imipenem, meropenem, or doripenem
Multidrug-resistant <i>Acinetobacter</i> spp.	MDR_Acine_HAI	Any <i>Acinetobacter</i> spp. that has tested either Intermediate (I) or Resistant (R) to at least 1 drug in at least 3 of the following 6 categories: <ol style="list-style-type: none"> 1. Extended-spectrum cephalosporin (cefepime, ceftazidime, ceftazidime/avibactam, or ceftazidime/avibactam) 2. Fluoroquinolones (ciprofloxacin, levofloxacin) 3. Aminoglycosides (amikacin, gentamicin, tobramycin) 4. Carbapenems (imipenem, meropenem, doripenem) 5. PIP/PIPTAZ (piperacillin, piperacillin/tazobactam) 6. Ampicillin/sulbactam
Vancomycin-resistant <i>Enterococcus faecalis</i>	VREfaecalis_HAI	<i>Enterococcus faecalis</i> that has tested Resistant (R) to vancomycin
Vancomycin-resistant <i>Enterococcus faecium</i>	VREfaecium_HAI	<i>Enterococcus faecium</i> that has tested Resistant (R) to vancomycin

5. Antibiotics Form – Intervention

- This is a rolling CRF to be updated as antibiotics prescribed change during a patient’s care, therefore ensure this is signed off as each page is completed or at the end of the intervention period, whichever is first.
- To access the form, navigate to the ‘Unscheduled Events’ section of the RDE system and select the *Antibiotics Form* (Figure 7).
- Select ‘Intervention’ at the top of the form to enter details of antibiotics taken whilst the patient is receiving the intervention (Figure 8).
- When completing a paper CRF there are separate forms for the intervention and follow-up phase. Begin by completing the *Antibiotics Form - Intervention* and, once the participant stops receiving antibiotics for initial sepsis, progress to the *Antibiotics Form - Follow-up*.

Figure 7: Accessing the Unscheduled Events Forms



The screenshot shows the ADAPT-Sepsis web application interface. The top navigation bar includes 'Recruitment' and 'Data Entry' tabs. The main content area displays a table of unscheduled events forms. The table has columns for 'UNSCHEDULED FORM', 'REFERENCE', 'CREATED', 'MODIFIED', and 'STATUS'. The 'Antibiotics Form' row is highlighted, and a mouse cursor is pointing to the 'Open' button next to it. The page number '1 of 6' is visible at the bottom.

UNSCHEDULED FORM	REFERENCE	CREATED	MODIFIED	STATUS
Open Daily Data - Intervention	Day: 2	16-Feb-2018 08:26:15	16-Feb-2018 08:26:15	
Open Daily Data - Follow-up				
Open Antibiotics Form				
Open Discharge Form				
Open Readmission Form				
Open Withdrawal Form				
Open Notification of Death Form				
Open Protocol Deviation & File Note				

Figure 8: Selecting the intervention or follow-up phase (1) and adding a new antibiotic entry (2)

The screenshot shows a web-based form titled 'ANTIBIOTICS FORM'. At the top, there is a blue header bar with a 'Back' button, 'TNO: 0001', 'DATE ENROLLED: 04-Sep-2017', and 'FORM: ANTIBIOTICS FORM'. Below the header, there is a section for 'When delivered' with a dropdown menu. The main section is 'Antibiotics administered', which currently shows 'No Records Have Been Entered'. A dropdown menu is open, showing 'Intervention' and 'Follow-up' options, with a mouse cursor pointing to 'Intervention' (labeled '1.'). Below the list, a plus sign icon is highlighted (labeled '2.'). The form also includes fields for 'FORM COMPLETION' (Form completed by, Date signed, Form status) and 'Save'/'Cancel' buttons.

A. Antibiotics administered

- Add a new entry each time a new antibiotic is administered or the regime changes. A regime change may include an altered dose, frequency or route.
- If an antibiotic administered is stopped or the regime is changed, update an existing record with a date and time stopped then add a new entry below for the current regime.
- Add a new entry by selecting the plus symbol (+, Figure 8) and use the arrow buttons to navigate between previously completed entries.
- Once the participant stops receiving antibiotics for initial sepsis, ensure all antibiotics administered in the intervention phase are recorded as stopped or changed. Then list any antibiotics received in the follow-up phase on the same form but select 'Follow-up'. See above for guidance when completing a paper CRF.
- Refer to Table 5 and enter the numerical code corresponding to the applicable antibiotic(s).
- Refer to Tables 6 and enter the numerical code corresponding to administered units, frequency, route and reason for change (if antibiotic has stopped or changed).
- For antibiotics given at regular intervals (e.g. antibiotic X three times a day), record the value of an individual dose and then complete relevant frequency.
- For antibiotics given as continuous infusions, record the total dose given over the last 24 hours based on the patient prescription and the recorded units and complete the frequency column with code 7 for continuous infusion.

Table 5: Antibiotic Delivered

Code	Antibiotic	Code	Antibiotic	Code	Antibiotic
1	AMIKACIN	26	CO-FLUAMPICIL	51	NITROFURANTOIN
2	AMOXICILLIN	27	COLISTIMETHATE SODIUM	52	NORFLOXACIN
3	AMPICILLIN	28	CO-TRIMOXAZOLE	53	OFLOXACIN
4	AMPICILLIN WITH FLUCLOXACILLIN	29	DALBAVANCIN	54	OXYTETRACYCLINE
5	AZITHROMYCIN	30	DAPSONE	55	PHENOXYMETHYLPENICILLIN (Penicillin V)
6	AZTREONAM	31	DAPTOMYCIN	56	PIPERACILLIN WITH TAZOBACTAM
7	BENZYLPENICILLIN SODIUM (Penicillin G)	32	DEMECLOCYCLINE HYDROCHLORIDE	57	PIVMECILLINAM HYDROCHLORIDE
8	CEFACLOR	33	DOXYCYCLINE	58	RIFAMPICIN
9	CEFADROXIL	34	ERTAPENEM	59	RIFAXIMIN
10	CEFALEXIN	35	ERYTHROMYCIN	60	SODIUM FUSIDATE (Fusidic acid)
11	CEFIXIME	36	FIDAXOMICIN	61	STREPTOMYCIN
12	CEFOTAXIME	37	FLUCLOXACILLIN	62	SULFADIAZINE
13	CEFRADINE	38	FOSFOMYCIN	63	TEDIZOLID
14	CEFTAROLINE FOSAMIL	39	GENTAMICIN	64	TEICoplanin
15	CEFTAZIDIME	40	IMIPENEM WITH CILASTATIN	65	TELAVANCIN
16	CEFTAZIDIME WITH AVIBACTAM	41	LEVOFLOXACIN	66	TEMOCILLIN
17	CEFTOBIPROLE	42	LINEZOLID	67	TETRACYCLINE
18	CEFTOLOZANE WITH TAZOBACTAM	43	LYMECYCLINE	68	TICARCILLIN WITH CLAVULANIC ACID
19	CEFTRIAZONE	44	MEROPENEM	69	TIGECYCLINE
20	CEFUROXIME	45	METHENAMINE HIPPURATE (Hexamine hippurate)	70	TINIDAZOLE
21	CHLORAMPHENICOL	46	METRONIDAZOLE	71	TOBRAMYCIN
22	CIPROFLOXACIN	47	MINOCYCLINE	72	TRIMETHOPRIM
23	CLARITHROMYCIN	48	MOXIFLOXACIN	73	VANCOMYCIN
24	CLINDAMYCIN	49	NALIDIXIC ACID	74	OTHER
25	CO-AMOXICLAV	50	NEOMYCIN SULFATE		

Tables 6: Unit, Frequency, Route and Reason for Change Codes

Code	Unit		Code	Frequency		Code	Route
1	g		1	Once daily – Od		1	IV
2	mg		2	Twice daily – Bd		2	Oral
3	Other, please specify		3	Three times daily – Tds		3	Rectal
			4	Four times daily - Qds			
			5	One off			
			6	Continuous infusion			
Code	Reason for Change						
1	Antibiotic escalation						
2	Antibiotic de-escalation						
3	Re-infection/recurrence						
4	New infection/superinfection						
5	Clinical relevant suspected antibiotic associated adverse reaction (complete Antibiotic Adverse reaction CRF)						
6	Antibiotics stopped						
7	Other, please specify						

6. Daily Data Collection – Follow-Up


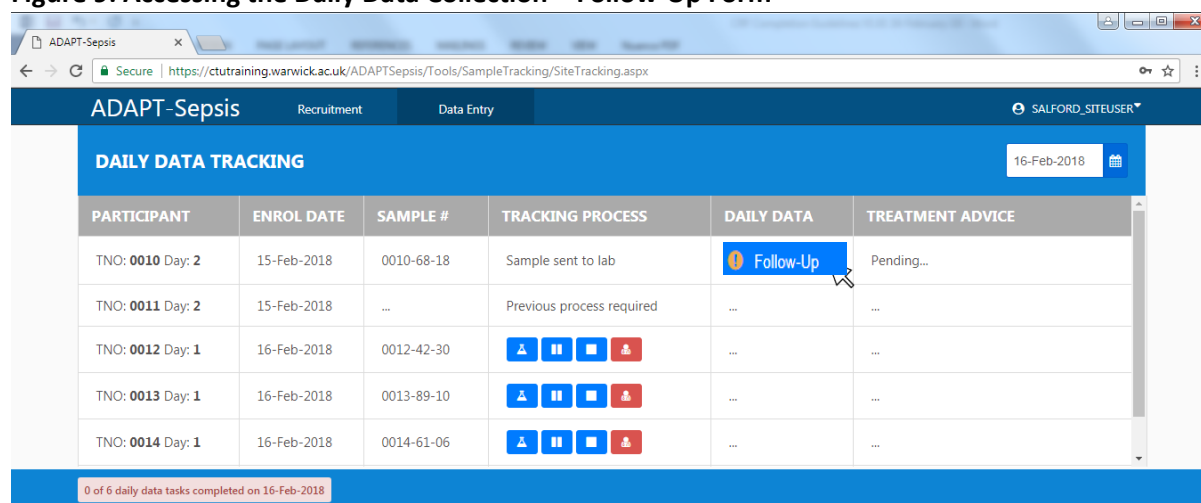



- This form should be completed once the patient has stopped receiving antibiotics for suspected sepsis and should be completed each calendar day that they are a hospital inpatient up until day 28.
- Once the patient is discharged, complete the discharge form and then the 28 day follow-up form as soon as possible after the patient reaches 28 days from randomisation.
- If the patient is readmitted after they have been discharged, or their care escalation increases whilst in hospital and this is not related to an infection please complete the hospital care escalation / readmission form and recommence completion of *Daily Data Collection – Follow-Up*.
 - It is important that the *Readmission Form* is completed as soon as possible after a patient is readmitted as this is the step which restarts the daily data tracking.
- To access the form, navigate to the 'Daily Data Tracking' section of the RDE system. Once antibiotics are marked as stopped () under 'Daily Data Tracking', a link entitled 'Follow-Up' will become available under the daily data heading (Figure 9). Daily Data collection is triggered by updating the 'Daily Data Tracking' tab. This includes 4 buttons:-
- Press the button marked 'Follow-up' to create the form and then press the "**Edit**" button in the bottom left to complete the form.
- Once a form has been created, the form can also be accessed by navigating to 'Unscheduled Events' (Figure 7).

Figure 9: Accessing the Daily Data Collection – Follow-Up Form



PARTICIPANT	ENROL DATE	SAMPLE #	TRACKING PROCESS	DAILY DATA	TREATMENT ADVICE
TNO: 0010 Day: 2	15-Feb-2018	0010-68-18	Sample sent to lab	Follow-Up	Pending...
TNO: 0011 Day: 2	15-Feb-2018	...	Previous process required
TNO: 0012 Day: 1	16-Feb-2018	0012-42-30	
TNO: 0013 Day: 1	16-Feb-2018	0013-89-10	
TNO: 0014 Day: 1	16-Feb-2018	0014-61-06	

A. Date of Evaluation

- This section will be prepopulated on the RDE system.
- **A1-** If completing a paper CRF, please enter the day and date of evaluation. Day 1 will be the first calendar day from baseline.

B. Patient Status

- **B1-** If the participant is not a hospital inpatient, skip to section D and ensure a discharge form has been completed.

- a. If 'Yes', specify whether they are a critical care inpatient (including level of unit) and whether they are deemed fit for discharge.
- b. If deemed fit for discharge, provide the date and time of this assessment.

C. Antibiotic Use

- **C1- *Systemic = Intravenous/oral/rectal.**
- **C1- If systemic antibiotics have been changed or restarted, ensure the antibiotics form is updated.**

D. SOFA Score

- Complete the SOFA score at Day 3 and 7 post-randomisation. On all other days, the SOFA score section will remain greyed out and cannot be completed.
- For the purposes of the ADAPT-Sepsis trial the following SOFA assessments will be calculated:

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiration					
Pao ₂ /Fio ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Billirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b	
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio₂, fraction of inspired oxygen; MAP, mean arterial pressure; Pao₂, partial pressure of oxygen.

^a Adapted from Vincent et al.²⁷

^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

- **#Conversion of mmHg to kPa = mmHg × 0.13332**
- If the participant is receiving assisted ventilation, please tick to confirm whether this was invasive or non-invasive.
- PLEASE NOTE- there is currently an error on the database which limits the values which can be entered for highest creatinine. If the score cannot be entered onto the system, please leave this blank and trial office will flag this as a data query once the issue is resolved.
- If a Glasgow Coma Score is provided, skip the remaining neurological questions.
- If it is not possible to provide a Glasgow Coma Score, tick to confirm whether the participant is sedated and whether the participant has an endotracheal tube for ventilation. If yes is ticked for this question, this should be recorded as invasive under assisted ventilation.

E. Protocol Adherence

- This section should only be completed once, on the first calendar day after stopping systemic antibiotics for suspected sepsis.
- **E1**- If advice from the previous 24 hour blood sample was not received, skip to question **E3** complete a *Protocol Deviation Form* to document the error. If received, tick 'Yes' for the advice that was provided and 'No' for the other options. Answer question ii) according to this advice provided.
- **E1ii**- '*If usual care advice was given for the previous 24 hour blood sample using our research protocol and the treating clinician stopped antibiotics, what influenced this decision?*'-
 - If antibiotic stop advice was not received, tick 'Not Applicable' and skip to question **E2**.
 - If antibiotic stop advice was received and followed, tick 'Not Applicable' and skip to question **E2**.
 - If antibiotic stop advice was received but not followed, tick 'Applicable' then tick 'Yes' for all applicable reasons and 'No' for the remaining options. If a applicable reason is not listed, tick 'Yes' for 'Other' and specify using free text entry.
- **E2**- If antibiotics have been stopped or changed during the last 24 hours, ensure the *Antibiotics Form* is updated.

F. Suspected Clinically Relevant Antibiotic Related Events

- **F1**- Tick to confirm whether the participant has experienced new suspected clinically relevant antibiotic related events in the last 24 hours. If 'Yes', tick 'Yes' below for all applicable events and 'No' for the remaining events. If the applicable event is not listed, tick 'Other' and briefly specify using free text entry.
- **F2**- Tick to confirm whether the patient has experienced proven new Clostridia Difficile diarrhoeal infection during this 24 hour period.
- **F3**- If the participant has experienced a proven new infection with a multi-drug resistant organism within the last 24 hours, specify the micro-organism name. See Table 4 for advice.

7. Antibiotics Form – Follow-Up

- If antibiotics are re-introduced in the follow-up period and up to 28 days post-randomisation, record the information on the *Antibiotics Form*.
- This is a rolling CRF to be updated as antibiotics prescribed change during the follow-up period, therefore ensure this is signed off as each page is completed or at the end of the follow-up period, whichever is first.
- To access the form, navigate to the ‘Unscheduled Events’ section of the RDE system and select the *Antibiotics Form* (Figure 7).
- Select ‘Follow-up’ at the top of the form to enter details of antibiotics taken whilst the patient is in the follow-up period (Figure 8).
- When completing a paper CRF there are separate forms for the intervention and follow-up phase. If the patient restarts antibiotics during the follow up phase complete the *Antibiotics Form - Follow-up*.

A. Antibiotics administered

- Add a new entry each time a new antibiotic is administered or the regime changes. A regime change may include an altered dose, frequency or route.
- If an antibiotic administered is stopped or the regime is changed, update an existing record with a date and time stopped then add a new entry below for the current regime, add a new entry by selecting the plus symbol (+, Figure 8) and use the arrow buttons to navigate between previously completed entries.
- Once the participant stops receiving antibiotics for initial sepsis, ensure all antibiotics administered in the intervention phase are recorded as stopped or changed. Then list any antibiotics received in the follow-up phase on the same form but select ‘Follow-up’. See above for guidance when completing a paper CRF.
- Refer to Table 5 and enter the numerical code corresponding to the applicable antibiotic(s).
- Refer to Tables 6 and enter the numerical code corresponding to administered units, frequency, route and reason for change (if antibiotic has stopped or changed).
- For antibiotics given at regular intervals (e.g. antibiotic X three times a day), record the value of an individual dose and then complete relevant frequency.
- For antibiotics given as continuous infusions, record the total dose given over the last 24 hours based on the patient prescription and the recorded units and complete the frequency column with code 7 for continuous infusion.

8. Discharge Form

- To access this form, navigate to the 'Unscheduled Events' section of the RDE system and select the *Discharge Form* (Figure 7).
- If the participant was not discharged alive from the treating hospital, skip the remainder of this CRF and ensure a *Notification of Death Form* is completed.
- Select where the participant was initially discharged to from the drop down menu. If other, specify using the free text entry.
- If the participant was discharged on a course of systemic antibiotics, ensure *CRF 7 Antibiotic Form* is completed.

9. 28 Day Follow-Up

- To access the form, navigate to the 'Scheduled Events' section of the RDE system and select the *28 Day Follow-Up Form* (Figure 1).

A. Source of Data

- Confirm source of data by selecting from the drop down menu. If the applicable source is not listed, tick 'Other' and briefly specify using free text entry.

B. Patient Mortality Status

- If the participant is not alive, complete the remainder of this CRF and ensure a *Notification of Death Form* is completed.

C. Follow-Up Data

- If the participant was readmitted to hospital following initial discharge and up to 28 days following randomisation, complete the following question.
- If the readmission was unscheduled ensure a Readmission Form is completed.
- Tick to confirm whether the participant received systemic antibiotics following hospital discharge. If 'Yes', ensure the *Antibiotic Form* is updated.

D. Suspected Clinically Significant Antibiotic Related Events

- Tick to confirm whether the participant has experienced any suspected clinically relevant antibiotic related events from hospital discharge to 28 days following randomisation. If 'Yes', complete the Antibiotic Related Events table.
- **Antibiotic Related Events Table**- Add a new entry for each applicable event by pressing the plus symbol (+). Navigate through previously completed entries using the arrow buttons (Figure 10).
 - Select each event from the drop down list.
 - If the applicable event is not listed, tick 'Other' and briefly specify using free text entry.
 - Enter start date. If the event is ongoing leave stop date blank (Figure 10). If the event is not ongoing, enter a stop date.
- Tick to confirm whether the patient has experienced proven new Clostridia Difficile diarrhoeal infection during this 24 hour period.
- If the participant has experienced a proven new infection with a multi-drug resistant organism within the last 24 hours, specify the micro-organism name. See Table 4 for advice.

Figure 10: Adding a new Antibiotic Related Event

← Back TNO: 0001 DATE ENROLLED: 04-Sep-2017 FORM: 28 DAY FOLLOW-UP

significant antibiotic related events from hospital discharge to 28 days following randomisation? Yes

Antibiotic Related Events [trash] [refresh] [add]

Event	Anaphylaxis
Other event	
Yes/No	Yes
Start date	10-jan-2018
Stop date	

« < 1 of 1 > » [add]

Save Cancel

10. Readmission Form

- To access this form, navigate to the 'Unscheduled Events' section of the RDE system and select the *Readmission Form* (Figure 7).

A. Unscheduled Hospital Readmission

- If the participant was readmitted to the same hospital, ensure the *Daily Data Collection – Follow-Up* is completed from readmission date up to 28 days after randomisation.
- If the participant was readmitted to a different hospital, provide the hospital name not the trust name.
- If you are unsure whether the hospital is a trial or non-trial hospital, contact the ADAPT-Sepsis trial team at Warwick CTU.
- Select where the participant was readmitted from using the drop down menu. If the applicable location is not specified, select 'Other' and briefly specify using free text entry.
- Please briefly specify main reason for hospital readmission using free text entry.
- If the participant required antibiotic treatment following their initial discharge or as part of the reason for readmission, ensure the *Antibiotic Form* is updated.

11. Withdrawal Form

- To access this form, navigate to the 'Unscheduled Events' section of the RDE system and select the *Withdrawal Form* (Figure 7).

A. Main Reason for Participant Withdrawal

- Please select the main reason for participant withdrawal from the drop down menu. If the applicable reason is not listed, select 'Other' and briefly specify using free text entry.
- If the participant/consultee decision is the main reason for withdrawal and they have offered information as to why, record this information as free text entry. If not, leave this blank.
- If reasons 3., 5. or 6. are the main reason, provide further information using free text entry.

B. Participant's Trial Status

- Select the participant's trial status using the drop down menu.
- If the participant has ceased trial treatment or procedures but remains on follow-up, all follow-up forms should continue to be completed as normal.

12. Notification of Death Form

- To access this form, navigate to the 'Unscheduled Events' section of the RDE system and select the *Notification of Death Form* (Figure 7).

A. Notification of Death

- Specify the primary cause of death only from the drop down menu.
- If primary cause of death was not related to sepsis, specify using free text entry and ensure an *SAE Form* is completed.

13. Serious Adverse Event Form – Initial

- SAEs should be reported **within 24 hours** of the research staff becoming aware of the event.
- Please send to the dedicated fax at Warwick CTU on **02476 150549**.
- Alternatively, **so long as the SAE form is anonymised**, we can receive it by email: WCTUQA@warwick.ac.uk and copied to the trial office email: adaptsepsistrial@warwick.ac.uk
- Please see the ‘Adverse Event Management’ section of the ADAPT-Sepsis Trial Protocol for further guidance.
- This form should be signed off by both the reporting clinician and the individual responsible for completing the *SAE Form*. Both individuals must be present on the site signatures and delegation log.
- This form should always be completed as a paper CRF.

A. Event Type

- Tick ‘Yes’ for each applicable category and ‘No’ for all remaining options. If ‘Other reason’ has been ticked, specify using free text entry.

B. Event Details

- **3i**- Specify relevant details of the event using free text entry.
- **3ii**- Specify relevant details of medical history, concomitant medication and associated dates of administration using free text entry.
- **3**- If necessary, a *SAE Continuation Form* should be completed to capture additional information. These forms should be signed and dated by the same reporting clinician and the same individual responsible for completing the *SAE Form*.

C. Severity Assessment

- Only one option should be indicated for Severity Assessment.

D. Causality

- Only one option should be indicated for causality.
- The treating clinician **MUST** initial this section to confirm their opinion.
- If ‘Definitely’, ‘Probably’ or ‘Possibly’ are ticked, Section E should be completed.
- If ‘Unlikely’ or ‘Unrelated’ are completed, Section E should be skipped.

E. Expectedness

- This section should only be completed if ‘Definitely’, ‘Probably’ or ‘Possibly’ are ticked for Section D.

F. Outcome of Event

- Only one option should be ticked for outcome.
- If **1.** is ticked, a resolution date should be provided.
- If **2.** is ticked, details of the sequelae and a resolution date should be provided.
- If **3.** is ticked, the *SAE Follow-up Form* should be completed at a later date.
- If **4.** is ticked, a *Notification of Death Form* should be completed.

14. Serious Adverse Event Form – Follow-up

- This form should be completed when further information comes to light regarding the initial SAE, when the SAE is resolved or to provide an update following queries from Warwick CTU.
- This form should be signed off by both the reporting clinician and the individual responsible for completing the *SAE form*. Both individuals must be present on the site signatures and delegation log. These individuals may not necessarily be the same as those who signed off the *Serious Adverse Event Form – Initial*.
- This form should always be completed as a paper CRF.

A. This Report Relates to the Adverse Event Deemed Serious On

- The date entered here must match the date provided on the initial report (**B1**).

B. Further Details of Event

- Relevant further details of the event should be entered using free text entry.
- If necessary, a *SAE Continuation Form* should be completed to capture additional information. These forms should be signed and dated by the same reporting clinician and the same individual responsible for completing the SAE form.

C. Severity Assessment

- Only one option should be indicated for Severity Assessment.

D. Causality

- Only one option should be indicated for causality.
- The treating clinician MUST initial this section to confirm their opinion.
- If 'Definitely', 'Probably' or 'Possibly' are ticked, Section E should be completed.
- If 'Unlikely' or 'Unrelated' are completed, Section E should be skipped.

E. Expectedness

- This section should only be completed if 'Definitely', 'Probably' or 'Possibly' are ticked for Section D.

F. Outcome of Event

- Only one option should be ticked for outcome.
- If **1.** is ticked, a resolution date should be provided.
- If **2.** is ticked, details of the sequelae and a resolution date should be provided.
- If **3.** is ticked, the *SAE Follow-up Form* should be completed at a later date.
- If **4.** is ticked, a *Notification of Death Form* should be completed.

15. Serious Adverse Event Continuation Form

- This CRF should be signed off by the same reporting clinician and the same individual responsible for completing the corresponding initial or follow-up *SAE form*.
- This form should always be completed as a paper CRF.

A. This Report Relates to the Adverse Event Deemed Serious On

- The date entered here must match the date provided on the initial report (**B1**).
- Tick to confirm whether the continuation form is linked to the Initial Report or a Follow-up Report.

- The *SAE form* section number should be completed to show which section the information relates to e.g. **B3i**.
- Additional information should be completed using free text entry.

16. Deviation and File Note Form

- To access this form, navigate to the 'Unscheduled Events' section of the RDE system and select the *Deviation and File Note Form* (Figure 7).
- Specify the date the event took place.
- Select 'Protocol Deviation' or 'Note to File' from the drop down menu.
- Specify details of the event using free text entry. Provide as much detail as possible including, where applicable, why an event took place and any preventative measures which have been put in place to prevent similar events in future.
- After completing a Protocol Deviation, please print and file a copy in the Investigator Site File