Guidance Sheet 1: Training

AZTEC trial training overview

AZTEC trial training is based on the Site Initiation Visit presentation sessions delivered to sites by the CTR AZTEC team. The PI/research nurse/pharmacy representative should hold a copy of these presentation slides and be able to deliver the presentations to staff, applicable to the roles to be undertaken.

1. Background and Rationale
2. Informed consent and randomisation
3. Prescription and Intervention procedures
4. Data Collection
5. Safety and non-compliance reporting
6. Sampling procedures
7. Pharmacy Procedures

Training for a delegated role is completed when an individual has received the appropriate session(s), has read the mandatory guidance sheets, and has been signed off by the trainer.

Guidance sheets

The following AZTEC guidance sheets for specific aspects of the trial are available in paper format in the Investigator Site File, or electronic versions can be obtained via AZTEC@Cardiff.ac.uk

▪ Guidance sheet 2: Screening and Consent	▪ Guidance sheet 9: IMP supply & accountability
▪ Guidance sheet 3: Notes on informed consent	▪ Guidance sheet 10: Oxygen reduction test
▪ Guidance sheet 4: Randomisation	▪ Guidance sheet 11: Withdrawal & Unblinding
▪ Guidance sheet 5a: Intervention	▪ Guidance sheet 12a: Preparing a transfer
▪ Guidance sheet 5b: IMP administration	▪ Guidance sheet 12b: Receiving a transfer
▪ Guidance sheet 6: Data collection	▪ Guidance sheet 13a: Sampling procedure
▪ Guidance sheet 7: Data entry	▪ Guidance sheet 13b: Sample shipment
▪ Guidance sheet 8: Safety and non-compliance reporting	

For any queries please contact the AZTEC Trial Manager at LoweJ3@Cardiff.ac.uk or 029 2068 7990. Study materials can be requested from the trial administrator, AZTEC@Cardiff.ac.uk.

It is recommended that all staff read:

Guidance sheet 8: Safety and non-compliance reporting
Guidance sheet 11: Withdrawal & unblinding
Guidance sheet 12A: Preparing a transfer

Guidance Sheet 1: Training

Training Requirements: Delegated Duties

All **MANDATORY** training other than GCP training must be recorded on the Training Log in the AZTEC Investigator Site File (or AZTEC Pharmacy Folder for pharmacy staff).

TRAINING DELIVERY

DUTY 1) DELIVER OVERVIEW TRAINING

MANDATORY

- Full GCP (evidenced by a certificate)
- Attend AZTEC site initiation visit/suitable alternative

RECOMMENDED

- All AZTEC guidance sheets

DUTY 2) DELIVER TRAINING ON PREPARATION AND ADMINISTRATION OF IMP

MANDATORY

- Full GCP (evidenced by a certificate)
- AZTEC trial overview- sessions 1, 3 & 4
- Guidance sheet 5a: Intervention
- Guidance sheet 5b: IMP administration

DUTY 3) DELIVER TRAINING ON SAMPLE COLLECTION AND SHIPMENT

MANDATORY

- Full GCP (evidenced by a certificate)
- AZTEC trial overview- sessions 1, 4 & 6
- Guidance sheet 13a: Sampling procedures
- Guidance sheet 13b: Sample shipment

CLINICAL TEAM

DUTY 4) CONFIRMATION OF ELIGIBIITY

Must be medically qualified to undertake this duty

MANDATORY

- AZTEC trial overview- sessions 1 & 2
- Any Trust-specific GCP requirements
- Guidance sheet 2: Screening and consent

RECOMMENDED

- Guidance sheet 4: Randomisation

DUTY 5) OBTAIN INFORMED CONSENT

MANDATORY

- Full GCP (evidenced by a certificate)
- AZTEC trial overview- sessions 1 & 2
- Guidance sheet 2: Screening and consent
- Guidance sheet 3: Notes on informed consent

RECOMMENDED

Guidance sheet 4: Randomisation

DUTY 6) RANDOMISATION

MANDATORY

- AZTEC trial overview- sessions 1 & 2
- Any Trust-specific GCP requirements
- Guidance sheet 4: Randomisation

RECOMMENDED

- Sortition randomisation user guide
- Guidance sheet 2: Screening and consent

DUTY 7) PRESCRIPTION OF IMP

Must be medically qualified or an Advanced Nurse Practitioner (ANP) with suitable qualification

MANDATORY

- AZTEC trial overview- sessions 1, 2 & 4
- Any Trust-specific GCP requirements
- Guidance sheet 5a: Intervention

RECOMMENDED

- Guidance sheet 5b: IMP administration

DUTY 8) OXYGEN REDUCTION TEST

MANDATORY

- AZTEC trial overview- sessions 1 & 4
- Any Trust-specific GCP requirements
- Guidance sheet 10: Oxygen reduction test

RECOMMENDED

- Guidance sheet 6: Data collection

DUTY 9) SAE CLINICAL REVIEW AND SIGN OFF

Must be medically qualified to undertake this duty

MANDATORY

- Full GCP (evidenced by a certificate)
- AZTEC trial overview- sessions 1 & 5
- Guidance sheet 8: Safety and non-compliance reporting
- Guidance sheet 11: Withdrawal & Unblinding

RECOMMENDED

- Sortition site unblinding user guide

RESEARCH TEAM

DUTY 10) COMPLETION OF eCRF AND RESOLUTION OF DATA QUERIES

MANDATORY

- AZTEC trial overview- session 1 & 4
- Any Trust-specific GCP requirements
- Guidance sheet 6: Data collection
- Guidance sheet 7: Data entry

RECOMMENDED

- Guidance sheet 9: IMP supply control and accountability

DUTY 11) INVESTIGATOR SITE FILE MAINTANCE

MANDATORY

- Any Trust-specific GCP requirements

DUTY 12) MANAGEMENT OF IMP ACCOUNTABILITY ON NEONATAL UNIT

MANDATORY

- AZTEC trial overview- session 1, 3 & 4
- Any Trust-specific GCP requirements
- Guidance sheet 4: Randomisation
- Guidance sheet 5a: Intervention
- Guidance sheet 9: IMP supply control and accountability

RECOMMENDED

- Sortition Randomisation user guide
- Guidance sheet 11: Withdrawal & Unblinding

DUTY 13) UNBLINDING

Must be medically qualified to undertake this duty

MANDATORY

- Any Trust-specific GCP requirements
- AZTEC trial overview- sessions 1 & 5
- Guidance sheet 8: Safety and non-compliance reporting
- Guidance sheet 11: Withdrawal & Unblinding

RECOMMENDED

- Sortition site unblinding user guide

PHARMACY

DUTY 14) IMP ISSUE AND ACCOUNTABILITY

MANDATORY

- AZTEC trial overview- session 1 & 7
- Any Trust-specific GCP requirements
- Guidance sheet 5a: Intervention
- Guidance sheet 5b: IMP administration
- Guidance sheet 9: IMP supply control and accountability

RECOMMENDED

- Guidance sheet 11: Withdrawal & Unblinding

DUTY 15: PHARMACY SITE FILE MAINTANANCE

MANDATORY

- AZTEC trial overview- session 1 & 7
- Any Trust-specific GCP requirements
- Guidance sheet 9: IMP supply control and accountability

RECOMMENDED

- Guidance sheet 11: Withdrawal & Unblinding

Training Requirements: Study-specific tasks

All **MANDATORY** training other than GCP training must be recorded on the Training Log: Study-specific tasks in the AZTEC Investigator Site File

PREPARATION AND ADMINISRATION OF IMP

This duty does NOT need to be recorded on the delegation log.

MANDATORY

- AZTEC trial overview- session 3
- Any Trust-specific GCP requirements
- Guidance sheet 5a: Intervention
- Guidance sheet 5b: IMP administration

RECOMMENDED

- AZTEC trial overview- session 1
- AZTEC IMP preparation webinar
- "Fundamentals of Clinical Research Delivery for Administering IMPs" document

COLLECTING RESPIRATORY AND STOOL SAMPLES

This duty does NOT need to be recorded on the delegation log.

MANDATORY

- AZTEC trial overview- session 6
- Any Trust-specific GCP requirements
- Guidance sheet 13a: Sampling procedures
- Guidance sheet 13b: Sample shipment

RECOMMENDED

- AZTEC trial overview- session 1

Guidance Sheet 1: Training

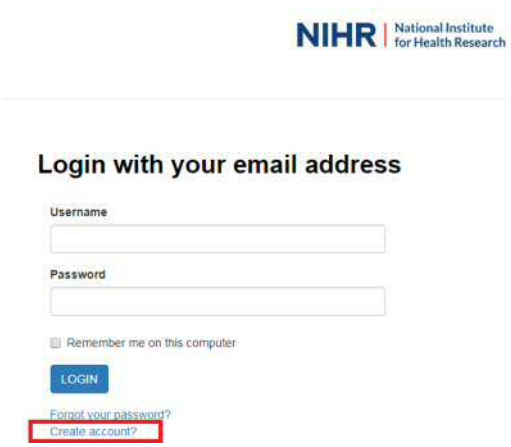
AZTEC
Azithromycin Therapy for Chronic Lung Disease

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Centre for Trials Research
Canolfan Ymchwil Treialon

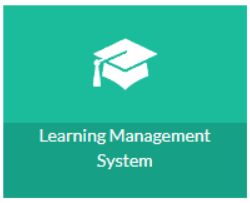
Access to NIHR online GCP training

- Any member of staff involved in an NIHR portfolio study can access online training in GCP (introduction and refresher training) and informed consent.

- To access the training, you first need to create an account on NIHR learning portal: https://learn.nihr.ac.uk



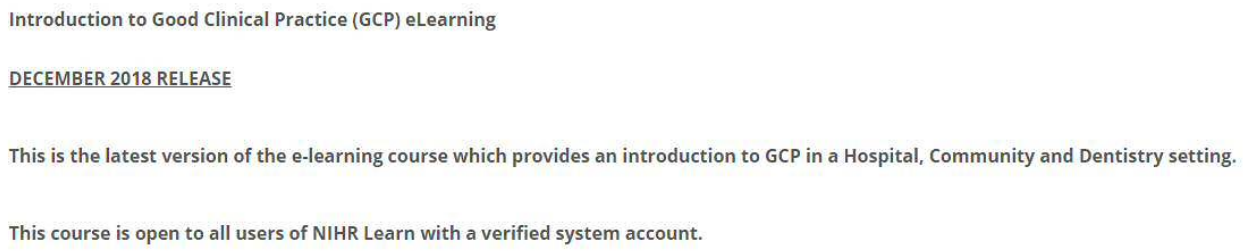
- Once an account is created, you can access the learning management system



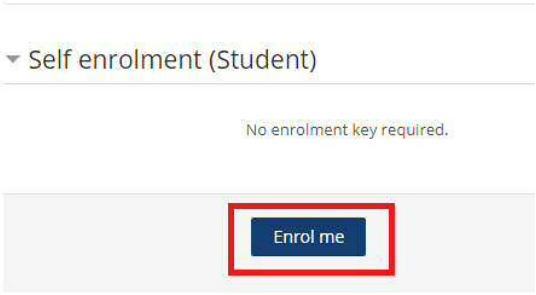
- The link to GCP training is in the bar at the top of the page

- A number of different courses are available. Refresher training is suitable for individuals who have previously completed the introductory course. Training on informed consent is also available here

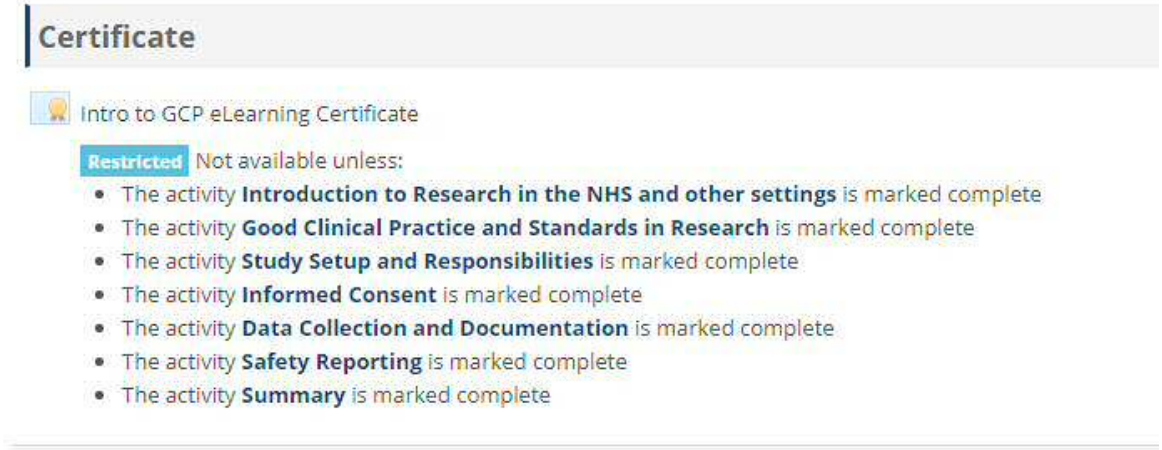
- Clicking on the appropriate course brings you to the start page



- You can then enrol on a course by clicking the link at the bottom of the page



- All modules have to be completed before a certificate can be issued. Please save the certificate and keep this in a safe place



Guidance Sheet 2: Screening and consent

AZTEC
Azithromycin Therapy for Chronic Lung Disease
Cardiff University
Prifysgol Caerdydd
Centre for Trials Research
Canolfan Ymchwil Treialon

Eligibility

Babies will be considered **eligible** for inclusion in the trial if:

a) They were born at <30 (up to 29w^{+6d}) weeks of gestation (including infants born as one of a multiple birth)
b) Have received respiratory support for at least 2 continuous hours duration during the first 72 hours of life (intubated, or by non-invasive mechanical ventilation including continuous positive airway pressure and high flow nasal cannula or a combination thereof)
c) Have an indwelling intravenous line for drug administration
d) Written informed consent has been obtained within 72 hours of birth
e) It is anticipated administration of first dose can begin within 72 hours of birth
f) It is reasonable to expect completion of 10 days of trial treatment whilst resident at the recruiting site
g) They are Inborn, or born at site within the recruiting site's neonatal network where follow up will be possible
h) In the opinion of the PI, they are likely to survive past 72 hours after birth

Babies will be **excluded** from participation in the trial if:

a) They have been exposure to another systemic macrolide antibiotic (not maternal): Including azithromycin, erythromycin, clarithromycin
b) There is presence of major surgical or congenital abnormalities (not including patent ductus arteriosus or patent foramen ovale)
c) There is a contraindication of azithromycin as specified in the summary of characteristics of the product
d) There is participation in another interventional trial that precludes participation in AZTEC

Guidance Sheet 2: Screening and consent

AZTEC Azithromycin Therapy for Chronic Lung Disease

Cardiff University Prifysgol Caerdydd

Centre for Trials Research Canolfan Ymchwil Treialon

Screening

To ensure that potentially eligible babies are not missed, it is important that all NICU staff are familiar with the AZTEC Protocol and can help with identification and recruitment.

Try to identify parents of potential recruits as early as possible in the antenatal wards, delivery suites and NICU.

- Please ensure that the Screening Log is completed and records all infants born less than 30 weeks' gestation. This should be done at least once a week using the eCRF . Please keep the log up to date by adding cases on a weekly basis. This should not include any personal identifiable information.

Informed consent

Consent may be carried out by any healthcare professional that has received **AZTEC training and GCP training** and is listed on the **Site Delegation Log** to take consent. However, please also **check** with your NHS organisation who may have more specific requirements.

1. Approach the parents to discuss the trial and provide a Parent Information Leaflet (located in the AZTEC document box). Ensure they are aware that participation is voluntary, and that consent may be withdrawn at any time without explanation.
2. Allow sufficient time for parent(s) to consider their decision and arrange a follow-up meeting to answer questions. Sometimes several meetings are needed.
3. As soon as the parent(s) decide that their baby may participate in the trial, the Consent Form must be completed. Written consent must be obtained before a baby may be randomised.
4. Written consent must be obtained before a baby may be recruited to AZTEC. Only the mother or father, or person designated formally by legal process, may sign the consent form.

- In law, unmarried fathers do not automatically have parental responsibility for their child, unless they are named on the birth certificate, or through a court order or parental responsibility agreement this can be given to them.
- In the case of twins or triplets, **each baby must** have a **separate signed consent form** and please indicate on the form the birth order of the baby (e.g. twin 1, triplet 3).

- The AZTEC trial involves recording the mother's information, so the mother must provide written consent. The father may sign the consent form (if he is married to the mother, named on the birth certificate/have been granted parental responsibility through a court order or parental responsibility agreement), but the mother must also counter-sign to provide written consent.

The consent process (i.e. important points to be covered in discussion) is discussed in more detail in **Guidance Sheet 3: Notes on informed consent**

TRANSLATORS

If a translator is used to explain the study and obtain informed consent, this must be an **adult who is unrelated to the parent** (hospital translation services may be used), and this must be **noted on the consent form**.

Completion of Consent Form

As soon as the parent(s) decide that their baby may participate in the trial, the **Consent Form** should be completed, and the baby randomised.

Whenever the baby's father signs the consent form, please ensure that the mother countersigns, as we need the mother's agreement to access her medical records. **If mother signs the consent form first, there is no obligation to collect the father's signature**, although the 2nd signature space provided can be used for this purpose**.**

Important points on completing the consent form

1) Please use the clipboard provided when the Consent Form is completed to ensure that the carbon copies are of good quality
2) Add participant's Study ID and NHS/CHI number to the consent form following randomisation
3) Please ensure the Parent **initials** all applicable boxes (not ticks) and then Prints, Signs and Dates the 'Name of Parent/Guardian' section. **NOTE: The date section should NOT be pre-populated for the parent**
4) The person taking the consent should also Print, Sign and Date in the 'Name of person taking consent' boxes.

5) There are **<u>three</u> coloured copies** of the **Consent Form**. **Remember** to ensure that any signatures/initials transfer through to the subsequent duplicate sheets, and add the Study ID and NHS/CHI number before separating as follows:
    a. original: scan and email to AZTEC@Cardiff.ac.uk. Please use an encrypted message as provided by your NHS organisation. Or, fax to the trial-specific number: 029 2251 9700. Then, place in the baby's clinical notes together with a copy of the **Parent Information Leaflet.**
    b. a copy to the **Investigator Site File**
    c. a copy to a parent

N.B. If the carbon copies are poor quality please photocopy the original consent form (top sheet) for the site file and parents.

It is important that clinical staff keep in contact with families throughout the baby's time in the trial to ensure that they understand the protocol and remain happy for their baby's continued participation.

Confirm eligibility before randomisation

Ensure the clinical assessment of trial eligibility is documented by a medically-qualified professional (who is listed on the Delegation Log) within the medical notes. An example statement is '**This baby meets the inclusion criteria and none of the exclusion criteria and is therefore eligible for entry into the AZTEC trial**'. Labels are provided in the document box to facilitate this process.

Contact details form

Please also complete a **Contact Details Form** on the eCRF if the parents have consented to follow-up contact.

Randomisation

Randomisation should be carried out prior to the intervention being given (refer to **Guidance Sheet 4: Randomisation**). **Remember** to add the Study ID to the consent form.

Guidance Sheet 3:
Notes on Informed Consent

AZTEC
Azithromycin Therapy for Chronic Lung Disease
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Centre for Trials Research
Canolfan Ymchwil Treialon

This guidance sheet provides a general guide to the process for taking informed consent for participation in the AZTEC trial.

General Guidance

- Introduce self (e.g. neonatal research nurse working within a research team)
- We have a trial your baby is eligible for. Is research something you are interested in? Would you like to know more?
- COMPLETELY VOLUNTARY, DO NOT HAVE TO TAKE PART AND CAN WITHDRAWAT ANY TIME
- Trial has been through ethics committee and drugs regulatory authority (MHRA), is funded by the NIHR HTA Programme and sponsored by Cardiff University
- Parent Information Leaflet (PIL) – give the parents a copy of the PIL for them to read
- Parents should be given adequate time to consider whether to take part. Allow sufficient time for parent(s) to consider their decision and arrange a follow-up meeting to answer questions. Sometimes several meetings are needed.

Recruitment

- Eligible babies born less than 30 weeks' gestation at risk of CLD
- Treatment to start within 3 days after birth, sooner if possible
- Other exclusion criteria include:
    - Exposure to another systemic macrolide antibiotic (not maternal)
    - Presence of major surgical or congenital abnormalities (not including patent ductus arteriosus or patent foramen ovale)
    - Contraindication to azithromycin
    - Participation in another trial that would preclude baby from inclusion in AZTEC
- Senior clinician to sign in notes to document inclusion in the trial to be appropriate

Study Aim/Background

- The trial your baby is eligible for is known as the AZTEC Trial and is looking at the effectiveness of azithromycin (an antibiotic) in treating babies at risk of lung problems
- At present, many preterm babies needing help with their breathing are at risk of developing CLD

- Azithromycin treats infections, and inflammation (soreness/redness) which may contribute to the development of CLD
- The aim of this study is to see whether using azithromycin can help babies' lung problems and reduce rates of CLD

What will happen if your baby participates?

- The trial is known as a Randomised Control Trial or RCT
- It is looking at an Investigational Medicinal Product or IMP. For this trial we are using azithromycin or what is known as an inactive placebo. The placebo is just water and has no active ingredients
- You will be asked to sign a consent form. As the study involves looking at the mother's medical records, we will ask the mother specifically to provide consent
- Your baby will be randomly allocated by a computer system to receive either azithromycin or the placebo
- The azithromycin or placebo will be administered to your baby intravenously (into a vein).
- The study is also blinded, so this means we do not know which drug your baby has received. This is to prevent bias in the analysis. If there are any emergencies, it is possible for staff to find out which drug your baby was given
- Azithromycin or placebo will be given to your baby once a day for 10 days
- Babies will be in the trial until they reach what would have been the 36th week of pregnancy (or discharge if this is sooner)
- Babies will be routinely monitored for this time period. Routine monitoring will include recording weight, head circumference, other medications, blood pressure etc.
- Your baby may have one additional assessment called an 'oxygen reduction test'. This is to establish whether your baby still needs additional oxygen when he/she reaches what would have been the 36th week of pregnancy or at discharge if this is sooner
- Consent will also be requested to look at how azithromycin works in the lungs
    - This involves collecting some mucus sucked up from your baby's breathing tube or nostrils, and some poo from their nappy

  - These would be collected up to 4 times (lung sample), and up to 3 times (poo sample) over a 21-day period (as long as the baby is not transferred or discharged)
  - Where possible the tiny samples are taken at the time of routine procedures and will not cause your baby any additional discomfort, harm or distress
- The samples will be sent to Cardiff University for analysis
- The samples may be kept by Cardiff University for use in other laboratory studies investigating preterm birth and the effectiveness of azithromycin. Consent for retention of samples is OPTIONAL.

Recruitment Plan

- Plan to recruit 800 babies over around 30 months. Trial started in 2019
- Approximately half the babies to receive azithromycin and half to receive placebo in randomised groups
- Possible advantages and disadvantages to taking part
  - Disadvantages to taking part may include side effects from the azithromycin.
  - However, previous use of this azithromycin has suggested that this dose is not associated with significant side effects
- We are not aware of any other risks for your baby in taking part in the study, and all babies who participate will be monitored very closely throughout the study by the staff on the Neonatal Intensive Care or Special Care Unit

Results

- Results will help us understand how whether azithromycin can help premature babies' lung function
- We will publish the results of our study in a medical journal so other clinicians/researchers can use them to help with treating pain
- We will publish a summary of the results on the trial website
- If you would like a copy of the full journal article, you can request this from the Centre for Trials Research, Cardiff

Other

- We also read babies' and mothers' notes to gather information on birth weight, gestation, age and any relevant past medical history. This is then recorded on a secure online system
- Sections of medical records may be looked at by the individuals from the Sponsor, MHRA, the CTR or the host NHS organisation
- NHS digital, or a named derivative, and other central UK NHS bodies will be used to keep in touch with and provide information about your baby's health status
- Each baby is given a study specific number and will be referred to using only this to help provide anonymity
- All relevant medical information will be kept securely
- Personal identifiable data will be treated confidentially and according to UK legislation
- If parents choose not to enter the trial, their baby will receive the same care that other babies receive
- When going back for consent after the initial information has been given – CHECK PARENTS HAVE READ AND UNDERSTOOD THE LEAFLET. Get them to run through what they think is involved in the study and fill in any missing information
- Run through the consent form with parents if needed
- Mother and father can sign consent form if parents are married or if the Father is/has:
    - married to the mother
    - listed on birth certificate
    - parental responsibility granted through a court order or parental responsibility agreement
    - If the father signs, this must be counter-signed by the mother as the study involves looking at the mother's medical information
- Ensure consent form completed accurately:
    - Full names of parent(s) and health professional is clearly recorded
    - Dates are fully completed for both parent and Health Professional
    - Parent name and date is not pre-populated by Health Professional
    - Parent has **initialled** each box

- Ensure that the consent form is completed using a clipboard and that the carbon copies of the consent form are legible. If not legible, photocopy the top copy and provide one to the parents, and one for the Investigator Site file. The original should per emailed/faxed to the CTR before being placed in the babies notes (**see guidance sheet 2**)
- Ensure that a Contact Details Form has also been completed on the eCRF (if the parent(s) consent to follow-up)

TRANSLATORS

If a translator is used to explain the study and obtain informed consist, this must be an **adult who is unrelated to the parent** (hospital translation services may be used), and this must be **noted on the consent form**.

Any final questions? Remind them they CAN WITHDRAWAT ANY TIME and participation is VOLUNTARY.

Guidance Sheet 4: Randomisation

AZTEC Azithromycin Therapy for Chronic Lung Disease

Cardiff University Prifysgol Caerdydd — Centre for Trials Research / Canolfan Ymchwil Treialon

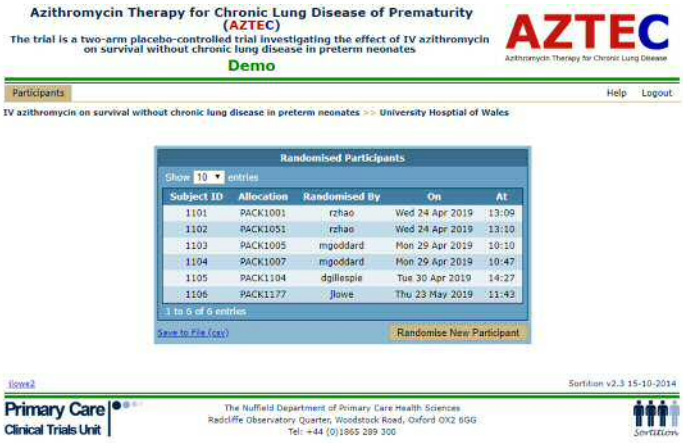
Randomisation must be carried out prior to administering the IMP

- Confirm that written informed consent from the parents has been taken by someone who has received suitable training and is named on the Delegation Log.
- Confirm the baby still meets all of the eligibility criteria and ensure a medically qualified person (who is delegated this duty on the Delegation Log) has documented clinical assessment of eligibility within the medical notes. The AZTEC eligibility sticker can used uses to support this (found in document box).

Steps to follow

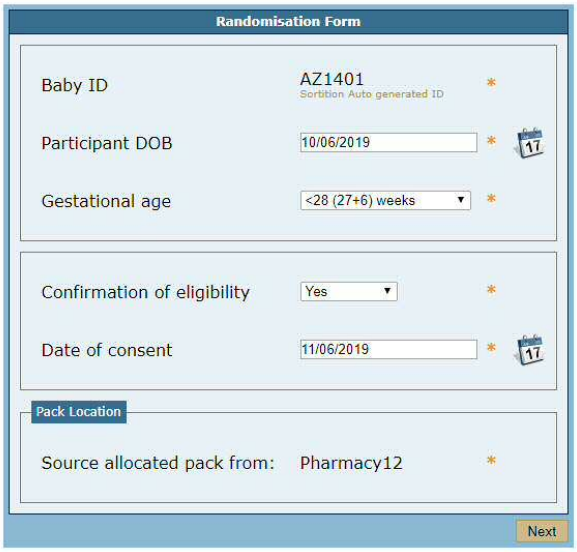
1. Access the study randomisation program (Sortition) at: https://ctu1.phc.ox.ac.uk/randomise/login
2. Log in using your individual credentials as assigned by the CTR team.

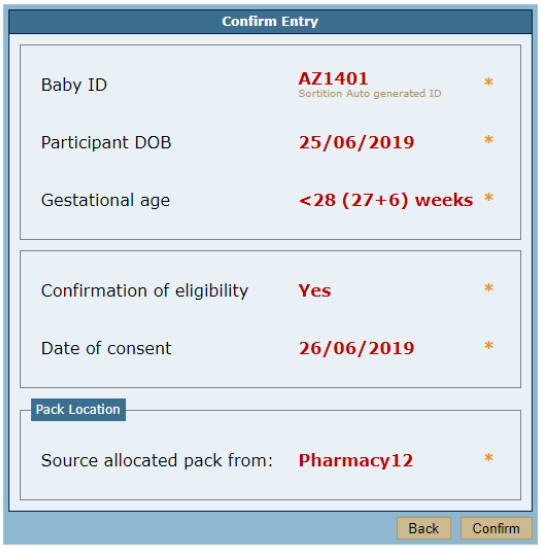
3. You will be taken directly to a randomisation page- note you should only be able to see a list of randomisations from your site



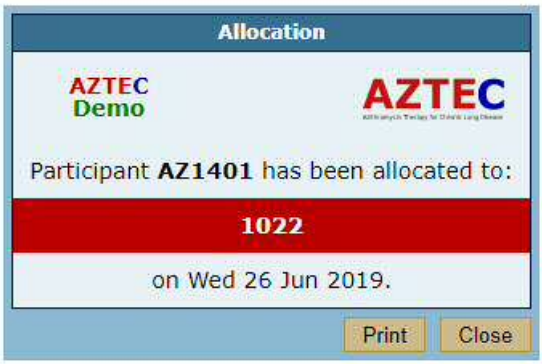
Guidance Sheet 4: Randomisation

4. Select 'Randomise new participant' from the menu and answer the inclusion/exclusion criteria to confirm eligibility. The baby is only recruited and randomised into the AZTEC trial when you confirm the data you entered is correct





5. The randomisation program will then confirm the baby's Study ID
   - Always starts with "AZ"
   - Then a 2-digit site identifier, which will always remain the same
   - Then a two-digit sequential number (i.e. "01" is first baby randomised)



6. The Baby is also allocated their IMP treatment **Pack ID**, a random 4-digit number

7. Before logging out print the randomisation details for the infant and place into the infant's clinical notes alongside the consent form. Allocations can be checked at any time by logging in to Sortition.

8. Check that the correct 'Pack ID' is available and unopened from the stock on the ward.

9. If the correct pack cannot be located, or the package is open, please report this to the trial manager urgently, LoweJ3@Cardiff.ac.uk, Tel 029 2068 7990

- Finally, please ensure the following:
    - Study ID recorded on the **Consent Form**
    - Study ID recorded on the **IMP pack label (outer box), and each vial label**
    - Pack ID recorded on the infant's drug chart or electronic prescribing system
    - **Screening Log** updated with the Study ID

- Put an **AZTEC Cot Card** on the infant's cot, and an **AZTEC Notes Sticker** (both documents located in the AZTEC document box) on the infant's clinical notes. Ensure that the neonatal team are aware that the infant is enrolled in AZTEC

Randomisation Backup

- If there are problems accessing the randomisation program during normal working hours (Monday-Friday 09:00-17:00), please contact the CTR data manager (029 2068 8105) or administrator (029 2068 7617) who are able to randomise on behalf of a site

Guidance Sheet 5a: Intervention

AZTEC
Azithromycin Therapy for Chronic Lung Disease
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Centre for Trials Research
Canolfan Ymchwil Treialon

a) Storage

The AZTEC medication is an Investigational Medicinal Product (IMP) and should always be stored appropriately.

Correct Storage at Site

In the AZTEC trial there is provision for IMP being held in pharmacy and on the neonatal unit. At recruiting sites, a stock of IMP will be held on the neonatal unit and resupplied from the pharmacy as and when required. It is essential that storage requirements are observed in all cases:

- On the neonatal unit, IMP should be stored in a locked cupboard or room. However, there are no specific temperature requirements for vials of IMP prior to reconstitution. The Local Research Nurse (LRN) or another member of the study team, in collaboration with pharmacy, should ensure a suitable storage area is identified prior to the start of the study.
- AZTEC IMP kept in the hospital pharmacy should be stored in a designated area for IMPs. Records will be maintained in accordance with that pharmacy's standard operating procedures.

b) Prescribing, preparation and administration of trial medication

Prescribing

Once it has been confirmed that a baby meets the eligibility criteria, written informed consent has been obtained, and the baby has been randomised, the AZTEC trial medication can be prescribed.

- The allocated medication will be:
  - **AZTEC IMP**: 10 ml/kg once daily, for 3 days; followed by 5 ml/kg once daily, for 7 days (10 days total).
- Babies will be allocated a **four-digit** Treatment Pack ID number during randomisation. This number will correspond to a pack containing 12 vials of either azithromycin or placebo. You will not know whether the baby has been allocated azithromycin or placebo. In the event of an emergency, unblinding is possible (**see Protocol, Section 12.3 and guidance sheet 11: Withdrawal & Unblinding**).

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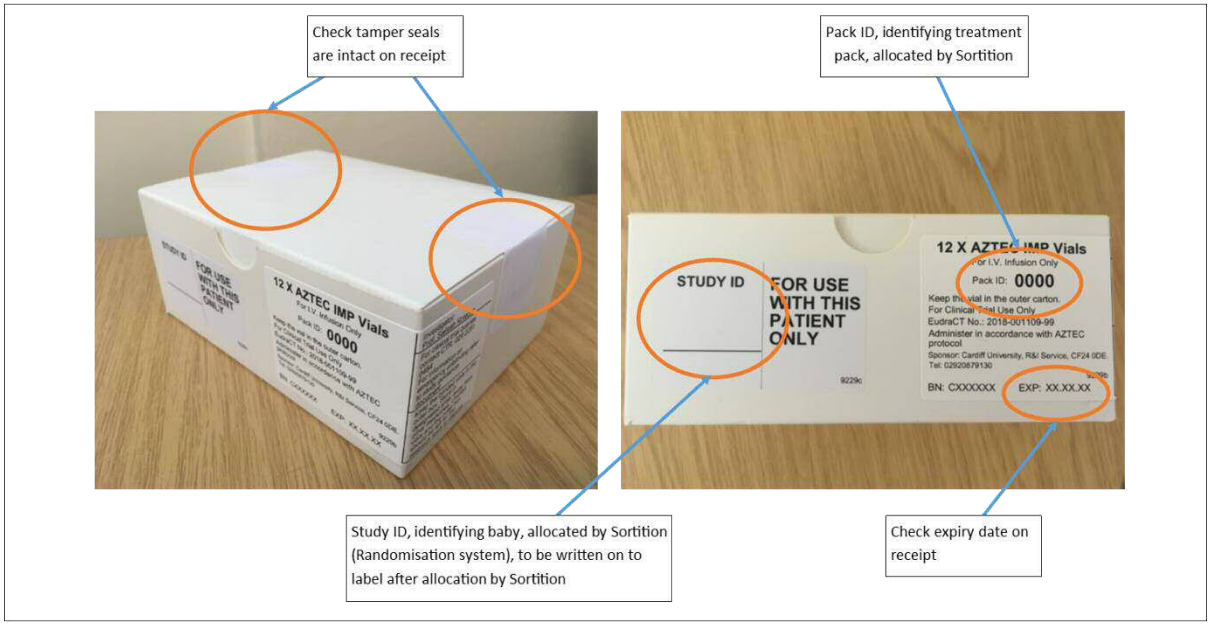
- The randomisation system will also allocate a Study ID to each randomised baby. This will always begin with the letters "AZ", followed by a two-digit site identifier; the second two digits are a sequential participant identifier (e.g. "AZ1103" for the third baby recruited at site 11). The study ID should be recorded on the treatment pack, and on each vial. A space is provided on the label for this purpose.

- Azithromycin or placebo as an IMP must be prescribed electronically or on the baby's drug chart, to be given by intravenous injection. Due to the changing of dose after day 3, two separate prescriptions are recommended. Suggested wording is as follows:
  - '**AZTEC IMP. Doses 1-3, 10 ml/kg once daily; [enter 4-character numeric value e.g. Pack ID 1234]**'.
  - **AZTEC IMP. Doses 4-10, 5ml/kg once daily; [enter 4-character numeric value e.g. Pack ID 1234]**'.
  - **The chosen diluent should also be described**
- The Pack ID 'e.g. 1234' of the allocated pack is an essential component of the prescription.

- Prescribers must be trained in the related trial procedures, and this documented on the training and delegation logs.



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Preparation & administration

- Packs of trial medication **must only be** administered to the baby to whom it was allocated. If there is any doubt about which pack a vial has come from, discard the vial (recording it on the "**Daily Log" CRF**).

- Each vial is enclosed in a cardboard blinding carton. The blinding carton **must** stay intact at all times and must not be removed.

- The IMP is provided as powder. Therefore, a reconstitution step must first be performed. **A separate guidance sheet is provided with more detailed information (see Guidance sheet 5b: IMP administration).**

- The dose MUST then be further diluted before administration. A standard strength dilution is used, with the volume given adjusted by weight and day of dosing for the individual baby. See **Guidance sheet 5b** for details.

- The required volume of IMP should be administered intravenously as an infusion over **at least 60 minutes**. The first dose must be administered soon after randomisation and within 72 hours of birth at the latest.

- Once given, record the administration on the baby's drug chart as usual **and** on the **"Daily log" form**.

Dose administration					
IMP given today?	Weight used to calculate dose (g)	Dose given (mL)	Reason if not given	Number of vials used	Number of vials wasted
☒ Yes ☐ No	500	5	☐ No I.V. access ☐ Other[2]	1	0

- Each of the steps should also be initialled by the individual leading the preparation

Preparation steps (sign each)			
Add 4.8 mL water	Invert 5 times	Stand for 5 mins	1ml in 49 mL diluent
AB	AB	AB	AB

- Omitted doses and any wasted vials (due to dropping, damage, spillage, expiration or contamination) must also be recorded on **"Daily log" form. A reason should be provided for omitted doses**

- Safety information for Azithromycin is contained within the SmPC (section 4.6), which is in the Investigator Site File and Pharmacy File.

Practical considerations

- A list of compatible products which can be administered alongside the AZTEC IMP is included on **Guidance Sheet 5b: IMP administration**. A complete list can be found in the document box and Investigator Site File.

- Dosing errors must be recorded on **Dosing Error Form**. Dosing Error Forms should be faxed/emailed to the CTR immediately with any accompanying information (Fax: 020 3043 2376; Email: CTR-Safety@Cardiff.ac.uk). The form can be found in the Investigator Site file.

- In the event the **dosing is postponed** for practical or clinical reasons administer the daily dose as soon as it is deemed safe to do so. If a dose is postponed, please consider rescheduling further doses and **maintain a minimum period of at least 12 hours between doses. Treatment should not be extended beyond 10 days** (missed doses should not be added to the end).

c) Reconciliation of trial medication at end of treatment

- The trial team need to be able to account for each vial of the AZTEC trial medication. There are three documents involved in tracking allocated medication use: **the baby's standard drug chart**, **Daily log**, and the **Treatment Pack Reconciliation Form**.
- At the **end of the baby's IMP course** (10 days after commencing treatment (regardless of number of doses received, but usually after 10), permanent discontinuation of treatment, or death) please do the following:

- Cancel the prescription and retain all unused vials in the allocated pack
- Ensure all doses are recorded and complete the accountability totals on the "**Daily log" form**

Dose administration					
IMP given today?	Weight used to calculate dose (g)	Dose given (mg)	Reason if not given	Number of vials administered	Number of vials wasted
Accountability check at end of dosing				10	1

- Place any unused packs away from unused supplies of IMP, in a designated location
- **All used packs will undergo a final reconciliation process prior to disposal (see Guidance sheet 9: IMP supply and accountability)**.

- The study team are also asked, with input from the nurses who prepared and administered the IMP, to answer the following question and record the outcome on the **Daily Log**

In the current opinion of the study team has the baby received	☐ Azithromycin, ☐ Placebo, ☐ unable to tell

d) Discontinuation of treatment

The daily administration of the trial medication should continue until 10 days after the first dose. Omitted or missed doses should not be replaced with additional doses beyond these 10 days. The medication may be discontinued sooner than this if the baby is transferred to a non-recruiting site, if the baby dies, or at clinician or parental request.

Data collection should continue until discharge, or death, except if the baby is completely withdrawn from the trial at parental request. This sheet details what should happen in each circumstance.

Baby transfer

- Provision has been made for IMP to be transferred with the baby if they are being moved to an AZTEC recruiting centre, or a continuation site. The Trial Manager will notify each recruiting site of arrangements in their local networks during site initiation.

- If the IMP is being transferred, the treatment pack will be re-sealed using an **IMP Transfer Sticker**, located in your site's document box.

- More detail on transfers is given in **Guidance sheet 12a: Preparing a Transfer.** Final reconciliation of the IMP will then be performed at the receiving site.
- A "**Transfer" form** should be recorded to record data regarding the period of hospital stay.

Baby death

- If a baby dies before being discharged home, complete form **"Outcomes at 36 weeks PMA"** covering the period that the baby was an inpatient in your hospital
- In addition, please send a copy of the **discharge summary** and, if and when available, a copy of the **post-mortem examination report**.

Clinician decision to stop the medication permanently

- There will be very few instances where the clinician will need to permanently discontinue the medication. It will be far more common for the medication to be temporarily discontinued for clinical reasons, and restarted when it is deemed safe to do so
- If permanently discontinued, cancel the prescription, but the baby should **remain in the trial** and complete data collection procedures as normal.

Parent request to withdraw from the trial

- A parent has the right to withdraw their baby from the trial at any time and for any reason, without prejudice to the baby's care; they do not have to provide a reason for their decision.
- It is **important that you clarify** with the parent(s) whether, despite stopping the medication, they would agree to:
    - retention and use of the data already collected,
    - for samples to be collected, and
    - for data collection to continue to completion, i.e. an Oxygen Reduction Test (due at 36 weeks of postmenstrual age) (if applicable)
- After consulting the parents complete a **withdrawal form** recording their wishes regarding the withdrawal
- Cancel the baby's prescription, and, i**n all instances** retain the unused vials in the allocated pack. The research nurse will collect all used packs and initiate the reconciliation process.

Guidance Sheet 5a: Intervention

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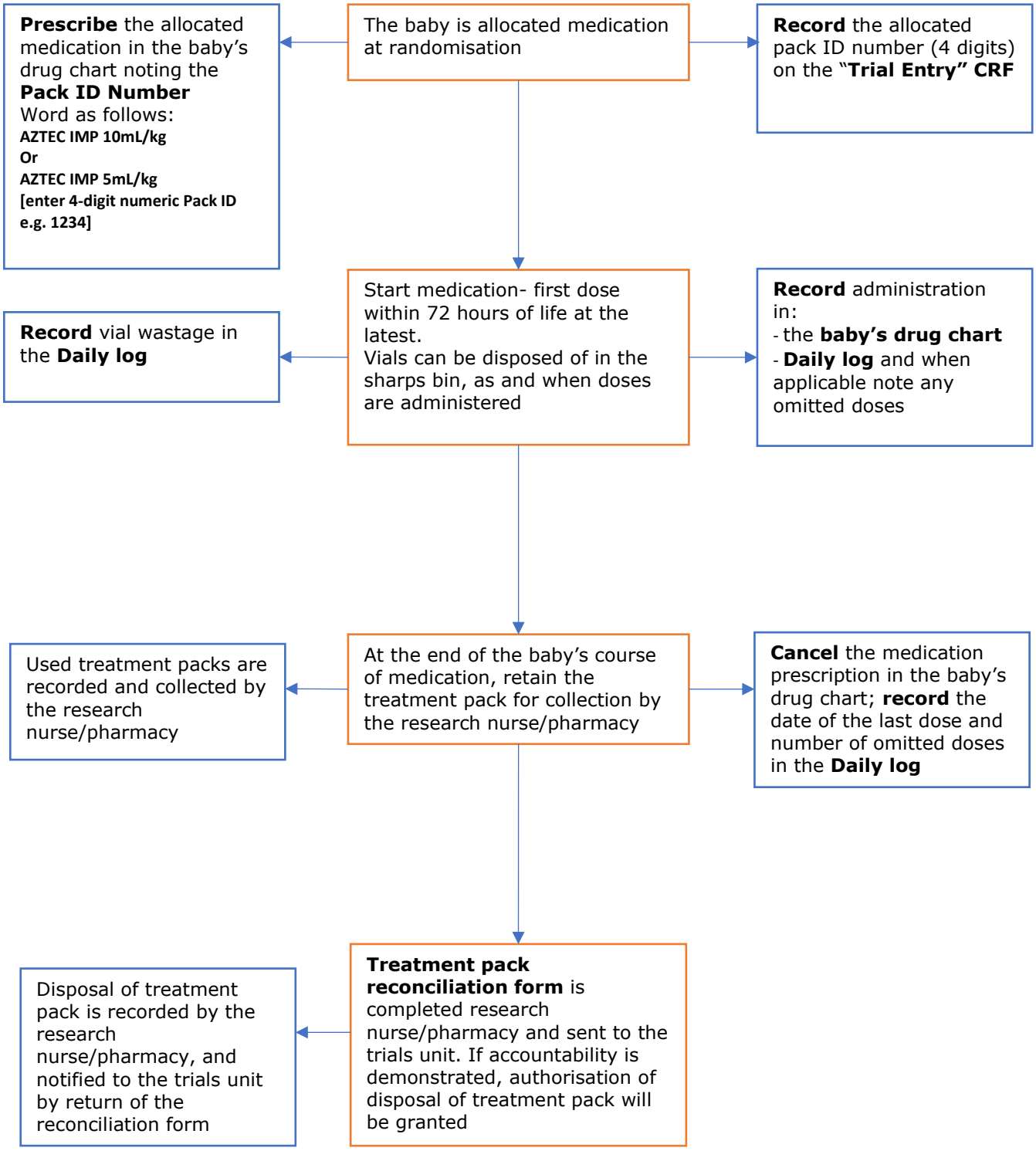
Summary flowchart



Guidance Sheet 5b: IMP administration

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Drug Name	AZTEC IMP for I.V. infusion	For AZTEC clinical trial use only
Dosage	Doses 1-3 inclusive: 10ml/kg once daily Doses 4-10 inclusive: 5ml/kg once daily	
Preparation	****Use aseptic technique, as per local guidelines**** Each AZTEC IMP treatment pack contains 12 vials (1 for each of 10 days treatment, plus 2 spare). Each vial is enclosed in a cardboard blinding carton. ****The vials must not be removed from the blinding carton**** 1) Check the Pack ID on the treatment pack label matches the Pack ID assigned to the baby (see printout from randomisation system and daily log) 2) Select one AZTEC IMP vial from the treatment pack (all are identical). Check vial ID also matches assigned number. 3) Add 4.8ml of sterile water for injection to an AZTEC IMP vial using a 5ml syringe 4) Discard the 5ml syringe. 5) Gently invert the vial 5 times. 6) Allow vial to stand for a **minimum** of 5 minutes. ****Reconstituted vial gives 100mg in 1ml solution- must be diluted prior to administration- follow dilution steps 7-10**** 7) Using a 50ml syringe, draw up 49ml of suitable diluent o 0.9% saline o 5% dextrose o 0.45% saline o 5% dextrose in 0.45% saline o 5% dextrose in 0.3% saline 8) Using a 2ml/2.5ml syringe, take 1ml (100mg) from the AZTEC IMP vial, and add to the 50ml syringe containing the diluent (this gives the correct IMP administration concentration of 2mg/ml). 9) Discard the used AZTEC IMP vial in its entirety (including the blinding carton), and 2ml/2.5ml syringe, as per local guidelines. 10) Label the syringe containing IMP as per local practise, including the baby's AZTEC study ID e.g.	

Drug added	Amount	Time	Initials
0.9% sodium chloride	49ml	10:00	HCL
AZTEC IMP	1ml	10:00	HCL
Total	50ml		
Patients name: Joseph Bloggs, AZTEC study ID AZ1101			
Date: 13/05/2019			

Guidance Sheet 5b: IMP administration

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Administration	▪ Adjust the infusion pump to deliver the required volume over at least 60 minutes. **Example**: Infusion volume= weight in kg x fluid volume needed (10ml or 5ml) For doses 1-3 for a 500g baby: 0.5 x 10ml = 5 ml 5ml/hour for 60 minutes On doses 4-10 for a 500g baby: 0.5 x 5ml = 2.5ml 2.5ml/hour for 60 minutes ▪ Administer intravenously ○ Umbilical venous catheter ○ Peripherally inserted central catheter (long line) ○ Peripheral cannula ▪ If access is 'lost' during infusion, continue any residual dose once new access is established, even if some appears to have 'tissued'. Do not repeat the dose with a new vial. Once prepared for infusion the solution is stable for a maximum of 24 hours at room temperature.
Diluents	○ 0.9% saline ○ 5% dextrose ○ 0.45% saline ○ 5% dextrose in 0.45% saline ○ 5% dextrose in 0.3% saline
Compatibilities	Total Parenteral Nutrition (TPN), Adrenaline, Dopamine, Dobutamine, Vancomycin. See full list in AZTEC document box.
Incompatibilities	Amikacin, amiodarone, aztreonam, cefotaxime, ceftazidime, ceftriaxone, chlorpromazine, ciprofloxacin, clindamycin, fentanyl, furosemide (frusemide), gentamicin, imipenem-cilastatin, ketorolac, midazolam, morphine sulphate, mycophenolate mofetil, pentamidine, piperacillin-tazobactam (EDTA-free), potassium chloride, thiopental sodium, ticarcillin-clavulanate, tobramycin.
Monitoring	During Infusion- heart rate and blood pressure IV site for signs of phlebitis Liver function
Side effects	Common: Nausea, vomiting, abdominal pain and diarrhoea (all less than erythromycin). Rare: Increased liver enzymes, hepatitis, hepatic necrosis, hypersensitivity reactions, hypertrophic pyloric stenosis, thrombophlebitis, ventricular dysrhythmias (In general, the risk of dysrhythmias is increased when these agents are administered in combination with other drugs that prolong the QT interval)

Guidance Sheet 6: Data Collection

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General

- AZTEC data will primarily be captured using an electronic Case Report Form (eCRF)

- There are some circumstances where the initial data collection is made on paper, and requires transcribing to the eCRF. These are outlined in the table below. Paper versions of each CRF form will be available and are kept in the AZTEC document box. If you are running low on stock you can request more by contacting the Trial Administrator at the CTR (AZTEC@Cardiff.ac.uk).

- If you make a mistake when completing a paper form, strike through once and initial and date the correction; please **do not** use Tipp-ex or scribble out the mistake.

- A screening log should be completed for each baby considered for entry to the trial. Consent form must be completed prior to any study procedures being undertaken should be completed for all babies in the trial.

- There are 10 case report forms (CRFs) for the study:
    - **Form 1: Eligibility**
    - **Form 2: Trial Entry**
    - **Form 3: Contact details**
    - **Form 4: Daily log**
    - **Form 5: Transfer (< 36 weeks PMA)**
    - **Form 6: Outcomes at 36 weeks PMA (discharge/death if sooner)**
    - **Form 7: Outcomes post 36 weeks PMA**
    - **Form 8: Adverse reactions**

- There are a further 2 CRFs in that may be required for some babies:
    - **Form 9: Baby withdrawal Form**
    - **Form 10: Serious Adverse Event Report Form (SAE)**

- For **all forms** (**Trial Entry** in particular), please add as much information about the baby as possible. This is particularly important if the baby has no first name yet, or it is a multiple birth e.g. Female or Male, Twin 1, Triplet 2 etc.
- All the data requested in the forms are routine clinical items that can be obtained from the clinical notes
- Please answer all questions, explain missing data, avoid ambiguous answers

Guidance Sheet 6: Data Collection

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Form	Electronic (E)/Paper (P)	Completion time	Completed by	Notes	Further information
Eligibility	E- directly to eCRF	At time of enrolment	Entry to eCRF by delegated individual	If completed on paper, transcribe to eCRF asap	Guidance sheet 2: Screening and consent
Trial entry	E- directly to eCRF	At time of enrolment (after eligibility confirmed by clinician)	Entry to eCRF by delegated individual	If completed on paper, transcribe to eCRF asap	Guidance sheet 2: Screening and consent
Daily log	P+E- paper then transcribed to eCRF	From enrolment until 21 days post start of treatment	Paper version completed at cot-side by qualified health professional. Transcribed to eCRF by delegated individual	Please en	Guidance sheet 7: Data entry
Transfer	E- data taken from clinical notes and directly entered onto eCRF P (for transfers occurring from continuing care sites only)	At the point of transfer, if this occurs prior to 36 weeks PMA	Entry to eCRF by delegated individual (including paper CRFs returned from continuing care sites)	If completed on paper, transcribe to eCRF asap	Guidance sheet 7: Data entry Guidance sheet 12a: Preparing a transfer
Outcomes at 36 weeks PMA	E- data taken from clinical notes and directly entered onto eCRF P (if data collected at continuing care sites)	At 36 weeks PMA (± 1 week)- discharge home or death if sooner	Entry to eCRF by delegated individual (including paper CRFs returned from continuing care sites)	If completed on paper, transcribe to eCRF asap	Guidance sheet 7: Data entry Guidance sheet 10: Oxygen reduction test

Guidance Sheet 6: Data Collection

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Form	Electronic (E)/Paper (P)	Completion time	Completed by	Notes	Further information
Outcomes post 36 weeks PMA	E- data taken from clinical notes and directly entered onto eCRF P (if data collected at continuing care sites)	At transfer, discharge home or death, if occurring after 36 weeks PMA	Entry to eCRF by delegated individual (including paper CRFs returned from continuing care sites)	If completed on paper, transcribe to eCRF asap	Guidance sheet 7: Data entry
Withdrawal	P+E- paper then transcribed to eCRF	As soon as withdrawal occurs	Entry to eCRF by delegated individual	Paper copy to go in baby' notes	Guidance sheet 7: Data entry Guidance sheet 11: Withdrawal & Unblinding
Adverse reactions	E- Directly entered onto eCRF P (if data collected at continuing care sites)	From randomisation, until 36 weeks PMA- discharge home or death if sooner	Entry to eCRF by delegated individual (including paper CRFs returned from continuing care sites)	If completed on paper, transcribe to eCRF asap	Guidance sheet 7: Data entry Guidance sheet: 8 Safety and non-compliance reporting
SAE form	P	Within 24 hours of becoming aware of the SAE	Section 1-16: any individual Section 17: medically qualified delegated member of the trial team	Fax/email to the CTR immediately, keep the original in the ISF	Guidance sheet: 8 Safety and non-compliance reporting
Screening log	E- directly entered onto the eCRF	At the time of screening	Trial team (after decision on eligibility made)	Please update on a weekly basis	Guidance sheet 2: Screening and consent Guidance sheet 7: Data entry
Accountability log	P	At receipt of IMP and on return of any unused IMP	Pharmacy team		Guidance sheet 9: IMP supply and accountability

Guidance Sheet 6:
Data Collection

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Form	Electronic (E)/Paper (P)	Completion time	Completed by	Notes	Further information
Drug quality form	P	On receipt of IMP shipment	Pharmacy team	Only of quality issues are noted	Guidance sheet 9: IMP supply and accountability
IMP reconciliation log	P	At the end of trial treatment for each baby	Research team/pharmacy, then CTR	Once completed, return to the CTR for checking and sign-off prior to disposing of used IMP, keep the original in the ISF	Guidance sheet 9: IMP supply and accountability
Dosing error report	P	Within 24 hours of becoming aware of the event	Trial team	Return to the CTR immediately via fax/email, keep the original in the ISF	Guidance sheet: 8 Safety and non-compliance reporting
Non-compliance report	P	Within 24 hours of becoming aware of the event	Trial team	Return to the CTR immediately via fax/email, keep the original in the ISF	Guidance sheet: 8 Safety and non-compliance reporting

Guidance Sheet 6: Data Collection

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Specific points to remember about each data collection form

Consent Form

- This is an NCR (carbon copy) form which comprises of 3 sheets - please ensure that any signatures/initials transfer through to the subsequent duplicate sheets
- ASAP after randomisation directly record the allocated Study ID given by the randomisation program on the consent form alongside the NHS/CHI number of the baby
- The sheets are colour-coded, the top original sheet should scanned/faxed back to the CTR before being placed in the clinical notes. Other copies are to go (i) into the Investigator Site File, (ii) to the parent(s)
- If the father consents for the baby to participate into the trial, **ensure** the mother countersigns in the space provided. We need her consent for some of the maternal data collected at trial entry/randomisation.

Eligibility form

- The decision for eligibility and trial enrolment must be made by a medically qualified doctor and there should be clear documentation of this in the baby's notes. Stickers are provided in the document box to facilitate recording of confirmation of eligibility.
- Please complete the eCRF **within 7 days of birth**

Trial Entry form

- Complete the first section of the form prior to randomisation so the required information is at hand to conduct the randomisation
- ASAP after randomisation directly record the allocated Study Number and Pack ID Number given by the randomisation program on the eCRF
- Please complete the whole eCRF **within 7 days of birth**

Guidance Sheet 6: Data Collection

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Daily log CRF

- The daily log is designed to be paper-based and completed at the cot-side
- The first two rows of the daily log capture a limited amount of data on days **prior to commencing the IMP** (as treatment may begin up to 72 hours after birth, at the latest).

Example completion if the baby does not start study treatment until day 3 of life:

Day 1 of life

Day 2 of life

Day 3 of life (start of study treatment)

	Date (dd/mm/yyyy)	Sampling: Airway sample type taken*	Sampling: Stool sample taken	IMP given today?
Day before study treatment	13/06/2019 ☐ N/A	☐ ETA ☐ NPA ☒ No[1]	☐ Yes ☒ No[1]	
Day before study treatment	14/06/2019 ☐ N/A	☒ ETA ☐ NPA ☐ No[1]	☐ Yes ☒ No[1]	
Day of study treatment 1	15/06/2019	☐ ETA ☐ NPA ☒ No	☐ Yes ☒ No	☒ Yes ☐ No

Example completion if the baby starts study treatment on day 1 of life:

Rows not required

Day 1 of life (start of study treatment)

	Date (dd/mm/yyyy)	Sampling: Airway sample type taken*	Sampling: Stool sample taken	IMP given today?
Day before study treatment	☒ N/A	☐ ETA ☐ NPA ☐ No[1]	☐ Yes ☐ No[1]	
Day before study treatment	☒ N/A	☐ ETA ☐ NPA ☐ No[1]	☐ Yes ☐ No[1]	
Day of study treatment 1	15/06/2019	☒ ETA ☐ NPA ☐ No	☐ Yes ☒ No	☒ Yes ☐ No

- If IV antibiotics have been given, use the coded list on page two to record which were given

I.V. Antibiotics given today?	If yes, which anti-biotics? **	Positive blood or CSF culture today?	If positive, which sample?	If positive, date sample taken (dd/mm/yyyy)	If positive, which organism(s)
☒ Yes ☐ No	1 2	☒ Yes ☐ No	☒ Blood ☐ CSF	29/08/2019	1. *Streptococcus* 2. _____ 3. _____

**Antibiotic code list	
1. Benzylpenicillin	8. Meropenem
2. Gentamycin	9. Teicoplanin
3. Amoxicillin	10. Piperacillin/tazobactam
4. Flucloxacillin	11. Cefotaxime
5. Ceftazidime	12. Ampicillin
6. Metronidazole	13. Clindamycin
7. Vancomycin	14. Ceftriaxone

- Complete the form up to 21 days post start of treatment (the last sampling timepoint).

- Please transcribe data from the paper daily log to the eCRF regularly **and at least every week**
- If the baby is **transferred**, please contact the CTR. See **Guidance sheet 12a** for more details regarding preparation of a transfer.

Transfer CRF (prior to 36 weeks PMA)

Information to be recorded on the Transfer form should only be for the time they spent in your unit.

- To be completed when the baby leaves your hospital to be transferred to another hospital, prior to reaching 36 weeks PMA
- If a baby is transferred for less than 24 hours, e.g. for surgery and returned to you, there is no need to complete a separate Transfer CRF for this brief stay, instead incorporate the associated data on the one form; You will need to inform the surgical centre of the transfer so that you can collect any relevant data easily.
- When reporting cerebral ultrasounds, if there are multiple scans, enter the data for the scan closest to date of transfer with the worst abnormality
- In addition, ensure that you have confirmed the 'abnormality' or responded 'none, and ticked at least one box in both 'left' and 'right' columns.

Outcomes at 36 Weeks PMA CRF

To be completed at 36 weeks of PMA or at discharge if discharged home earlier, or dies.

- Only perform the oxygen reduction test if baby has received oxygen, and/or respiratory support for ≥ 28 days and the following:
    - the baby is not receiving mechanical ventilation (invasive and non-invasive), CPAP, or high flow oxygen therapy
    - FiO2 < 0.3, or low flow oxygen < 1.1 L/min to maintain saturations of ≥ 91%
    - In previous 24 hours, baby has not required respiratory support.
- When reporting cerebral ultrasounds, if there are multiple scans, enter the data for the scan closest to 36 weeks of postmenstrual age with the worst abnormality
- In addition, ensure that you have confirmed the 'abnormality' or responded 'none', and ticked at least one box in both 'left' and 'right' columns.

- In the event of death please send a copy of the discharge summary and, if and when available, a copy of the post-mortem examination report. This should be redacted of personal identifiers and labelled with the baby's Study ID.

Outcomes post 36 weeks PMA CRF

To be completed at transfer to another hospital, discharge home or if the baby dies post-36 weeks PMA. The information to be recorded on the form should only be for the time they spent in your unit post 36 weeks PMA.

Adverse Reactions CRF

- The safety reporting period will be defined as beginning at the point of randomisation, and will continue until 36 weeks' postmenstrual age, or discharge home from hospital (whichever is soonest).
- Use this form to record
    - Events which a study physician considers to be attributable to azithromycin (causality assessment: probably, definitely, almost certainly). **This is regardless of whether they meet the criteria for being 'serious'.**
- Any **unforeseen** serious adverse event, or serious adverse reactions must be recorded on **a Serious Adverse Events form**
- Please see **Guidance Sheet 8: Safety and non-compliance** for more details

Baby withdrawal CRF

- To be completed and signed by the Principal Investigator or delegated deputy for any baby who is totally withdrawn from the trial, or whose parents request to stop their baby's ongoing participation in the trial
- It is important that you clarify with the parent(s) and record on the form whether, despite stopping the medication, they would agree to retention and use of the data already collected, for data collection to continue to completion and for the oxygen reduction test to be conducted (if applicable)

- Depending on the wishes of the parent(s) further data collection and form completion may be required
- Remember to place a copy of the completed Form in the baby's clinical notes.

Serious Adverse Event Report Form (SAE) CRF

- The safety reporting period will be defined as beginning at the point of randomisation, and will continue until 36 weeks' postmenstrual age, or discharge home from hospital (whichever is soonest).
- Unforeseeable Serious Adverse Events will be reported to the CTR within 24 hours of staff at the site becoming aware of the event using this form
- A study physician (Investigator) is responsible for reviewing the SAE and considering whether the event was related to the study drug.
    - If a study physician is not available to make the causality assessment send in the SAE Reporting Form without this information and re-send the form as soon as this assessment has been made.
    - A Physician who is not a member of the study team may offer an opinion as to whether the event was related to the study drug(s) and this opinion should be documented in the participant's medical records.
- For further information, please see **Guidance Sheet 8: Safety and compliance**

AZTEC: Azithromycin Therapy for Chronic Lung Disease of Prematurity

A randomised, placebo-controlled trial of azithromycin for the prevention of chronic lung disease of prematurity in preterm infants

Guidance Sheet 7:

Data Entry

This document is only to be used by staff trained in the Aztec study. The purpose of this document is to provide guidance for the use of the Aztec database for data entry.

Contents

AZTEC Database Guidance Version Details

Version number	1.0	Effective Date	10.07.2019
Supersedes version:			
Prepared by	Mark Goddard Research Assistant/ Data Manager		08.07.2019
		Signature	Date
Authorised by	John Lowe Research Associate/ Trial Manager		08.07.2019
		Signature	Date

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Contacts

If you have any problems, please get in touch -

Name	Role	Email	Tel No:
Mark Goddard	Data Manager	goddardm@cardiff.ac.uk	029 22511592
John Lowe	Trial Manager	LoweJ3@cardiff.ac.uk	029 2251 0484
Generic email	Aztec@cardiff.ac.uk		

Database Access

Aztec will be using an online database for data collection located here-

http://aztec.sewtudb-test.cf.ac.uk/

Research nurses will be given access to the database on receipt of –

- GCP certificate
- Current CV
- Signed delegation log
- Signed training log

Randomisation

Please note, you must randomise a trial participant into the Sortition randomisation system before they can be entered onto the database, as you will need to enter the 4-digit number generated during the randomisation process.

Logging Onto The Aztec Database

Enter the username and password emailed to you. On first log in you will be given the opportunity to change your password.

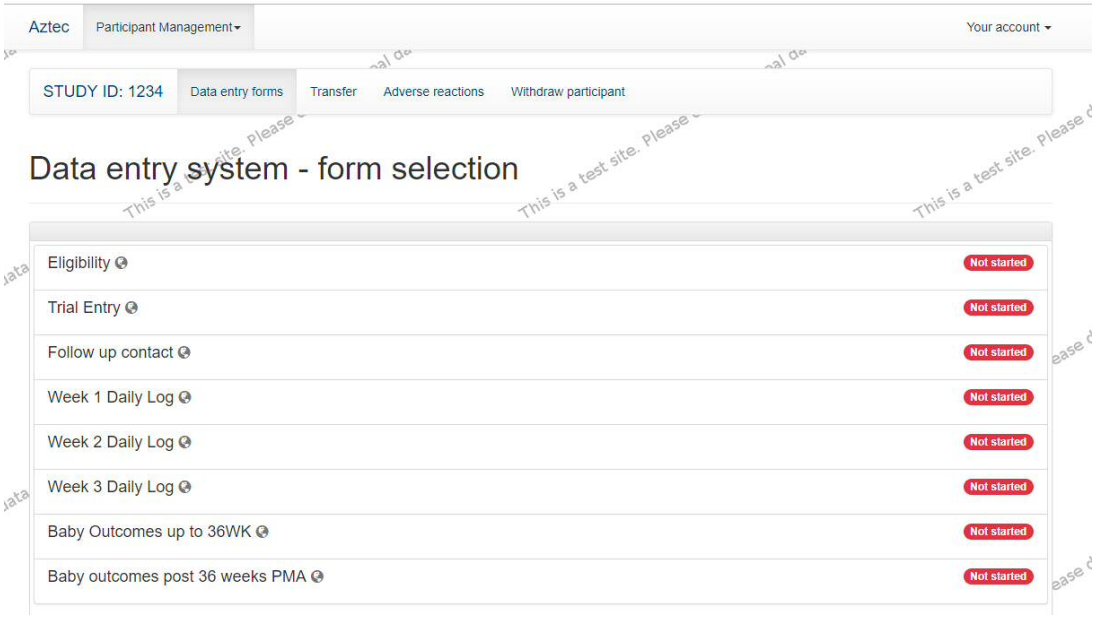
Adding A New Participant

Once logged in, you can then add a new trial participant as follows –

Please enter the 4-digit study ID that was generated from the Sortition randomisation system and complete all other fields. Then press 'Save details'.

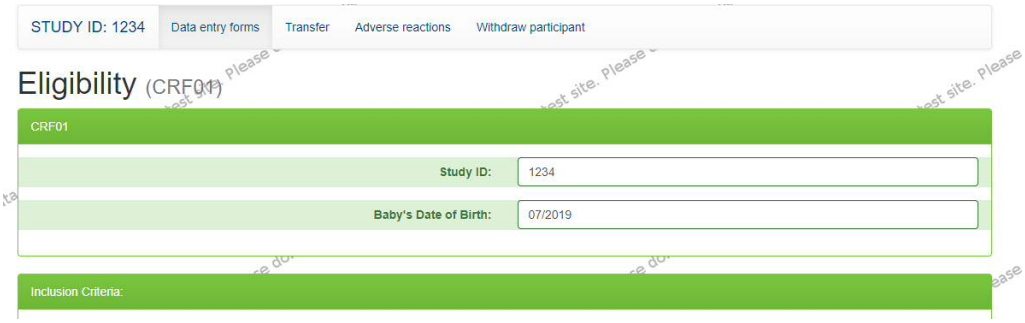
Data Entry

Once the participant has been entered into the system, data entry of the forms can begin by selecting the relevant one from the list below.



At the top of every form you will need to confirm the study ID and baby's date of birth (mm/yyyy). This is to make sure data entered is for the correct baby. If an incorrect study ID or date of birth is entered, they will be highlighted in red.

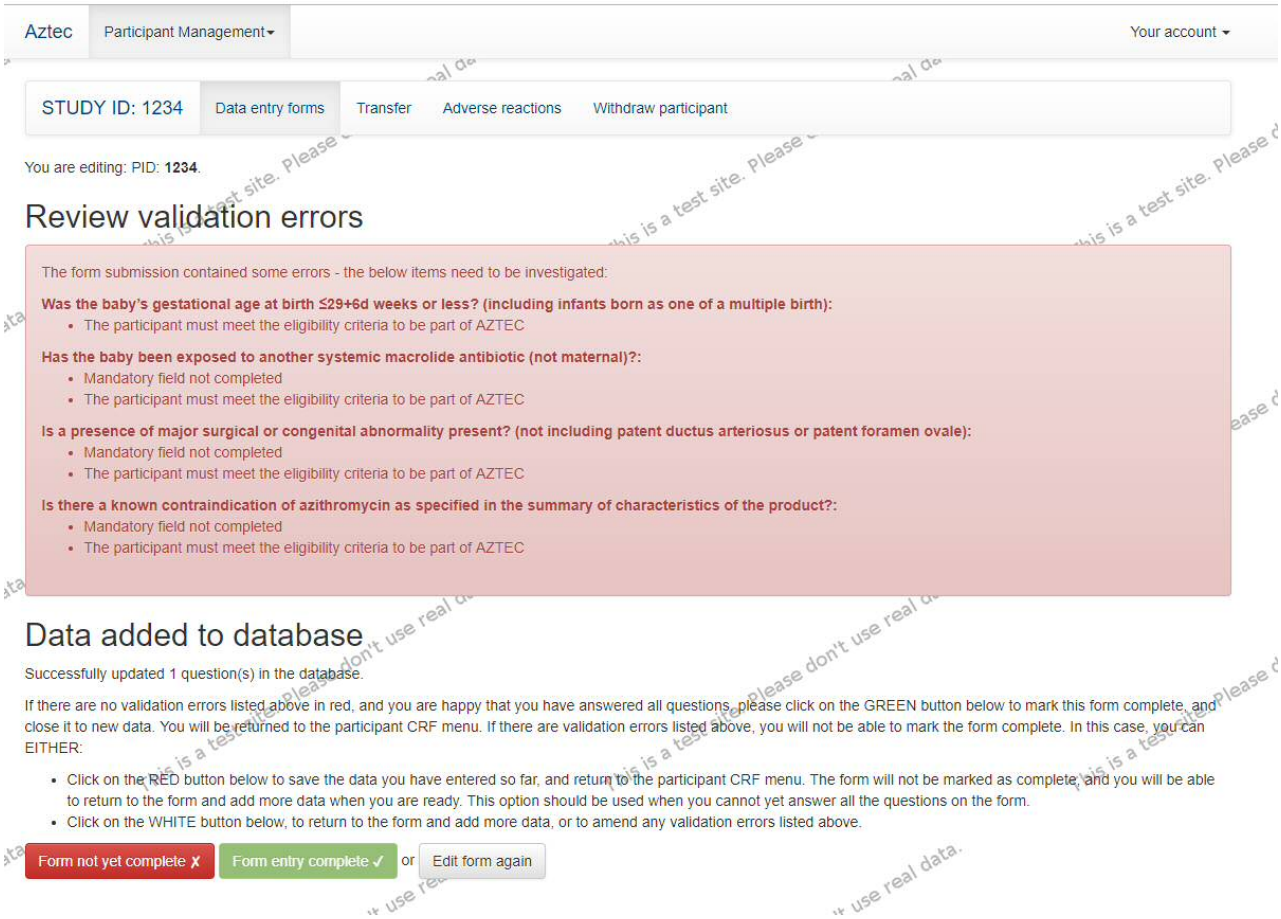
When correct study ID and date of births are entered, they will be highlighted in green.



When completing forms, all questions must be answered. If the database detects anomalies, these will be highlighted in red.

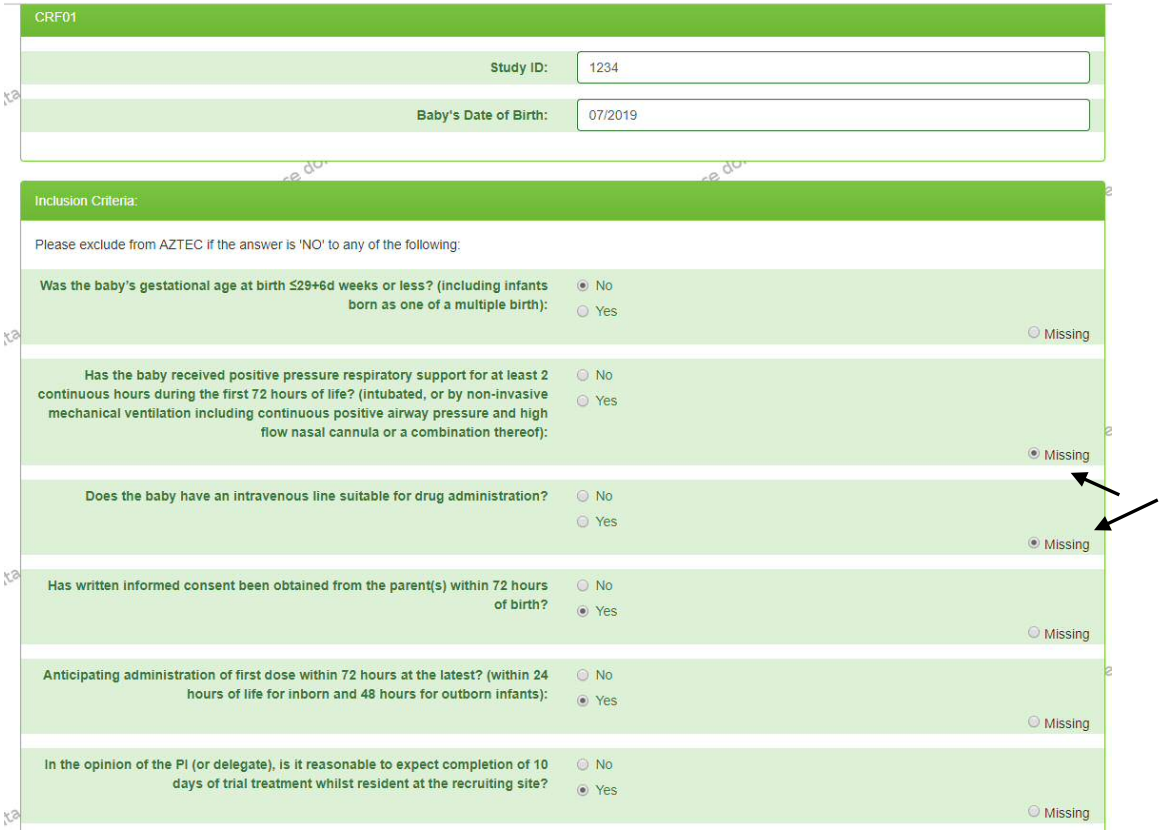
When all questions have been answered, you can save the form by clicking 'Save details' at the bottom of the page.

After clicking 'Save details' you might be shown a list of errors that the database has detected. This might include any questions that have not been answered.

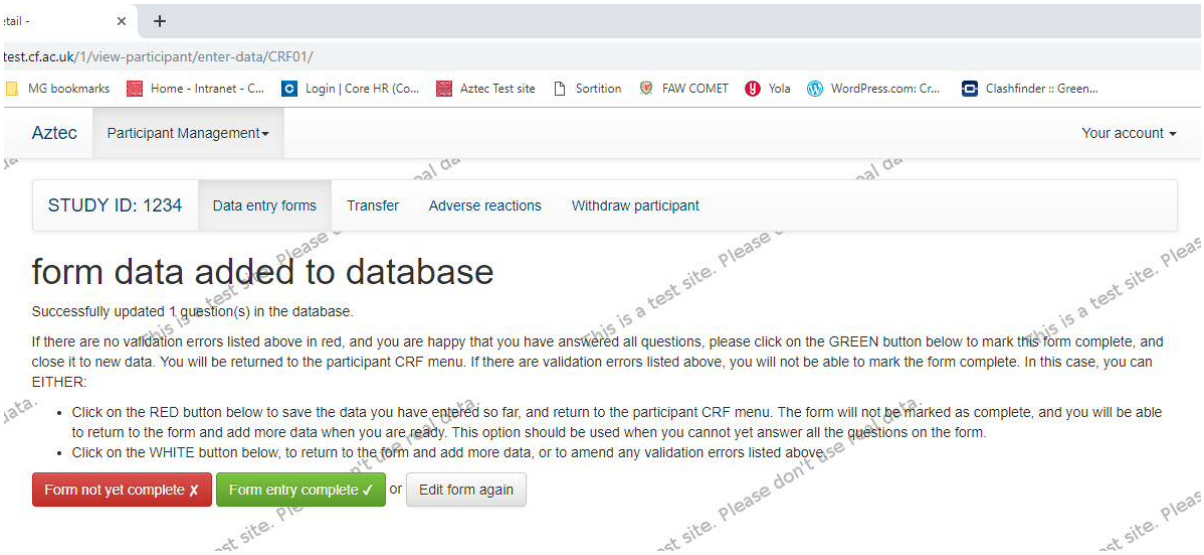


The form will still be saved but you will be unable to mark the form as complete until these errors have been addressed. To save the incomplete form select the red box at the bottom - 'Form not yet complete'.

If you want to address the errors at the present moment, select the grey box 'Edit form again'. If any unanswered questions are not able to be completed, please tick the missing box at the end of the question.

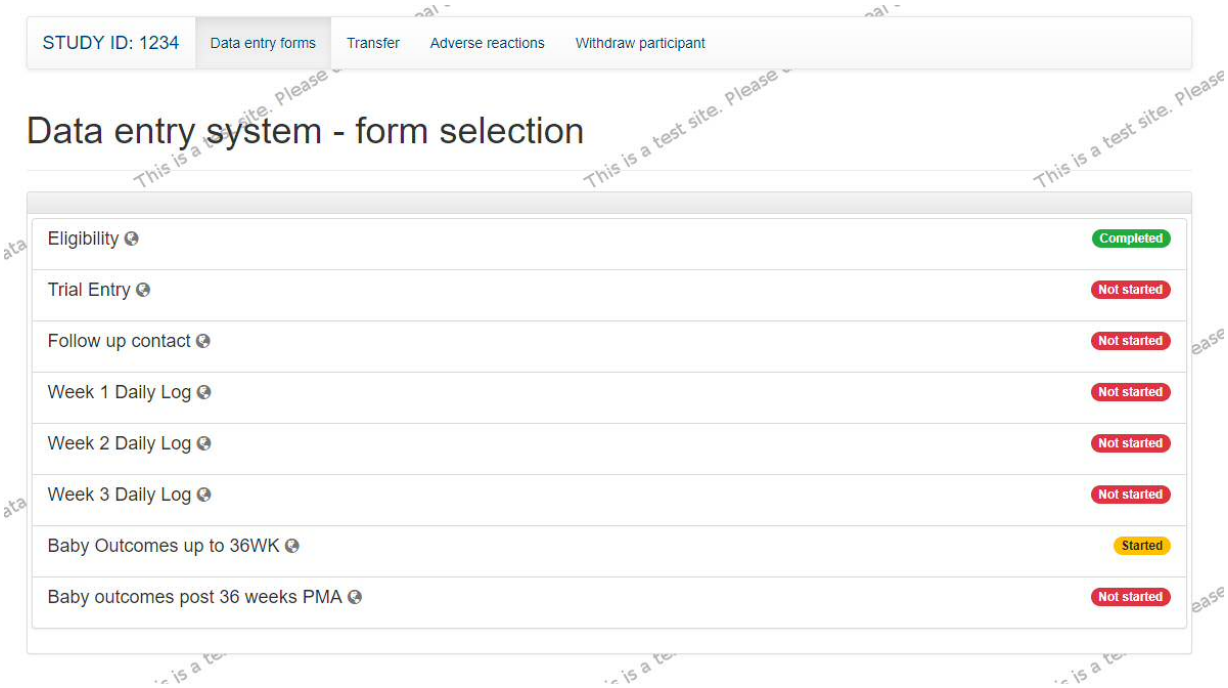


Once the errors have been addresses you will be able to save the form and mark it as complete, (see green button below).



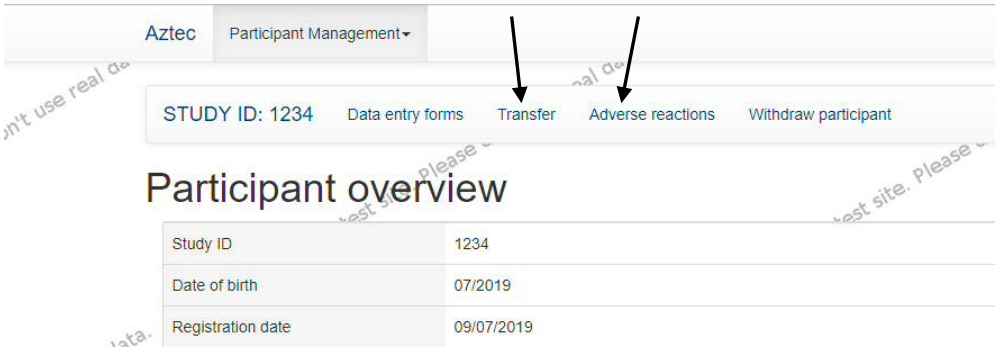
If you are in the middle of data entry and get called away, you can save the form at any point and mark it as not complete.

Forms will be listed as either not started, started or complete as data entry is carried out, see below.

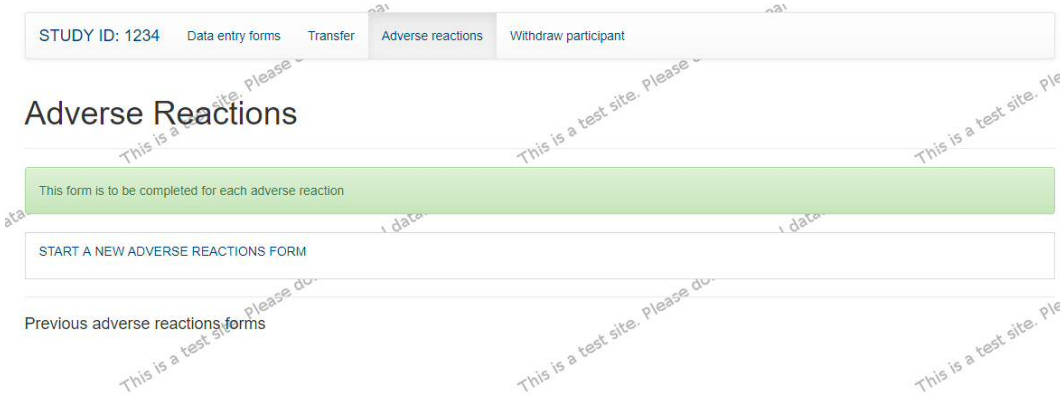


Multiple Entry Forms

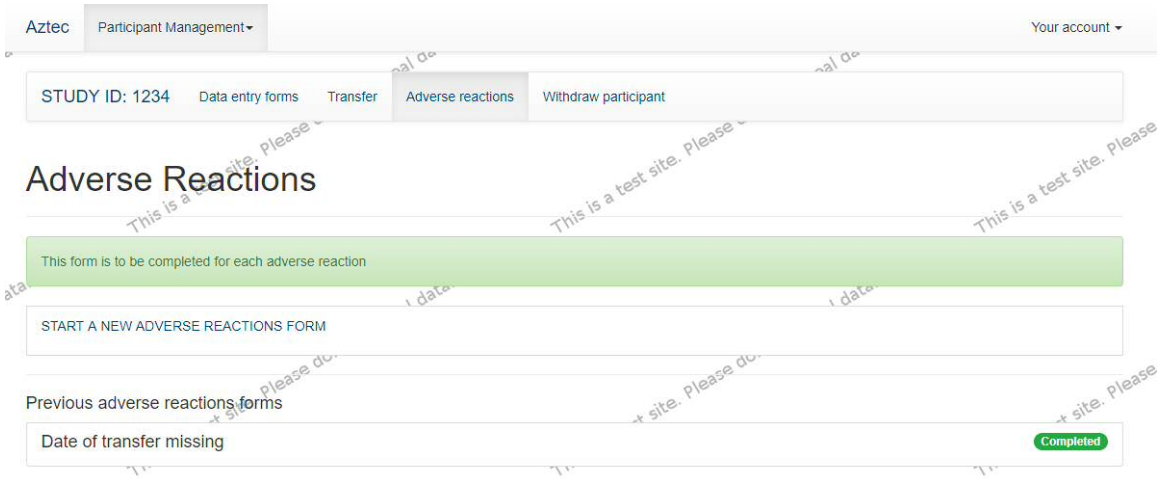
Two forms – Transfer and Adverse Reactions, can be completed multiple times. These are listed, alongside the withdrawal form, at the top of the screen.



To start a form, click on the link as listed above and you should see a screen as below. Click on 'START A NEW …… FORM'



Once that form has been saved, you can then create a new one or open a previously entered one, listed below as 'Completed'.



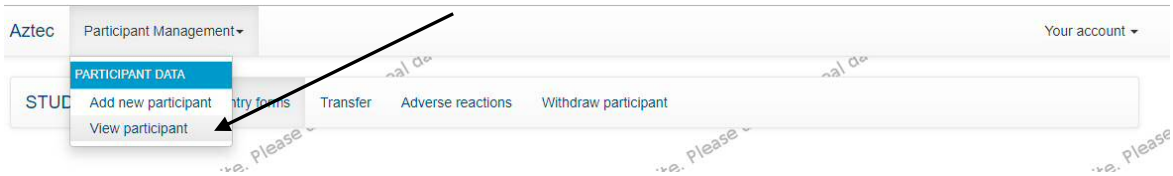
Withdrawal Form

When a withdrawal occurs, depending on the level, other forms will become 'read only'. To summarise –

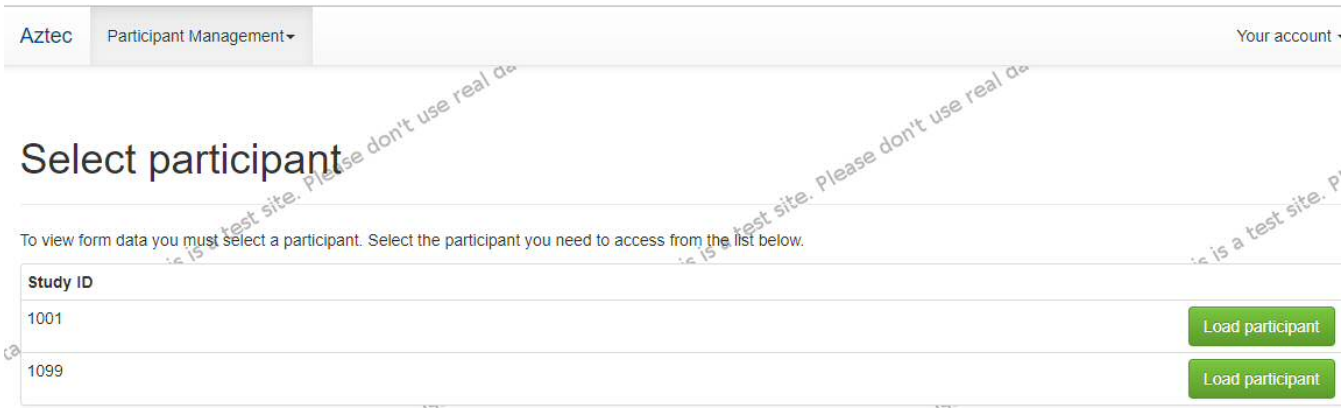
Level	**Form that becomes Read Only**		
Withdrawal of trial treatment	Week 1 daily log	Week 2 daily log	Week 3 daily log
Withdrawal from samples -	Week 1 daily log	Week 2 daily log	Week 3 daily log
Withdrawal from follow-up assessments	Follow up contact	Baby outcomes 36 weeks	Baby outcomes post 36 weeks
Withdrawal of consent to all of the above	All forms including Adverse reactions, withdrawal and transfer		
Full data withdrawal:	All forms including Adverse reactions, withdrawal and transfer		

Viewing Participants

To view, add or amend data on a previously entered participant, you need to select 'View participant' as follows –



This will then allow you to view all participants entered for your site, as below.

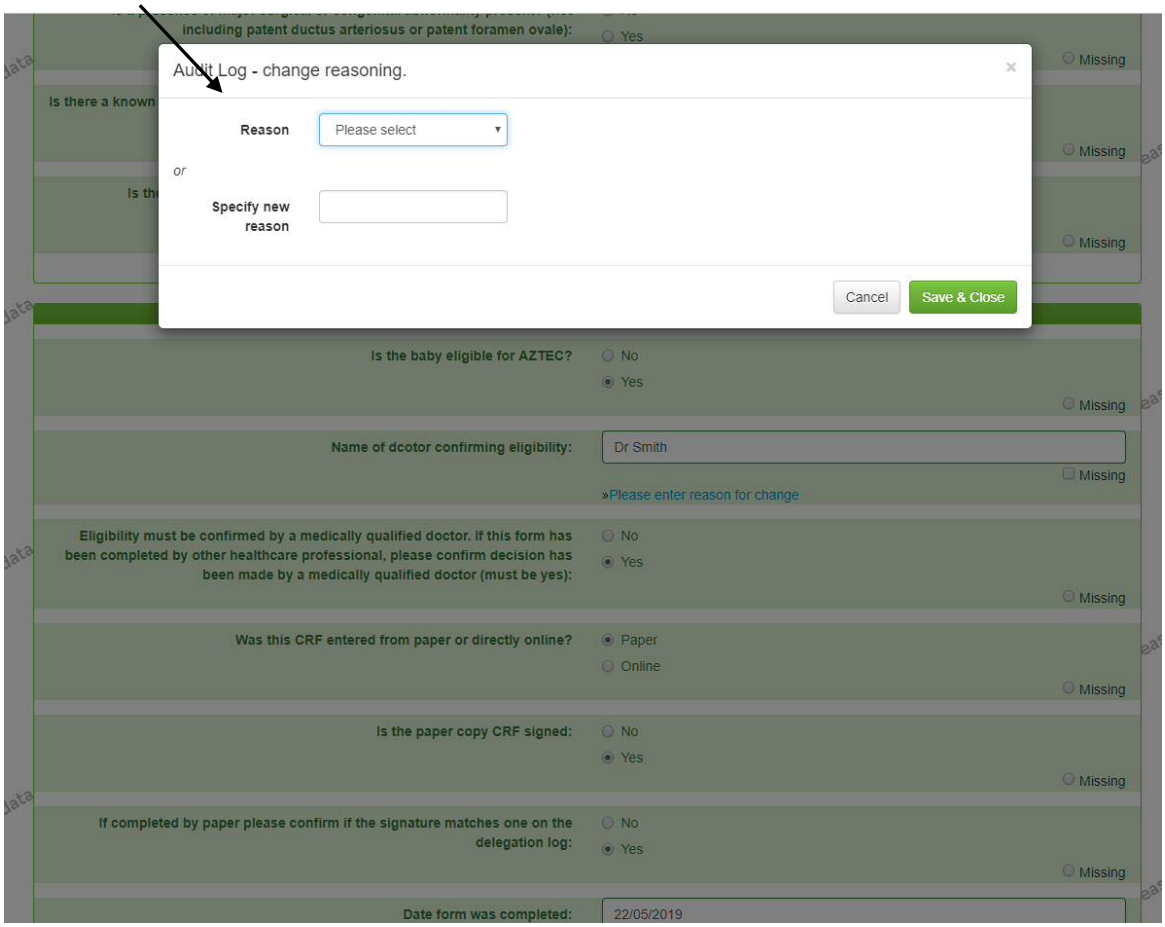


Making Changes To Data

You can add, amend and edit all forms by selecting the form and opening it, carrying out the amendment and saving. However, for forms that have been completed, i.e. appear green as below, if you need to make changes to this form's data, you will see an Audit pop-up box appear.

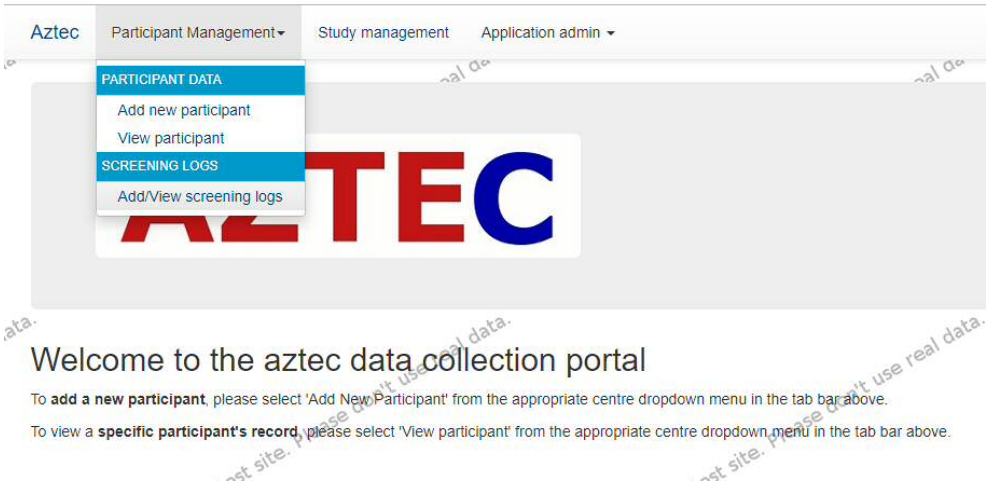
Audit Log

When changes are made to data on forms that have already been saved as complete, the following box will appear. You need to select a reason for the change or specify a new one, save and close.

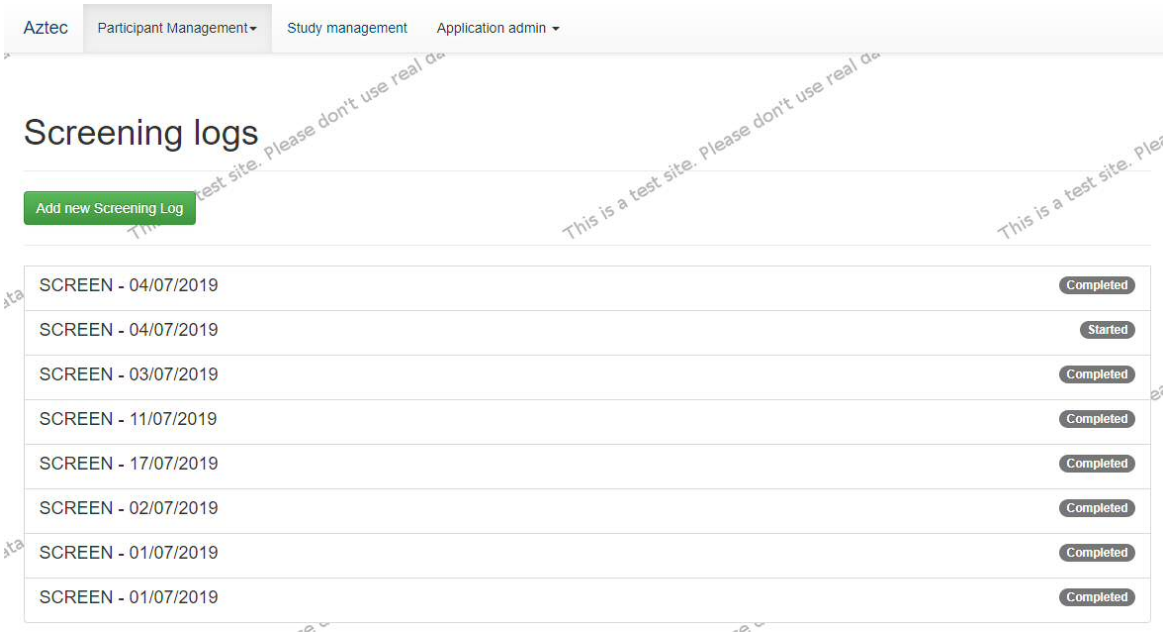


Screening Logs

The screening log form can be accessed under Participant Management.



Clicking on Add/View screening log brings up the following screen –



Click on any previously created screening logs to view their details. Making changes to data already entered on a complete form will follow the same procedures as already discussed above.

To create a new screening log, click on the green button. Entering data onto a new form will also follow the same procedures as discussed previously above.

Guidance Sheet 8:
Safety and non-compliances

Any staff member can report safety events or non-compliances at any time during the trial. For information on withdrawal and unblinding, please see **Guidance Sheet 11: Withdrawal & Unblinding**.

OVERVIEW

- Safety data will be recorded during administration of the IMP and up to 36 weeks post-menstrual age
- ANYONE can report ANY events at ANY TIME
- Events should be reported as follows:
    - **Adverse Events or Reactions (AEs)**

      - Non-serious adverse events will not be routinely recorded. Adverse events which are part of the safety outcomes of this trial will be recorded in the case report form (CRF), where appropriate.
    - **Adverse reactions (AR)**

      - Adverse reactions (those with a suspected causal relationship to azithromycin) will be recorded on the Adverse Reactions CRF
    - **Serious Adverse Events or Reactions (SAE)**

      - Foreseeable serious adverse events (listed in the protocol) should not be reported as SAEs. Unforeseeable serious adverse events should be reported to the CTR as SAEs. The protocol contains a full list of foreseeable SAEs.
    - **Serious Adverse Reactions (SAR)**

      - SARs (SAEs which are related to the IMP) should be reported in the same manner as unforeseeable SAEs

CAUSALITY

- The casual relationship of each adverse event to the trial medication must be determined by a medically qualified individual
- This individual must be delegated this duty on the study delegation log
- Causality assessment cannot be downgraded by others

Guidance Sheet 8:
Safety and non-compliances

AZTEC
Azithromycin Therapy for Chronic Lung Disease
CARDIFF UNIVERSITY
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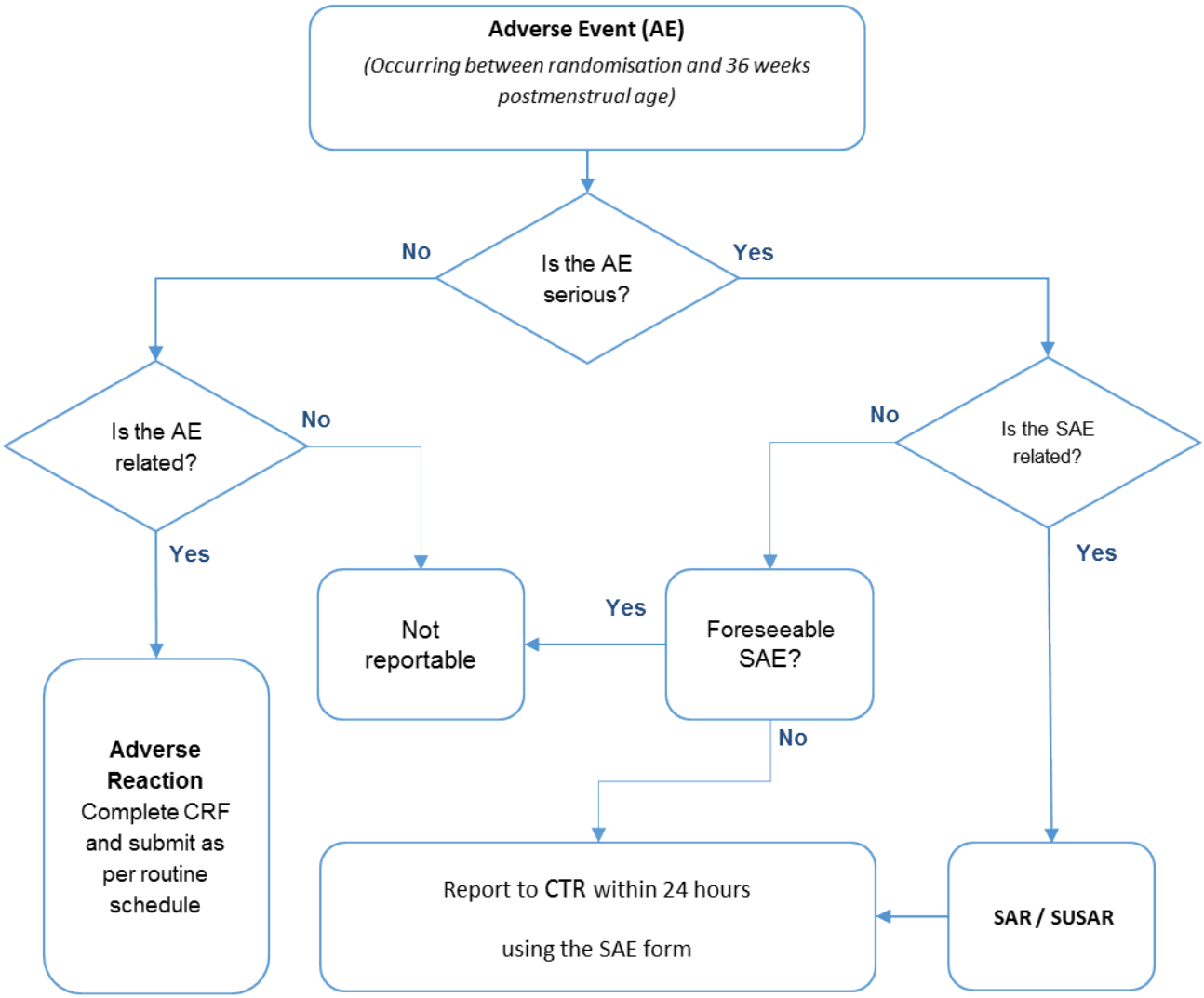
REPORTING

- Foreseeable Serious Adverse Events
  - The foreseeable adverse events listed in the protocol do not require immediate reporting as SAEs to the CTR or the CI. Only if these events are thought to be causally related to the IMP (SARs) would they require immediate reporting to the CTR.



- Unforeseeable Serious Adverse Events and adverse reactions
  - SAEs not on the list of foreseeable SAEs, and SARs must be reported to CTR immediately, but at least within 24 hours of the research site becoming aware of the event

Guidance Sheet 8:
Safety and non-compliances

- A paper SAE form will be completed (located in the document box) and faxed/emailed to CTR (Fax: 020 3043 2376 Email: CTR-Safety@Cardiff.ac.uk) and the original filed in the ISF
- Site staff may report an SAE immediately to the CTR by telephone, but this must be followed up with a SAE report form as soon as possible and within 24 hours of the site becoming aware of the event to the CTR
- The outcome of events "Resolving" or "Not Resolved" must be followed up until the status of the SAE changes
- CTR will review the report, request additional information and ensure assessment by the CI/delegate
- The CI will inform all PIs of relevant information that could adversely affect the safety of the participants

List of AZTEC foreseeable Serious Adverse Events	
Anaemia requiring blood transfusion+ Anaemia requiring blood transfusion+ Intracranial abnormality (haemorrhage or focal white matter damage) on cranial ultrasound scan or other imaging Chronic lung disease of prematurity (or bronchopulmonary dysplasia) Coagulopathy requiring treatment+ Culture-proven infection or sepsis Death (unless unforeseeable in this population) Fluid retention Fractures Gastrointestinal bleeding Haematuria Hydrocephalus Hyperbilirubinemia necessitating phototherapy and/or exchange transfusion+ Hypercalcemia Hypocalcaemia Hyperglycaemia Hypoglycaemia	Hypertension Hypotension treated with inotropes+ Impaired renal function (urine output <0.5 ml/kg/hour and/or serum creatinine defined as >100 µmol/L) Left ventricular hypertrophy on echocardiography Low serum sodium level/hyponatremia (defined as sodium <130 mmol/L) Liver failure, clinically significant Necrotising enterocolitis or gastrointestinal perforation Neutropenia (defined as $<1x10_9$/L) Patent ductus arteriosus (PDA) Pneumothorax requiring treatment Pulmonary haemorrhage, significant Pulmonary hypertension requiring treatment with pulmonary vasodilator+ Respiratory failure Retinopathy of prematurity Seizures requiring treatment+ Thrombocytopenia
Events marked with + that do not require treatment will not be deemed serious	

Guidance Sheet 8:
Safety and non-compliances

AZTEC
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Non-compliances: protocol deviations and serious breaches

- Any member of the study team can report incidents or protocol deviations
- Any incidents or deviations from the protocol, trial procedures, GCP, or regulatory requirements will need to be reported as soon as site staff become aware of the incident. Please email AZTEC@Cardiff.ac.uk, or call 029 2068 7990.
- Incidents relating to a dosing error should be notified to the CRF using a **Dosing Error Form**. Dosing error forms should be faxed/emailed to CTR immediately with any accompanying information (Fax: 020 3043 2376; Email: CTR-Safety@Cardiff.ac.uk)
- The original dosing error/non-compliance forms should be kept in the ISF
- CTR staff will review the report and assess whether the incident should be considered a deviation, violation, or potential serious breach, and to agree in collaboration with the site any corrective and protective actions to be implemented

Guidance Sheet 9:
IMP Supply and Accountability

AZTEC
Azithromycin Therapy for Chronic Lung Disease
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Receipt of trial intervention

- The AZTEC treatment packs are manufactured and supplied by the Saint Mary's Pharmaceutical Unit (SMPU). All deliveries of trial packs will be received by the hospital pharmacy.
- Upon receipt of a delivery, pharmacy should check the delivery for any damage or inconsistencies against the dispatch information enclosed on the **AZTEC drug order form**.
- Section 4 of the drug order form should be completed by pharmacy and returned to the CTR via fax/email and to SMPU. Any issues should be reported to the CTR using the **Drug Quality Form.**
- Each AZTEC IMP treatment pack should be booked in on the **Treatment Pack Accountability Log**.
- Stock levels will be monitored by Sortition, which will instruct the CTR to initiate resupply from SMPU.

Maintaining stock of the trial intervention on the neonatal unit

- To enable prompt randomisation and initiation of trial treatment, a proportion of packs (ideally all) should be transferred from pharmacy for storage on the neonatal unit.
- The **Treatment pack tracking log** will be used to record receipt on the neonatal unit, allocation to baby, return to pharmacy, and transfers to other centres.

Receipt from pharmacy/transfer in			Randomisation			Return to pharmacy		Transfer	
Date received (dd/mm/yy)	Pack ID	Received by (initials)	Date of Pack Allocation (dd/mm/yy)	Patient Study ID number	Recorded by (initials)	Date returned to pharmacy (dd/mm/yy)	Returned by (initials)	Date pack transferred with baby (dd/mm/yy)	Transfer prepared by (initials)
01/07/19	1045	AB	04/07/19	AZ1101	AB	17/07/19	AB		

- When a baby is randomised (see **Guidance Sheet 4: Randomisation)**, the randomisation website will allocate a Study ID and a Pack ID to the baby and populate a Pack Allocation Form. This should be printed out and kept with the baby's notes. Nominated site staff, and the clinical trials pharmacy, will receive an email notification of randomisation. The allocated study ID should be recorded on the **Treatment pack tracking log** next to the appropriate Pack ID

Guidance Sheet 9:
IMP Supply and Accountability

AZTEC
Azithromycin Therapy for Chronic Lung Disease
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Missing treatment packs

- In the event an allocated treatment pack cannot be found on the neonatal unit, check with Pharmacy to confirm it has been received. If the allocated treatment pack still cannot be located contact the Trial Manager to report the issue (LoweJ3@Cardiff.ac.uk, 029 2068 7990)

Accountability

- It is essential that the movement and allocation of AZTEC packs are carried out and recorded in an accurate and timely fashion to allow effective control of stock by Sortition.
- **Guidance Sheet 5a: Intervention** has further information for the neonatal study team on how to maintain an accurate accountability record
- Once the intervention is complete, unused vials and the external treatment pack box must be reconciled prior to being disposed. This activity will be performed by the research nurse or pharmacy team (as arranged locally) using the **Treatment Pack Reconciliation Form** (Completing section A). This is then emailed to the CTR team (AZTEC@Cardiff.ac.uk), with the site clinical trials pharmacy copied in.
- The Trial Manager/Data Manager (based at CTR) will review the **Treatment Pack Reconciliation Form**. Where accountability is demonstrated CTR staff will complete section B of the log. The form will be returned to site as authorisation to dispose the outer packaging and any unused vials from the relevant IMP pack.
- Finally, the site will complete and return section C to confirm disposal as per local practice. The fully completed log should then be faxed/emailed to CTR and the original stored in the Investigator Site File/Pharmacy Folder.
- Following expiry of a batch, or at the end of the trial, any **unused** treatment packs stored on the NICU will be returned to pharmacy. Alongside any stock which has not been issued, and on permission with the Trial Manager at the CTR, this stock may be disposed. Disposal will be recorded on the **Treatment pack accountability log**.

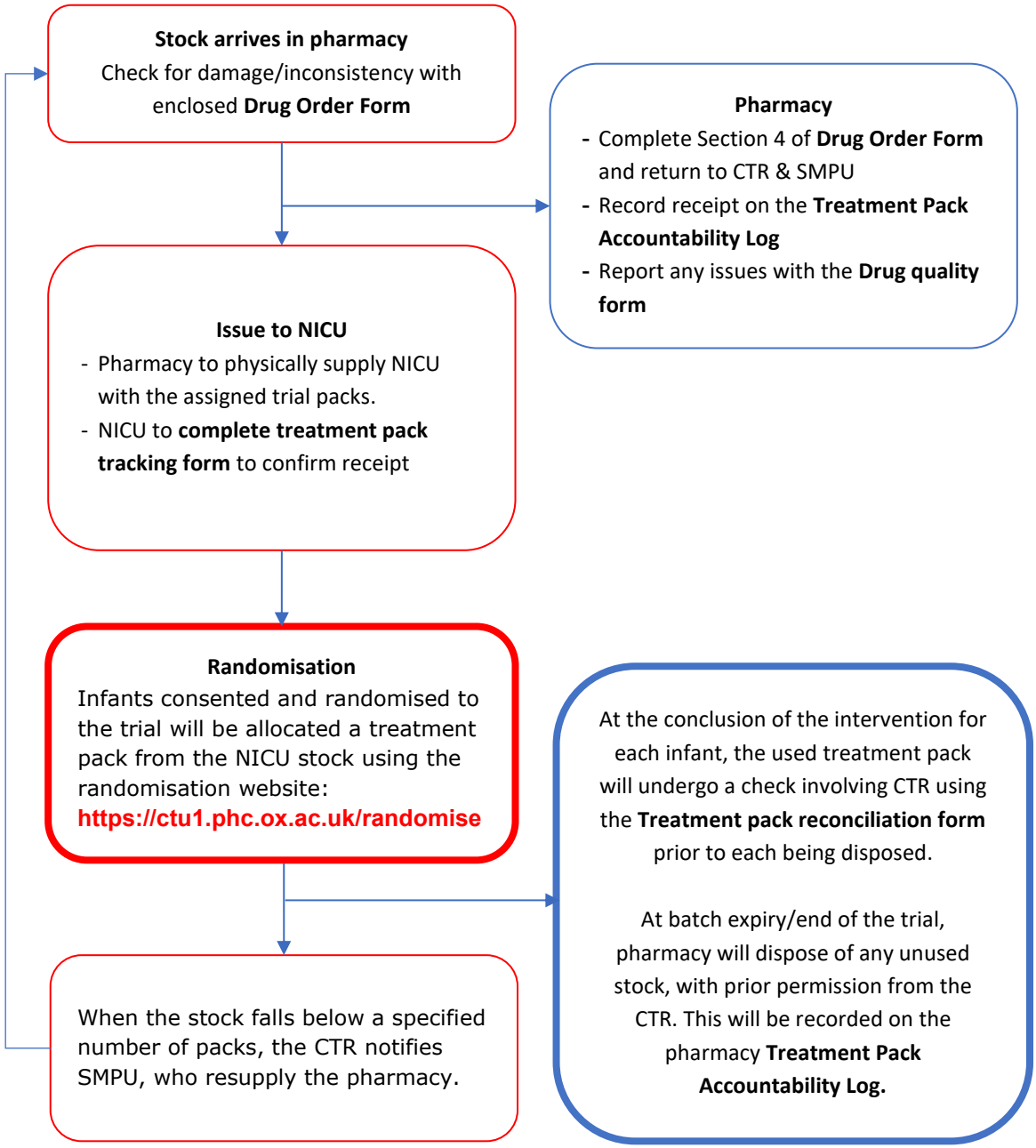
Guidance Sheet 9:
IMP Supply and Accountability

Transfers

- Provision has been made for IMP to be transferred with the baby if they are being moved to an AZTEC recruiting centre, or a site where approvals for continuation of IMP administration are in place. The Trial Manager will notify each recruiting site of arrangements in their local networks during site initiation.
- Pharmacy must be made aware of any transfers that take place during the intervention period.
- If the IMP is being transferred, the treatment pack will be re-sealed using an **IMP Transfer Sticker**, located in the site's document box.

- More detail on transfers is given in **Guidance sheet 12a: Preparing a Transfer.** Final reconciliation of the IMP will then be performed at the receiving site.
- The receiving site will take responsibility for reconciliation and destruction of any packaging and unused IMP.

Guidance Sheet 9:
IMP Supply and Accountability



Guidance Sheet 10: Oxygen Reduction Test

AZTEC Azithromycin Therapy for Chronic Lung Disease
Cardiff University Prifysgol Caerdydd
Centre for Trials Research
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General points

- Please complete the Primary Outcome assessment as close to 36 weeks post-menstrual age as possible (±5 days), or prior to discharge home if sooner.
- Only perform the oxygen reduction test if baby has received oxygen and/or respiratory support for ≥ 28 days cumulatively and the following:
  - The baby is not receiving mechanical ventilation (invasive and non-invasive), CPAP, or high flow oxygen therapy
  - FiO2 < 0.3, or low flow oxygen < 1.1 L/min to maintain saturations of ≥ 91%
  - In previous 24 hours, baby has not required respiratory support

Procedure

Has the baby received oxygen and/or respiratory support ≥28 days?

→ **ANSWER- No**
No CLD- do not continue with flowchart

ANSWER- Yes
Has received oxygen and/or respiratory support ≥28 days

Still in oxygen?

→ **ANSWER- No**
Mild CLD- do not continue with flowchart

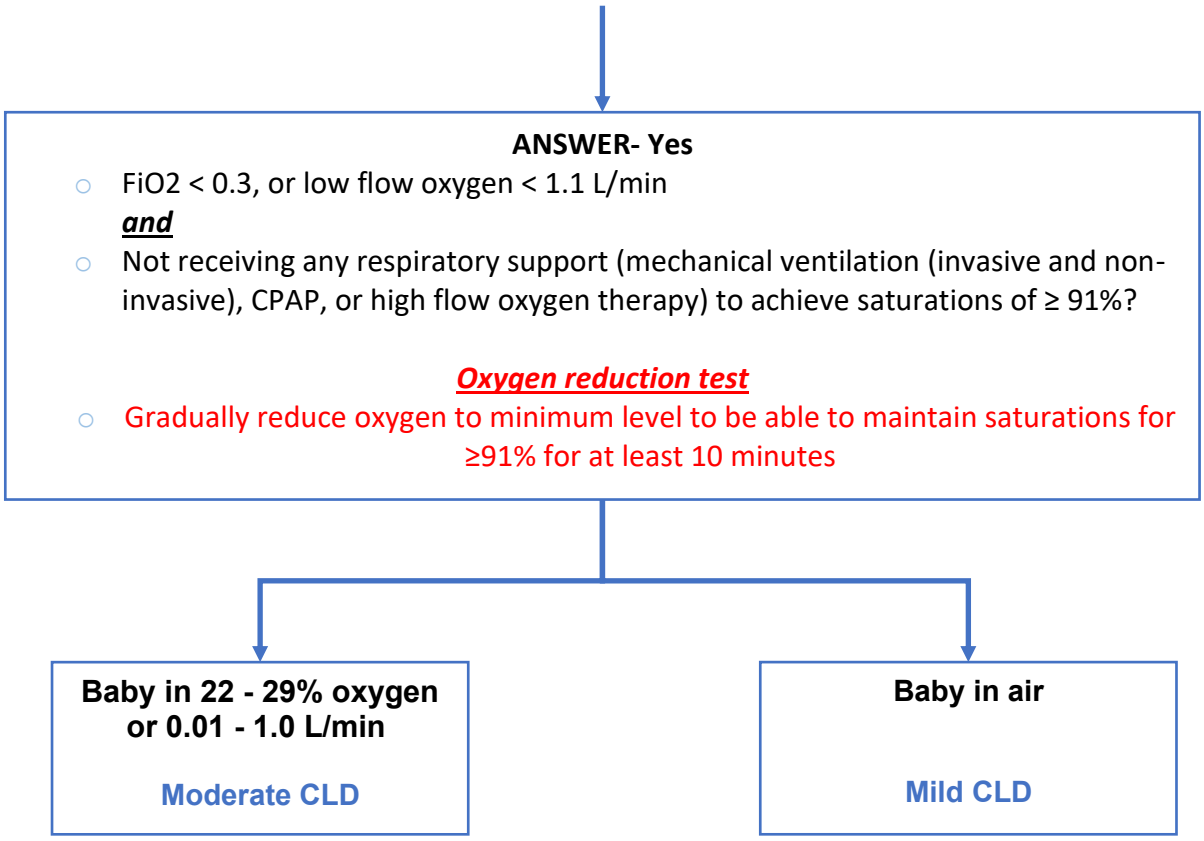
ANSWER- Yes
Still in oxygen
Are their requirements:

- FiO2 < 0.3, or low flow oxygen < 1.1 L/min, ***and***
- not receiving any respiratory support (mechanical ventilation (invasive and non-invasive), CPAP, or high flow oxygen therapy) to achieve saturations of ≥ 91%?

→ **ANSWER- No**
Severe CLD- do not continue with flowchart

Continued…

Guidance Sheet 10: Oxygen Reduction Test



Guidance Sheet 11: Withdrawal & Unblinding

AZTEC Azithromycin Therapy for Chronic Lung Disease | Cardiff University Prifysgol Caerdydd | Centre for Trials Research Canolfan Ymchwil Treialon

Withdrawal

- Staff can withdraw a baby from the AZTEC trial or discontinue AZTEC IMP at any time if parents wish or if it is deemed necessary for baby treatment.
- Parents do not have to give a reason for withdrawing a baby. Please ensure that you ask if:
  - The parents agree that the data already collected can be used
  - The parents agree that clinical data can be collected until their baby is discharged/reaches the end of the trial participation period
  - The parents agree for sample collection to continue
  - The parents agree to be contacted for later follow-up (if they originally consented)
- The time and date at which the baby was withdrawn from the clinical trial or the intervention discontinued should be documented in the baby's medical notes, together with any other necessary information.

Emergency Unblinding

- Emergency unblinding should only be carried out if the clinician carrying out the unblinding procedure is certain that:

  A) This is a **genuine emergency** AND

  B) Knowledge of the treatment allocation (either azithromycin or placebo) is **necessary to guide the clinical management of the participant**.

- Appropriate clinical management will be possible in the majority of cases without the need for unblinding by treating the participant as though they have received azithromycin.

Web- based procedure for emergency unblinding:

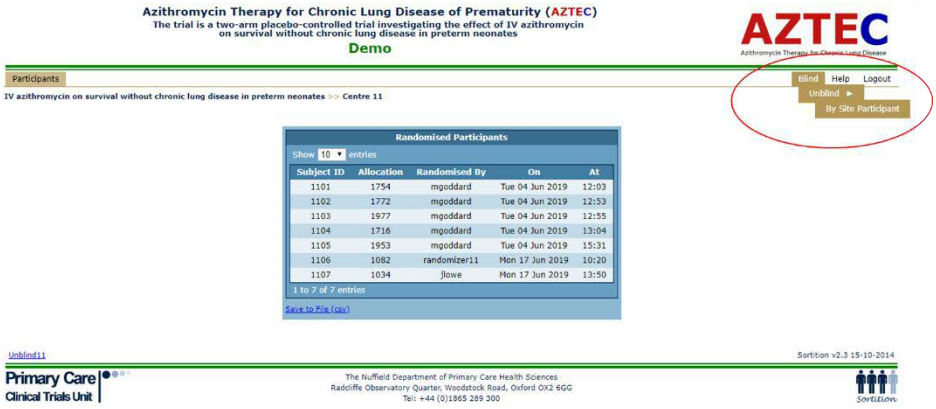
- Emergency unblinding must be conducted by a medically qualified individual who is named on the delegation log

- During office hours (Monday-Friday 09:00-17:00), an attempt should be made to contact the Chief Investigator or designated clinical reviewer via the CTR (Tel: 029 2068 7990) to discuss the circumstances under which unblinding is being considered

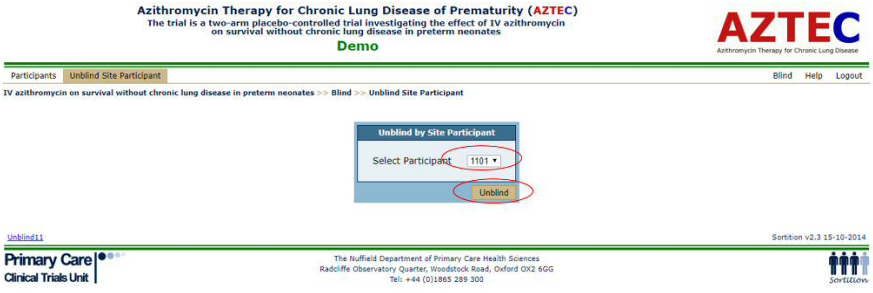
Guidance Sheet 11: Withdrawal & Unblinding

- An **Unblinding CRF** (in document box) should be completed prior to conducting unblinding, where possible
- In the AZTEC document box there is a sealed envelope containing the following information:
  A) AZTEC randomisation website address
  B) Single-use login details and password

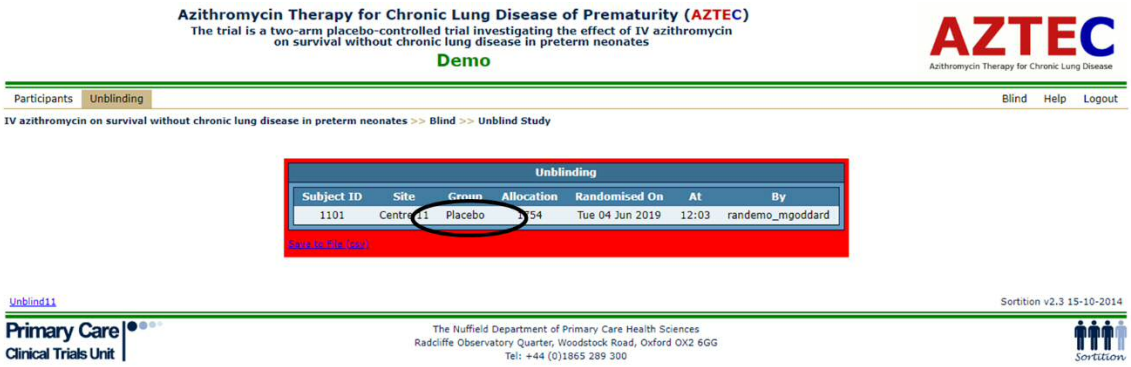
- Once logged in, select the "Blind" menu in the top right-hand corner to highlight Unblind, and then "By site participant"



- Carefully select the appropriate **Study ID**, and select unblind



- The system will then reveal the arm allocation of the infant- **knowledge of the allocation** should be strictly limited to those individuals who need to know for guiding the clinical management of the baby



- After the unblinding procedure is completed, please email or fax the **Unblinding CRF** to the CTR as instructed on the form

- The AZTEC Trial Team will be automatically informed of any cases of unblinding.

Back-up procedure for emergency unblinding:

- In the event the randomisation website cannot be accessed (e.g. issues with login details or access to the website), CTR can be contacted during office hours (Monday-Friday 09:00-17:00) to perform unblinding on behalf of a site

- Contact the pharmacovigilance and safety team on 029 2068 7462, CTR-Safety@Cardiff.ac.uk with the particulars of the request, **including the baby's Study ID.** Please note that the team may wish to facilitate a discussion with the Chief Investigator or designated clinical reviewer prior to actioning the request

- The treatment allocation of the baby will be transmitted to a named induvial at site using a password protected email- **knowledge of the allocation** should be strictly limited to those individuals who need to know for guiding the clinical management of the baby

Guidance Sheet 12a: Preparing a Transfer

AZTEC
Azithromycin Therapy for Chronic Lung Disease
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Centre for Trials Research
Canolfan Ymchwil Treialon

General guidance

- Trial activities (e.g. data collection or 36 week oxygen reduction test) **can only be carried out** at hospitals that have the necessary authorisations (i.e. Organisation Confirmation of Capacity & Capability). It is therefore important that you notify the CTR of any transfer as soon as it is considered.
- You are asked on the **Trial Entry CRF** to list all hospitals that the baby may be transferred to so that the Trial Office can anticipate transfers and obtain authorisations in advance.
- You can check hospitals that are participating (and those that are not) in the AZTEC trial by reviewing the list in the document box, or by speaking to the AZTEC team at the CTR to the AZTEC website (https://www.aztec-trial.uk) and selecting the '**Participating sites**' link.
- If the hospital the baby is being transferred to is not listed there or is listed as 'NHS Permission NOT granted' then they do not have the necessary authorisations and you should **contact the CTR immediately**.

As well as alerting the CTR of transfers, the smooth completion of the trial Protocol across different hospitals is dependent upon adhering to the following procedure. Any transfer for less than 24 hours e.g. for surgery **is not** classed as a transfer. The responsibility for data collection remains with the recruiting site and a separate **Transfer from** for the brief stay does not need to be completed; instead the brief transfer can be incorporated into the one **Baby Outcomes form**.

Procedure

- If the transfer is to another **AZTEC approved recruiting site during the intervention period** you should ensure:
  - That the receiving hospital is aware that the baby is in the AZTEC trial.
  - That a **Transfer CRF** is completed covering the period that the baby has been an inpatient in your hospital.
  - That the **AZTEC Transfer envelope** is completed and is transferred with the baby. Transfer envelopes are kept in the AZTEC Documentation Box and contain:
    - Cover letter
    - Guidance sheet 12b: Receiving a transfer

- That the Daily log CRF is completed as much as possible and data is entered to the eCRF. Then, photocopy the Daily Log and place the photocopy in the ISF and the **original in the transfer envelope**
- That the infant's treatment pack is sealed using the supplied IMP Transfer label.
- Record the transfer of the IMP on the **Treatment pack tracking log**
- Make Pharmacy aware that the IMP pack has been transferred to the receiving hospital with the baby. Pharmacy should update the accountability log accordingly.

- If the transfer is to an **AZTEC approved continuing care site** you should ensure:
  - That the receiving hospital is aware that the baby is in the AZTEC trial.
  - That IMP is **Not** transferred with the baby
  - If the baby is transferred before 21 days after the start of the intervention, then ensure the **Daily log CRF** is completed as much as possible and data is entered to the eCRF. Then, photocopy the Daily Log and place the photocopy in the ISF and the **original in the transfer envelope**
  - If the baby is transferred **prior to reaching 36 weeks PMA**, that a **Transfer eCRF** is completed covering the period that the baby has been an inpatient in your hospital.
  - If the baby is transferred **after reaching 36 weeks PMA**, that a **Baby outcomes post 36 weeks eCRF** is completed covering the period that the baby has been an inpatient in your hospital.
  - That the Adverse Reaction eCRF is up to date
  - That the **AZTEC Transfer envelope** is completed and is transferred with the baby. Transfer envelopes are kept in the AZTEC Documentation Box and contain.
    - Cover letter
    - Blank Withdrawal CRF
    - Blank Adverse Reactions CRF
    - Blank SAE report form
    - Blank paper **Baby outcomes at 36 weeks CRF**
      - Or, if the baby is transferred post 36 weeks PMA
    - Blank paper **Baby outcomes post 36 weeks PMA CRF**

Guidance Sheet 12a: Preparing a Transfer

- Guidance sheet 1: Training
- Guidance sheet 8: Safety and non-compliance reporting
- Guidance sheet 10: Oxygen reduction test
- Guidance sheet 12b: Receiving a transfer
- Summary of product characteristics

- Please seal the transfer pack and complete the information on the front
  - Complete the baby's details and the local PI and research nurse at the recruiting site
  - Confirm that the required tasks have been completed
  - Document who prepared the transfer pack, the date, and their telephone number
  - Record the date of when the 36-week oxygen reduction test would be due

- The research team at the recruiting site should liaise with the continuing care site to ensure a smooth transfer of AZTEC babies.
- **Successful completion of the trial protocol** relies on a completed 36-week oxygen reduction test and the associated data collection.
- It is the responsibility of the research team at the recruiting site to ensure that any CRFs that are completed by the continuing care site are returned to the recruiting site and data uploaded where necessary. Please ensure regular correspondence between the recruiting and continuing care sites.

- If the transfer is planned to a **site which does not yet have approval** for the AZTEC trial: This must not interfere with the planned timing of the baby's transfer.
  - If the receiving hospital does not have the necessary authorisations the CTR will try to gain these urgently. Please complete **steps as above** and transfer the baby just as you would if the authorisations were in place.
  - The CTR will liaise with the receiving hospital and keep them informed as to when they may continue data collection.

Guidance Sheet 12b: Receiving a Transfer

AZTEC Azithromycin Therapy for Chronic Lung Disease

Cardiff University Prifysgol Caerdydd

Centre for Trials Research Canolfan Ymchwil Treialon

General considerations

- **Thank you** for support in ensuring that follow up of AZTEC babies is possible
- Please contact the Centre for Trial Research (CTR) (Tel: 029 2068 7990, email: Aztec@Cardiff.ac.uk) to confirm that the baby has been transferred
- The Centre for Trial Research will confirm who the pre-arranged local PI is and that the site has approval to continue the AZTEC trial. If a local PI has not yet been arranged, please continue the steps below and the Centre for Trial Research will arrange this as soon as possible
- Please check that all documents indicated on the AZTEC transfer envelope are included in the pack. If any documents are missing, please contact the Centre for Trial Research
- Please check the front of the transfer pack to confirm whether or not the baby has finished the intervention period and the date at which the 36-week oxygen reduction test is due

Receiving a baby who has not finished the AZTEC intervention period (RECRUITING SITES ONLY)

- Please follow the procedures are per **Guidance Sheet 5a: Intervention,** and **sheet 5b: IMP administration**
  - The IMP should be prescribed in the infant's drugs chart by a clinician/ANNP
  - Please complete the Daily Log (in the transfer pack)

End of intervention procedures (RECRUITING SITES ONLY)

- At completion of the intervention (after 10 days), ensure the Daily Log is completed accordingly
- Follow the procedures as outlined in **Guidance sheet 9: IMP supply and accountability** to complete the reconciliation process for the baby's treatment pack. Following permission from the CTR, the pack can be disposed

Safety reporting

- Safety reporting should continue until 36 weeks postmenstrual age
  - Please refer to Guidance Sheet 8: Safety and non-compliances for detailed guidance
  - Please report any events, which in the opinion of the local PI, are associated with azithromycin, using the **Adverse Reactions form**

- A list of foreseeable SAEs is included in **Guidance sheet 8**- any SAEs that are not included in the list of foreseeable SAEs must be reported to the CTR immediately, but at least within 24 hours of the research site becoming aware of the event
- A paper SAE Report Form must be completed (in the transfer pack) and faxed/emailed to the CTR Safety team (Fax: 020 3043 2376 Email: CTR-Safety@Cardiff.ac.uk)
- Please telephone the Safety team (029 2068 7462) to confirm receipt
- Further information received must be detailed on a new SAE form (contact AZTEC@Cardiff.ac.uk) and faxed/emailed to the CTR Safety team
- The outcome of events "Resolving" or "Not Resolved" must be followed up until the status of the SAE changes
- Please send the **original SAE report form** to the recruiting site

Outcome assessment and data collection at 36 weeks PMA

- Ensure the remainder of the **Daily Log** has been completed (up to 21 days post-commencement of the intervention)
- At 36 weeks PMA (or discharge home if sooner), the **Outcomes at 36 weeks PMA form** should be completed

****An oxygen reduction test should also be conducted if required and results recorded on this form****

For more information please refer to **Guidance Sheet 10: Oxygen reduction test**

- Update the paper **Adverse Reactions form** with any new events (the final time new events are reported)
- Once complete, please return the paper **Daily Log** and **Outcomes at 36 weeks PMA form** to the recruiting site

Data collection after 36 weeks PMA

- When the baby is discharged home (transfers, or dies), please complete the **Outcomes post 36 weeks PMA form**
- Update the paper **Adverse reactions form** for the final time, reviewing any ongoing events (if persisting- record "ongoing at final follow up")
- Once complete, please return the two paper forms to the recruiting site

Guidance Sheet 12b: Receiving a Transfer

Withdrawal

- Staff can report withdrawal of a baby at any time if parents wish or if it is deemed necessary for baby's clinical care, by completing a paper **Withdrawal form**
- The time and date at which the baby was withdrawn should be documented in the baby's medical notes with any other necessary information.
- Please fax/email the form to the CTR (Fax: 029 2251 9700, AZTEC@Cardiff.ac.uk)
- Place a photocopy in the baby's medical notes, and return the original to the recruiting centre

Unblinding

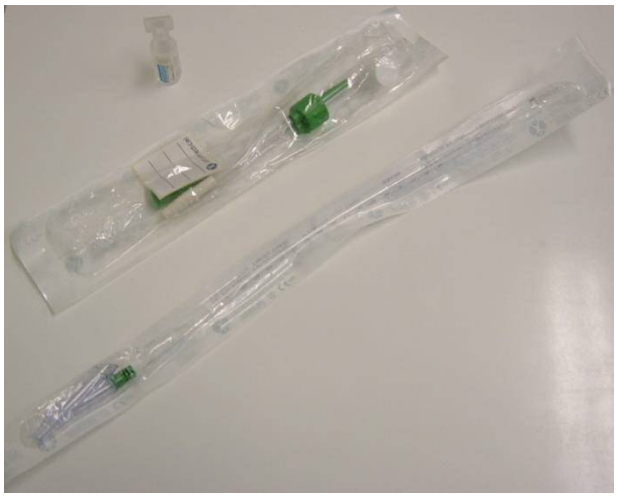
- A baby should only be unblinding if it is a genuine emergency AND knowledge of the treatment allocation is necessary to guide the clinical management of the participant. To unblind a baby please contact the recruiting centre, who will unmask the baby and inform you of arm allocation

Guidance Sheet 13a: Sampling procedures

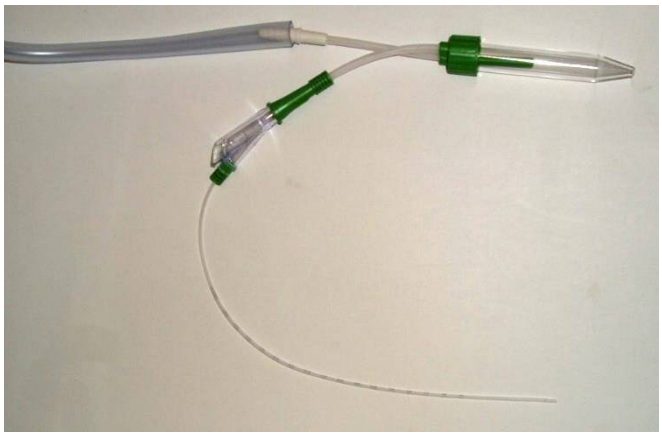
AZTEC Azithromycin Therapy for Chronic Lung Disease
Cardiff University Prifysgol Caerdydd
Centre for Trials Research
Canolfan Ymchwil Treialon

A. Procedure for endotracheal samples

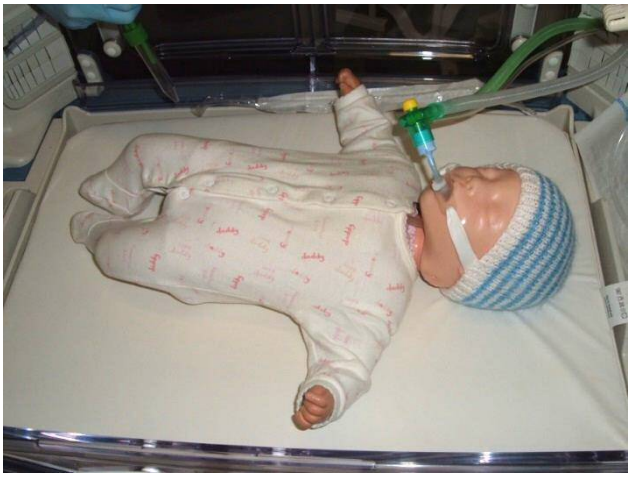
- Materials required:
  - One sterile suction catheter
  - One ampule of sterile IV grade 0.9% sodium chloride
  - One sterile suction specimen collector set (provided)
  - Sample labels (provided, in document box)



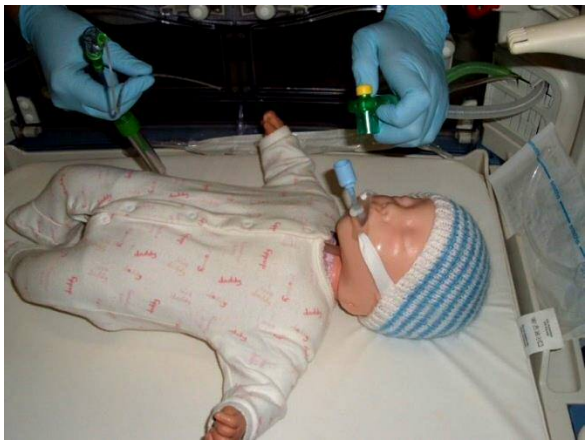
- Remove the suction set from the packaging and attach the adaptor to the suction tubing (hospital suction source).
- Open the suction catheter packaging and attach the tip to the green adaptor (leave the thin tubing in the packaging until ready to use to maintain sterility- figure shows packaging removed from catheter just for illustration purposes)
  - If using an in-line suction system, it is preferable to collect the sample immediately after the device has been changed to avoid contamination of samples from previous aspirations

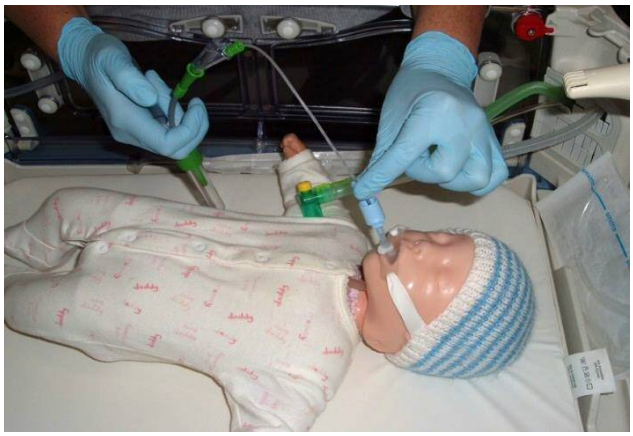


- Now you are ready to remove the endotracheal secretions from the endotracheal tube



- When ready with suction trap apparatus, disconnect the ventilator and insert the catheter to a depth of approximately 0.5cm. If using an in-line suction device, disconnection from the ventilator is not required.

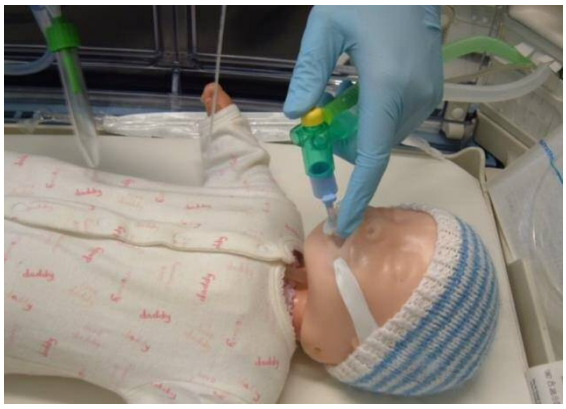




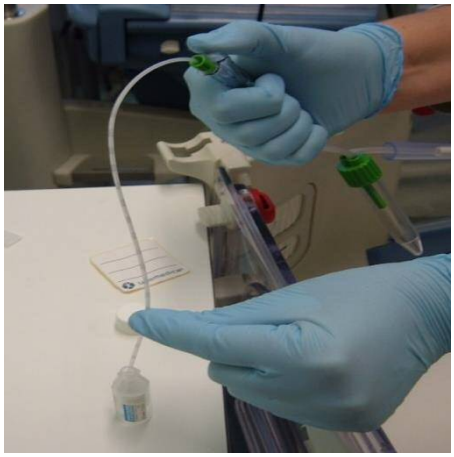
- Place thumb over the suction catheter control to apply suction (5-7kPA/37-52mmHg) and move catheter in the endotracheal tube to extract the accumulated secretions- gradually withdraw the catheter

If no secretions are present, consider instilling up to 0.5ml/kg of normal saline down the endotracheal tube, and re-suction after a brief pause

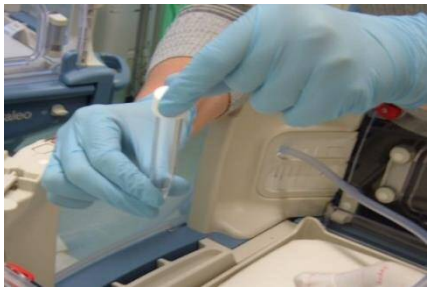
- When finished extracting the endotracheal secretions, reconnect the ventilator (if applicable)



- Rinse the secretions from the catheter into the trap by sucking up approximately 1ml of sterile saline by inserting the tip and closing the suction circuit with your thumb



- Unscrew the capture tube from the suction apparatus, seal with the sterile cap and apply the appropriate label to identify the baby and the sample. Labels are provided, corresponding to the sample type and the sampling timepoint


- Place the sample in the specimen fridge until the appropriate time to package before shipping. Take care to store in a clearly marked space, away from general clinical samples. Shipping guidelines are in **Guidance sheet 13b: Sample shipment**

B. Procedure for nasopharyngeal samples

- Materials required:
  - One sterile suction catheter
  - One ampule of sterile IV grade 0.9% sodium chloride
  - One sterile trachea suction specimen collector set (provided)
  - Sample labels (provided, in document box)

- Follow steps as in part A) to prepare the catheter for use

- Insert the catheter gently via the nostril to the nasopharynx. Place thumb over the suction catheter control to apply suction (5-7kPA/37-52mmHg) and gradually withdraw the catheter

If no secretions are present, consider instilling up to 0.5ml/kg of normal saline in to the nostrils and re-suction after a brief pause

- Rinse the secretions from the catheter into the trap by sucking up approximately 1ml of sterile saline by inserting the tip and closing the suction circuit with your thumb

- Unscrew the capture tube from the suction apparatus, seal with the sterile cap and apply the appropriate label to identify the baby and the sample.

- Place the sample in the specimen fridge until the appropriate time to package before shipping. Take care to store in a clearly marked space, away from general clinical samples. Shipping guidelines are in **Guidance sheet 13b: Sample shipment**

C. Procedure for stool samples

- Materials required:
  - One sterile universal container with spatula (provided)
  - Sample labels (provided)

- Use the spatula to obtain stool sample from the baby's nappy (meconium is acceptable as a sample)

- Seal the container securely and apply the appropriate label to identify the baby and the sample

- Place the sample in the specimen fridge until the appropriate time to package before shipping. Take care to store in a clearly marked space, away from general clinical samples. Shipping guidelines are in **Guidance sheet 13b: Sample shipment**

Guidance Sheet 13b: Sample shipment

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General information

- The following is guidance on how to package AZTEC trial clinical specimens for shipment with DX courier. It is important the packaging provided is used and each step followed, as this is compliant with the appropriate regulations (UN3373, Biological substances Category B)

- If you are running low on packaging materials, please contact the AZTEC team at the Centre for Trials Research (AZTEC@Cardiff.ac.uk). Please order in plenty of time as the resupply can take up to a week

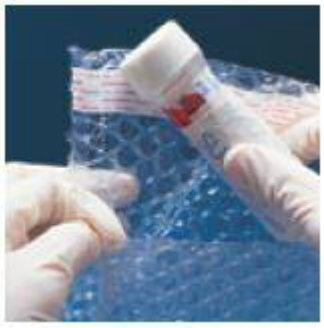
- If you experience any issues with the process, or with DX courier, please contact the AZTEC trial manager (LoweJ3@Cardiff.ac.uk, Tel 029 2068 7990)

Procedure

- Materials required:
    - Bubble wrap pouch
    - 50ml Absorbent sheet
    - Blue top secondary container
    - External cardboard container
    - Green sack and barcode security seal

- Complete an **AZTEC sample transfer form** noting the study ID of the baby ("AZ" followed by 2-digit site identifier, and 2-digit baby identifier e.g. "AZ1101"), sample timepoint, and date obtained for each sample.

- It is acceptable to package more than one sample together, including from different babies



- Place the sample tube within a bubble wrap pouch and insert an absorbent sheet. Seal the pouch using the adhesive strip. If multiple samples are to be included, each must have their own pouch and sheet.

Guidance Sheet 13b: Sample shipment

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- Roll the pouch(es) in to a cylindrical shape and place it in to the secondary container- secure the lid

- Place the secondary container into the external cardboard carton, and place the sample transfer form between secondary container and the external carton

- Apply the tamper seal. Please do not use any other form of tape.

- Complete and attach the DX tracked specimen label to the package
  - Recipient's details:
    Dr Lei Zhang
    Cardiff University
    5FT177 Main Building
    University Hospital of Wales
    DX number: 335001
    DX Exchange: Cardiff 94 CF

- Remove the peal-off sticker from the tracking label, attach this to the DX log book and complete the additional dispatch details. This is your record of the samples you have sent

- Place all cartons in a **green sack** (even if there is only one), and seal with a **barcoded security seal**. Take the sample to your exchange location for collection.