ARTIC PC IMP drug handling, delivery, storage distribution and destruction SOP

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Revision History

Version	Revision	Date
1	New document	07 April 2016
2	Clarity over IMP storage temperatures and daily checking of storage temperature	30 August 2016

Effective Date	16 Sept 2016	Review Date	15 Sept 2018

Definitions and abbreviations

Centre	The University department supporting recruitment to the trial. In this trial the lead Centre is the University of Southampton and the specific department is Aldermoor Health Centre. The coordinating Centres are the Universities of Bristol, Oxford and Cardiff.
CCF	Coordinating Centre File, a file similar to the TMF held by the centres supporting the trial

	which holds all the information relevant to that centre.
CI	Chief Investigator, is in overall charge of the project.
CRF	Case Report Form, the form that collects all the data about participants.
CTA	Clinical Trials Authority
CTIMP	Controlled Trial of an Investigational Medicinal Product.
CTU	Clinical Trials Unit, a supporting unit often within a University.
DL	Development Lead (SOP); anyone with previous experience of the procedure / completing the procedure being described, who will take the lead in drafting the SOP or delegating specific section of the SOP to the appropriate person.
DG	Development Group (SOP); A group of approximately 2-4 personnel who are responsible for helping develop, maintain and improve the SOP system, consists of other suitably experienced members.
DM	Data Manager, an individual with responsibility for ensuring data is captured in an ethical manner and a useable format.
GCP	Good Clinical Practice, the regulations that govern the practice of researchers.
GMP	Good Manufacturing Practice, of IMP.
IMP	Investigational Medicinal Product
ISF	Investigator Site File, a file held by a Local Investigator containing all information they need to safely conduct the project.
LI	Local Investigator, the individual with responsibility for the conduct of the study at their site. In a CTIMP this has to be a medically qualified doctor or pharmacist.
MHRA	Medicines Healthcare Regulatory Authority

PI	Principal Investigator, an Individual responsible for the safe and ethically conduct of the study, often leading a centre in academic research.
S(T)A	Study (Trial) Administrator a member of staff from the Centre.
S(T)C	Study (Trial) coordinator a senior member of staff who may have delegated tasks
S(T)M	Study (Trial Manager) a senior member of staff from the Centre who will have delegated tasks to run the project.
SOP	Standard Operating Procedure, specifies what should be done, when, where and by whom
Site	Primary care Centre that recruits into the study or trial
Sponsor	The University of Southampton
TMF	Trial Master File, a file containing all relevant information about the running of the project.

Contents

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1.Introduction

Clinical Trial material and Investigational Medical Products (IMP) must be delivered, stored, distributed and destroyed in accordance with Eudralax Vol4, Annexe 13 and The Medicines for Human Use (Clinical Trials) Regulations SI 2204 1031 and SI 2006 1928.

This document describes all the procedures to be followed in the ARTIC PC trial for the handling and manufacture of the Amoxicillin and matched placebo. This is a reference document for the trial and should be used by all members of research and administrative staff working on the trial.

For the purposes of this Standard Operating Procedure (SOP) amoxicillin and matched placebo will be referred to as 'IMP'.

The IMP will be held at four Centres for distribution to GP Sites. The four Centres are the University of Southampton (Primary Care & Population Sciences, Aldermoor Health Centre, Aldermoor Close, Southampton, Southampton SO16 5ST); the University of Bristol (Centre for Academic Primary Care, 39 Whatley Road, Bristol BS8 2PS); the University of Oxford (Nuffield Dept of Primary Care Health Sciences, Gibson Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG); Cardiff University (South East Wales Trials Unit, Cardiff University School of Medicine, Neuadd Meirionnydd, Heath Park, Cardiff CF14 4YS).

For the purposes of this SOP the GP practices will be referred to as Sites and the University Centres as Centres.

2. Scope

This SOP describes IMP management for ARTIC PC trial only and includes the processes for delivery, storage, distribution and destruction of IMP.

This is a reference document for the trial and should be used by all members of research and administrative staff working on the trial.

3. Process

3.1 Equipment, Materials and Tools

Maximum/minimum thermometer.

Copies of delegation log, drug accountability log, temperature log.

IMP storage risk assessment form.

3.2 Procedure

Each of the stages through which the IMP will move during the progress of the trial is described below in sequence.

- Risk assessment of IMP storage location
- Storage of IMP at Centres and Sites
- Temperature Monitoring
- Temperature Variations
- Receipt of IMP at Centres
- Transfer of IMP between Centres and Sites
- Issue of IMP to Sites by Centres
- Receipt of IMP at Site
- Issue of IMP to patient by Sites
- Return of any unused IMP from patients
- Return of any unused IMP from Sites
- Return of IMP to Southampton Centre
- Management of unused IMP at Southampton Centre
- Destruction of unused medication

3.2.1 Risk assessment of IMP storage location

Prior to receiving any IMP each Centre or Site is required to complete a risk assessment using the ARTIC PC IMP storage risk assessment form with reference to the proposed storage location. The aim of the risk assessment is to ensure that the IMP is handled and stored in accordance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) regulations and as specified in this SOP.

The risk assessment will be completed by a member of staff at the Centre or Site as indicated on the ARTIC PC delegation log stored in the Trial Master File (TMF) and Coordinating Centre file (CCF) and the local Investigator Site File (ISF). Further discussion must occur with the linked ARTIC PC coordinating Centre coordinator/manager if any answer in the risk assessment is 'no'.

The Local Investigator (LI) should sign the completed form to acknowledge they are satisfied with the outcomes of the risk assessment.

The completed risk assessment form should be filed in the TMF, CCF and ISF. A copy of the signed form must be faxed or scanned and emailed to the lead Centre Aldermoor Health Centre on 023 8000 2380 / artic-pc@soton.ac.uk. Completion of the risk assessment form is part of the 'green light' process for this trial and IMP will not be distributed until a completed and signed copy has been received.

NB any change in storage location requires a re-assessment to be carried out.

Storage of IMP at Centres and Sites

The IMP must be stored in a secure environment i.e. a locked cabinet and/or room with access limited to authorised member of staff.

The IMP should be stored separately from other medication and clearly distinguished.

If it is possible to store in a space in which temperature can be monitored this should be used. An appropriate maximum/ minimum thermometers should be used. The IMP should be below 25°C. With daily temperature monitoring of the storage facility. A thermometer can be provided if required.

At least two individuals should be named on the delegation log for IMP responsibility. This is for temperature monitoring and the reporting of temperature deviations.

3.2.2 Temperature Monitoring

Designated members of staff, as per delegation log, will monitor the trial medication daily.

Temperatures should ideally be read preferably first thing in the morning.

The maximum temperature is recorded on the ARTIC PC Drug temperature monitoring log.

Completed temperature logs will be filed in the TMF/ISF and copies sent from Sites to the Southampton Centre by fax or email (023 8000 2380 / artic-pc@soton.ac.uk).

3.2.3 Temperature Variations

If for any day the recorded temperature exceeds 25°C the IMP should be segregated immediately into a container (box or plastic bag] clearly marked 'IN QUARANTINE DO NOT USE'. All members of staff involved in the trial and issuing the IMP should be informed.

NB Quarantined stock should be stored separately from 'active' stock.

The University of Southampton ARTIC PC Centre should be notified immediately and a copy of the temperature monitoring log sent to them by fax or email (023 8000 2380 / artic-pc@soton.ac.uk).

Upon being advised of a temperature deviation the ARTIC PC lead coordinating Centre will contact the Qualified Person (QP) for advice based on all the information available as to whether the IMP is fit for use. The Sponsor should also be informed.

If the IMP is deemed unfit for use the ARTIC PC lead coordinating Centre will send information by email and the affected stock must remain in quarantine. Replacement stock will be ordered. The affected Centre or Site should contact the ARTIC PC lead coordinating Centre to arrange transfer back to Aldermoor Health Centre for destruction.

Receipt of the returned IMP must be recorded as per the delegation log for the ARTIC PC coordinating Centre on the ARTIC PC Drug Return & Destruction log. The completed ARTIC PC dispatch form will be sent to the Study coordinator/manager at Aldermoor Health Centre confirming the pack numbers sent and this will be used to update the ARTIC PC IMP Tracking log filed in the TMF. A copy of the ARTIC PC Dispatch form should be filed at Site in the ISF and the TMF.

If the IMP is deemed fit for use the ARTIC PC Study coordinator/manager will send an email to confirm this. The stock can be removed from quarantine and all members of staff involved in the trial and issuing the IMP should be informed.

All written (or email) communications re the IMP should be filed in the ISF/TMF.

3.2.4 Receipt of IMP at Centres

The IMP will be manufactured by Tio Farma (Hermanus Boerhavenstaat 1, Oud Beijerland 3261 ME, Nerherlands) but provided by Pilatus Pharma (Pilatus Pharma Ltd, 3 Regal Way, Watford WD24 4YJ telephone number 01923 204310) in bottles containing Amoxicillin or Amoxicillin placebo with instructions as how to reconstitute the powder. Each bottle will be labelled with MHRA approved labels. The packs are packaged by Pilatus Pharma Ltd in bundles according to the randomisation schedule provided by Peter Smith. Peter Smith is a Professor of Social Statistics at the University of Southampton but independent of the study.

Prior to delivery the QP batch receipt will be sent to the ARTIC PC lead Centre at the University of Southampton, this will be filed in the TMF. Copies of this certificate will be sent to the other three Centres and filed. Each Centre will send a copy of this to their participating Sites.

The patient packs will be transported under ambient conditions (15°C – 25°C) in standard cardboard boxes. During transit temperature will be monitored by a temperature data logger supplied by Pilatus Pharma Ltd..

The three Centres will take delivery of IMPs and upon arrival at the Centre the delivery will be signed for and a note of the time of delivery made.

A member of staff (as per delegation log) will complete the following quality checks to ensure the contents are in good condition, all stock is present and the patient numbers match those on the delivery note. If there are any concerns the Study coordinator/manager at Aldermoor Health Centre should be informed immediately. Any IMP in poor condition should be quarantined until assessed as described in the temperature variation section of this SOP.

Receipt of the IMP must be documented by a delegated member of staff for Pilatus Pharma Ltd in the delivery note and also in the ARTIC PC Centre Drug accountability log. The completed delivery note should be filed and a scanned version emailed to the Pilatus Pharma company (nick@platuspharma.com) and to the study lead coordinator/manager at Aldermoor Health Centre. The ARTIC PC lead coordinating Centre will update an ARTIC PC IMP tracking log in the TMF and add the email with its attachment.

The temperature data logger accompanying the shipment must be returned to Pilatus Pharma in a jiffy bag marked FTAO Nick Dowds, Pilatus Clinical Services, Hampton House Unit 3D, Regal way, Watford WD23 4YJ with a copy of the completed delivery note. The staff at Pilatus Pharma will ensure the temperature has remained in range during transit and inform the ARTIC PC lead coordinating Centre of the reading. If any temperature deviation has occurred the stock will be placed in quarantine until assessed.

NB the supporting Centres should not issue IMP to Sites until a confirmatory email has been received from the ARTIC PC study lead coordinator/manager. This email should be filed in the Coordinating Centre File (CCF).

The IMP will be stored and dailly temperature monitoring will be completed by delegated personnel.

3.2.5 Transfer of IMP between Centre and Sites

NB IMP should not be transferred from one Site to another due to the blocks of randomisation. This process below is for transfer between Centres and Sites.

The transfer can occur by the Centre staff performing the delivery or by using next day courier.

Participant packs will be transported in blocks with the original packaging in-tact.

Temperature monitors must be prepared and activated in line with the instructions provided with them.

The activated temperature monitor must be attached to the delivery package.

The dispatching Centre/ Site will complete the first section of the ARTIC PC dispatch form detailing the receiving Centre/Site and Patient pack numbers.

The dispatch form is placed within the shipment container along with the IMP and any Temperature Monitoring sheet.

A copy of the completed dispatch note should be filed in the IMP section of the TMF/CCF/ISF.

The box should be sealed and clearly addressed.

If a courier is being used the receiving Site should be alerted by email of the collection of the parcel.

Upon receipt the package should be signed for and a member of the trial team informed.

An authorised (as per delegation log) member of receiving staff must undertake the quality checks of – the participant packs in the box match those on the dispatch sheet, the condition of the IMP, temperature has remained below 25°C during transit (see temperature deviations should this not be the case). Any concerns should be raised immediately with the ARTIC PC lead coordinating Centre at Aldermoor Close, Southampton.

Receipt and quality checks must be documented in the second part of the ARTIC PC dispatch form by the receiving Centre/Site. A copy of the completed form should be emailed or faxed to the dispatching Centre. This document should then be filed in the TMF/CCF/ISF.

The ARTIC PC Tracking log will be completed.

3.2.6 Issue of IMP to Sites by Centres

At the start of recruitment each Site will be provided with Participant packs containing IMP.

The ARTIC PC lead coordinating Centre at Southampton will inform other Centres when Sites need restocking.

The local Centre will record details of which packs have been sent to which Sites on the ARTIC PC Drug accountability log. This log is filed in the CCF.

IMP will be transferred as detailed above.

3.2.7 Receipt of IMP at Site

The Site will acknowledge receipt of IMP as above. This includes completion of the ARTIC PC Drug accountability log which is filed in the ISF. A copy provided for the TMF and CCF.

IMP will be stored and daily temperature monitoring as described above.

3.2.8 Issue of IMP to patient by Sites

Patient packs will be allocated to participants deemed to be eligible and who have signed an informed consent form in sequential order.

When a pack has been allocated the detachable sticky label containing the Patient pack number should be removed and attached to the ARTIC PC Notification of registration form and this returned to the ARTIC PC lead coordinating Centre at Aldermoor health Centre.

The clinician must ensure the participant is aware of how to store the IMP at home.

A record of the allocation of IMP is made in the ARTIC PC Site accountability log.

The ARTIC PC lead coordinating Centre will update the ARTIC PC coordinating Centre Tracking log in the TMF and inform the local Centre for them to update the ARTIC PC Centre drug accountability log.

The ARTIC PC lead coordinating Centre will monitor the number of packs remaining at each Site and when only 2 packs remain the local Centre will be asked to restock the Site.

3.2.9 Return of any unused IMP from patients

Participants are asked to return unused IMP at the day 28 visit to their recruiting Site. This will in turn be collected by the Centres.

All returned IMP will be estimated for the amount used and recorded in the ARTIC PC coordinating Centre IMP return and destruction log. The coordinating Centre will update the lead Centre and the master ARTIC PC IMP tracking log will be updated in the TMF.

Returned IMP will be stored separately form IMP waiting to be distributed to Centres/Sites.

The empty patient packs and returned unused IMP will be stored until the end of recruitment.

3.2.10 Return of any unused IMP from Sites

Sites will be required to return any unused Patient packs to their local Centre at the end of their involvement in recruitment. The method will be determined by the number of packs at Site.

A record of any returns must be made in the ARTIC PC Site Drug accountability log in the ISF.

Upon receipt the Patient pack ID numbers are checked against the dispatch form and against the ARTIC PC Centre Drug accountability log to ensure all packs from the recruiting Site are accounted for. Receipt of IMP will be made in the ARTIC PC Centre Drug accountability log in the CCF.

Any unused IMP will be stored in case of need of reallocation. This will be determined by the management group.

3.2.11 Return of IMP to Southampton Centre

When recruitment is complete any unused IMP will be returned by local Centres to the ARTIC PC lead coordinating Centre for destruction. The method will be determined by the number of packs.

A record of returned packs will be kept in the ARTIC PC lead Centre drug accountability log.

IMP will be transferred in the procedure outlined above.

Returned IMP will be recorded in the ARTIC PC lead coordinating Centre IMP return and destruction log. The ARTIC PC IMP tracking log in the TMF will be updated.

The returned IMP from each Centre will be checked against the ARTIC PC Master patient pack accountability log to ensure all packs are accounted for i.e. issued or returned.

When each sheet is complete staff at Aldermoor health Centre will sign that the medication as accounted for.

4. Management of unused IMP at Southampton Centre

Once recruitment is complete and all unused IMP has been returned to then ARTIC PC lead coordinating Centre the medication will be stored for disposal.

Any movement of the IMP from this point will be accompanied by the ARTIC PC lead coordinating Centre drugs return and destruction log.

4.1 Destruction of unused medication

The unused IMP will be destroyed in line with standard pharmaceutical procedures.

5. Warnings/ Notes/ General Information / Safety

None.

5. Risk assessment

As in ERGO Reference 13381. In addition see the Trial Risk Assessment and Unblinding Risk Assessment in the TMF.

6. Additional Glossary of terms

Investigational Medicinal Product – A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. This includes products which already have a marketing authorisation but are being used or assembled (including packaging) in a different way from the authorised form.

Clinical trial materials - A term referring to a set of supplies provided to an investigator by the trial Sponsor.

Qualified Person (QP) – An individual with responsibility for the safe control of medicines with extensive training and an in-depth critical understanding of all the aspects associated with pharmaceutical manufacturing. The QP has a legal responsibility to ensure the IMP has been manufactured in accordance with EU GMP and meets the condition of the CTA and the product specification file.

QP Batch certificate – Each batch of IMP must be certified by the QPO as being suitable for use prior to its release for use in a clinical trial. The QP must certify that each batch complies with Article 13.3(a), (b) or (c) of Directive 2001/20/EC and documented in accordance with Article 13.4 of the same.

GMP – The standard to which a medicines manufacturer must reach in their production processes. Products must be produced of consistently high quality, be appropriate for their intended use and meet the requirements of the marketing authorisation or product specification.

ISF – a file which forms part of the Trial Master File. It is held and maintained by the local Principal investigator or persons identified in the delegation log at each Site participating in the clinical trial.

CCF – a file which forms part of the Trial Master File. It is held and maintained by the local Principal investigator or persons identified in the delegation log at each Centre participating in the clinical trial.

Centre – The University establishment from which IMP distribution is coordinated.

Site – The GP surgery or health Centre from which the trial is conducted, patients are screened, consented and randomised with the issue of IMP.

7. Role and Responsibilities

As described above.

8. Policies, Guidelines and References

External

- GMP Annexe 13
- Medicines for Human use (Clinical Trials) Regulations SI 2004 1031
- Medicines for Human use (Clinical Trials) Regulations SI 2006 1928

9. Training

All research and administrative staff working on ARTIC PC must read this SOP. Training will be included in the Site initiation presentation delivered to Site staff. The training and delegation logs will support this process.

10. Supporting documents

ARTIC PC Drug storage risk assessment

ARTIC PC Site drug allocation log

ARTIC PC drug temperature monitoring log

ARTIC PC Drug return and destruction log

ARTIC PC Dispatch form

ARTIC PC Notification of registration form