ARTIC PC Trial Emergency Unblinding SOP

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Role	Name	Signature	Date
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Revision History

Version	Revision	Date
1	New document	26 July 2016
2	Clarity about use of MID to unblind if nothing else available.	19 August 2016
3	Correction of MID and PID to be 4 digits and 6 digits	15 September 2016

Effective Date	16 Sept 16	Review Date	15 Sept 17

Definitions and abbreviations

A2	The company that will provide the unblinding service.
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.
UoS	University of Southampton

Contents

1.Introduction and Background

The ARTIC PC study and nested trial is Sponsored by the University of Southampton. ARTIC PC trial emergency unblinding requests are handled by Professors Paul Little /Theo Verheij the trial co-CIs (or their designate) at all possible times during the working week (Monday – Friday 09:00-17:00). It is recognised that unblinding may be required outside these "normal working hours" and as such direct access to the unblinding service will also be available but our preferred route is via one of the Cis.

Unblinding is the process by which the randomisation code is broken so that clinical staff, the trial and study Data Monitoring Committee and/or the Trial and Study Steering Committee become aware of the intervention for a person participating in a trial.

Unblinding must be undertaken by a pre-determined process to ensure that researchers and participants are not unblinded unnecessarily and the study results are not compromised. Equally, unblinding should occur in a responsive manner when it is clinically indicated. This will be facilitated by the call centre used for unblinding following a script of questions developed by the study staff.

The ARTIC PC trial is supplied IMP by Pilatus Pharma, 3 Regal Way, Watford WD24 4YJ. This company will keep a list of the Medication IDs (MIDs) provided. They, Pilatus, will provide A2, the unblinding company, with a list of MIDs. Neither participants nor the study team will know the arm to which they have been allocated – active or placebo.

2. Purpose

This document describes the conditions under which a request may arise to unblind a randomised patient from the ARTIC PC trial and the steps that must be taken by the research team in all circumstances to ensure the correct unblinding procedures are followed both before and after Professors Little or Verheij (or his designate) requests the specific act of an unblinding request. It also describes the additional actions required of all staff, in the event of unblinding for ARTIC PC, before and after following the standard procedure

3. Scope

The document refers to emergency unblinding for the ARTIC PC trial only.

Unblinding can occur in two contexts in the ARTIC PC trial:

- when clinically indicated (emergency unblinding)

- for data analysis purposes. Unblinding is the process by which the allocated arm is revealed for understanding the effect of the medication on an individual's outcome.

4. Process

4.1 Clinical indications/emergency unblinding circumstances:

- there is a medical emergency and unblinding will influence the patient's treatment;
- clinical deterioration means knowledge of treatment is required;
- the patient has suffered an Unexpected Serious Adverse Event or Suspected Unexpected Serious Adverse Reaction and the intervention must be made known.

Requests for emergency unblinding will ideally be made by a healthcare professional with clinical responsibility for the patient's care and these requests are handled by Professors Little/Verheij (or his designate) when possible, during the working week (Monday – Friday 09:00-17:00). See earlier about out of hours unblinding and the script provided to the unblinding service.

Other than in very exceptional circumstances, requests to unblind should not be accepted from patients and relatives, but referred instead to the patient's GP/medical professional.

4.2 Data analysis purposes:-

- Unblinding can also occur at the request of the Data Monitoring Committee (DMC), and at the conclusion of the trial to determine the effect of the intervention.
- Unblinding requests for data analysis purposes, e.g. as may be requested by the DMC, may additionally be handled by the Sponsor via the Data Manager. See section 9.

5. Pre-Requisites

5.1 Pre-Requisite Knowledge & Training

- Certified training in ICH-GCP (Good Clinical Practice).
- ARTIC PC Trial recruitment training

The process will be using the MID/patient pack number. This is something added to the pack by Pilatus pharmacy and they will have made to reflect the contents active or placebo in line with the random block size from the excel list. The list provided by UoS ARTIC PC study team statistician.

This will be added to the pack by the pharmacy and not tampered with by recruiting staff.

The site, when they recruit a child, take the next pack and then the Patient Identifier (PID) will be added. The PID will be from the consent form.

The site tells the ARTIC PC Study manager the recruitment has occurred so he/she knows the pack has been used and provides him/her with the MID and PID. This is in the CRF faxed to the ARTIC PC team or entered in Research Online.

The ARTIC PC Study manager can then update the unblinding service to allow them to correlate who has received what arm treatment.

5.2 Pre-Requisite Equipment & Systems

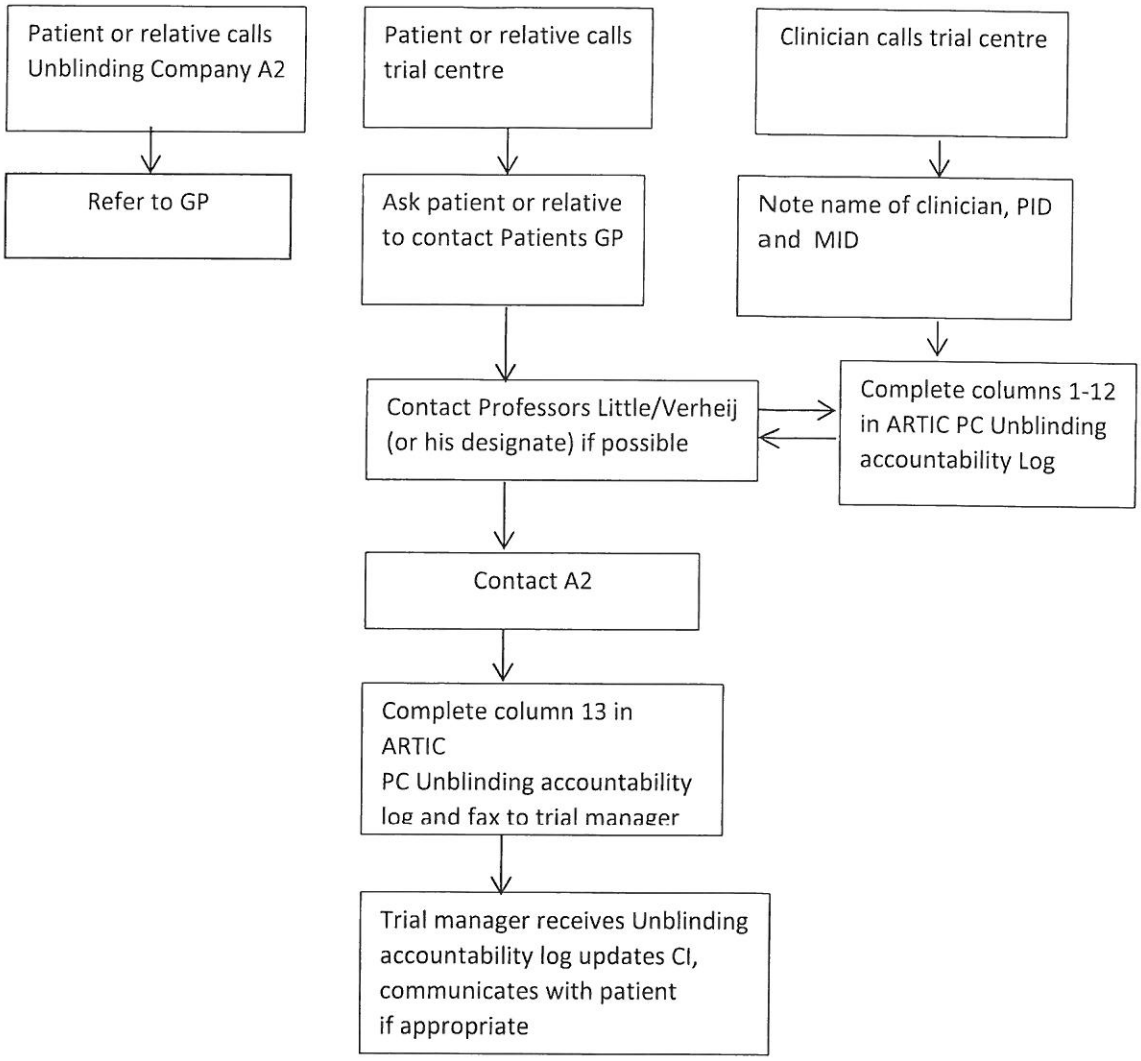
None.

6. Roles & Responsibilities

Who	What & Why
A2	• The company that will provide the unblinding service. • Reports all unblinding requests (but not the outcomes) to the study manager. This relates to medication issued so that any follow up is not compromised by the manager being aware of the individual's allocation. • Have access to unblinded data.
(Co) Chief Investigator	• Reviews this SOP jointly with the study Sponsor.
Principal Investigator	• Ensures SOP is adhered to in all local centres/sites.
Local Investigator	• Ensures SOP is adhered to in all local sites.
Sponsor and DMC	• Has access to the unblinded data; provides 'unblinding' function for study data analysis for review by DMC for safety monitoring purposes but not to ARTIC PC SMG unless previously authorised by the S/TSC. • Does not provide a role in clinically indicated (emergency) unblinding.
Pilatus Pharma	• Provides the IMP and placebo in a manner that prevents unblinding and labelled in a manner that is acceptable to the MHRA.
Study Sponsor (UoS)	• Is responsible for the integrity of the research project. • Reviews this SOP jointly with the CI.
Study Manager	• Acts in a manner so as to maintain blinding of whole study research team. • Maintains Unblinding Accountability Log (which does not include the outcome of unblinding, i.e. the treatment allocation, so that blinding of the research team is preserved) • Ensure all requests for unblinding are reported to the CI. • Will train recruiting clinicians to explain to patients about the Trial Participation Card.

Who	What & Why
	• Will train recruiting clinicians in the use of the emergency unblinding service.
GP Practices	• To be aware of the ARTIC PC trial emergency unblinding procedure and to take responsibility for making any emergency unblinding requests on behalf of ARTIC PC trial patients where clinically indicated. • To teach each recruited patient about the purpose of the Trial Participation Card and that the patient should carry it on their person.
Data Monitoring Committee	• Monitors the safety of the study by scrutinising the adverse event data. • May request unblinded data via Professor Little/Verheij for safety monitoring purposes.
Trial and Study Steering Committee	• Makes decisions regarding the safety of the trial and study and whether the trial or study should at any time be stopped due to safety concerns.
Trial and Study Management Group	• To be aware of the ARTIC PC trial emergency unblinding procedure and to agree on the management of individual emergency unblinding requests in terms of inclusion in the trial dataset.

7. Procedure



7.1 Procedure Narrative

Each of the points at which the question of unblinding arises will be described below, with the actions that should be taken.

7.1.1 Emergency unblinding requests received by the trial research team

7.1.1.2 From research participants

1. If a patient or patient's relative contacts the study team with a request to be unblinded, the research team will ask the caller to contact the patient's GP/healthcare professional.

2. If the situation appears to be medically exceptional, e.g. the patient has called an ambulance, the situation must be referred immediately by the trial team to the following sources in order of priority:-

- Professor Little/Verheij at all possible times during the working week (Monday – Friday 09:00-17:00);
- ARTIC PC Study Manager (Monday – Friday 09:00-17:00);

- If none of these staff are available the responsible clinician should call A2 direct.

3. The member of the research team or unblinding company who has received and responded to the request, as above, will complete the ARTIC PC Unblinding Accountability Log, whether the request results in unblinding or not.

7.1.1.2 From clinicians

1. Professor Little/Verheij should be the first point of contact where ever possible:-

   - In a medical emergency, healthcare professionals will have access to the unblinding service provided, the details of which are provided in the Study Site File, on the Trial Participation Card carried by ARTIC PC trial patients, on the label of the study medication and on the ARTIC PC trial website.

     i) In normal working hours (Monday - Friday, 09:00 – 17:00), the clinician will attempt to call Professor Little/Verheij (or his designate) on 023 8024 1024/ 0778 6126108 and quote the PID and the MID numbers from the patient's Trial Participation Card.

     ii) Out-of-hours, clinically indicated treatment will be undertaken by a qualified medical doctor.

2. Recruiting clinicians will explain the purpose of the Trial Participation/Unblinding Card to all patients recruited into the ARTIC PC trial. The clinician will recommend that the patient carries the Trial Participation Card on their person for the duration of their involvement in the trial.

3. Clinicians participating in the ARTIC PC trial will receive training on how to use the trial unblinding service before recruitment starts at the site.

4. When a clinician decides whether unblinding of the ARTIC PC patient is clinically necessary, they must put the request directly to Professor Little/Verheij (or his designate) when ever possible.

5. The Medicine ID (MID) and Participant date of birth will be the default and preferred combination of data used to unblind ARTIC PC patients where clinically indicated. If in doubt the MID will be used.

6. The ARTIC PC trial will make provision for unblinding in the (unlikely) emergency situation where the clinician does not have access to the Trial Participation/Unblinding Card (and therefore to the Medicine ID and Participant ID numbers) and it is necessary to be able to unblind the patient from the participant's date of birth.

7. To enable this, the ARTIC PC team will provide the company with a complete list of Participant ID numbers against which the arm will be revealed when the MID or PID is entered, the unblinding company will keep a secure copy. This confidential list will be updated by the Company team on each day that a patient (or patients) are recruited to the trial.

8. The Company will store this list with the ARTIC PC trial unblinding data in the trial file, and replace outdated lists on receipt of any updated lists from the trial team.

9. This information will be filed in the Company trial file for access during working hours, and will be transferred to the on-call workspace.

7.1.1.3 If the clinician contacts team first

1. If the clinician contacts the trial team first, and the team therefore becomes aware of the unblinding request before Professor Little/Verheij, the Trial Manager will:

- Record the clinician's name and the relevant MID on the ARTIC PC Unblinding Accountability Log (Appendix 1).
- Ensure the clinician has the relevant information to hand (MID number).
- Ask the clinician to contact Professor Little/Verheij (or his designate) directly on the above telephone number if possible.
- Professor Little/Verheij (or his designate) will call the relevant company to advise them that the request has been made.
- All requests for unblinding that are made known to the research team must be recorded on the ARTIC PC Unblinding Accountability Log, whether or not unblinding occurs.

7.1.1.4 Emergency unblinding requests from ARTIC PC study PIs / CI

1. An ARTIC PC study team investigator (centre or site PI) may issue a clinically indicated request for emergency unblinding in response to a reported SAE or SUSAR.

2. In this case, the PI / CI will make the request directly to the relevant Company as a clinician.

3. The request would be handled by the relevant Company as per their SOP

7.2 Emergency unblinding requests from ARTIC PC DMC

1. A request for emergency unblinding by the DMC in response to trial adverse event data will be referred to the RG office.

7.3 Emergency unblinding requests received by the unblinding company

For any ARTIC PC emergency unblinding request received from a clinician taking responsibility for the participant's care, A2 the unblinding company will respond as follows:

- Collect the following information from the caller and record on the ARTIC PC Trial Unblinding Accountability Log:

  i) Patient's **6-digit ARTIC PC PID number**

  ii) Patient's **4-digit ARTIC PC MID number**

  iii) Patient's initials

  iv) Tick box to confirm request made by clinician

  v) Name of clinician making request

  vi) Location / site from which request being made

  vii) Contact number of clinician making request

  viii) Reason for unblinding

  ix) Name of relevant company staff member taking the call

  x) Tick box to confirm call is being received at the company

  xi) Date of call

  xii) Time of call

- If it is not possible to complete unblinding immediately take the caller's details and tell them that they will be phoned back within the clinical session, while unblinding is completed in line with the company SOP. The medical professional responsible for the child's care will be have completed their number on the unblinding card and this can be provided to the unblinding company.

- Once unblinding is completed, inform the caller of the treatment allocation.

- Update column 13 of the ARTIC PC Unblinding Accountability Log to confirm whether the unblinding occurred or did not occur. **Do not** write the outcome of the unblinding.

- Fax the ARTIC PC Unblinding Accountability Log (which does not give the treatment allocation) as soon as possible to the ARTIC PC Study Manager: 023 8000 2380 (secure fax).

- Keep a copy of the ARTIC PC Unblinding Accountability Log in the Company trial file.

8. Recording and reporting ARTIC PC unblinding requests

1. On receipt of a faxed copy of the ARTIC PC Unblinding Accountability Log, the Study Manager will check that the log is completed fully.

2. Call the relevant company to let them know that the log has been received, and to query any information gaps in the Log.

3. Inform the CIs of the Log contents.

4. Notify the relevant centre PI.

5. Ensure the Study Manager informs the participant of the following:
   - the Manager is still blinded to the trial medicines;
   - the participant can continue to take part in the trial if they wish;
   - if appropriate, the participant can continue to use the trial medicines if they wish;
   - the importance of continuing with the trial.

6. Update the Trial Management Database with the information on the Unblinding Accountability Log;

9. Other unblinding requests

1. Non-emergency non-clinically indicated unblinding requests may be made by the DMC to the TMG for data analysis purposes. All such requests will be handled by the Sponsor as follows:
   - The trial team will forward the clinical dataset (the ARTIC PC clinical database download as a result of which the DMC data analysis unblinding request has arisen) to the allocated member of staff within the Research governance team;
   - The RG staff member will identify the patients by treatment group but still blinded to allocation (i.e. Group 1 or Group 2);
   - If the DMC so request, RG will provide the DMC with the same information as above, but unblinded (i.e. Group 1 = active; Group 2 = placebo);
   - The RG staff will forward these data directly to the DMC so as to maintain blinding of the trial team.

2. All DMC requests for unblinded data must be channelled through the CI / SMG; the request itself will be handled only by the relevant member of staff within RG so as to maintain blinding of the trial team.

3. Non-clinical unblinding requests will be recorded on the same accountability log.

10. Quality Control Measures

A "mock unblinding" will be carried out prior to the start of recruitment (issue of patient packs to GP practices) to ensure that the above processes work. This will be documented and filed.

11. Related Documents

ARTIC PC Adverse Event Reporting SOP v3.0 (06 Jan 2016)

Unblinding script

12. Additional Guidelines

N/A

13. Appendices

Unblinding accountability log

Unblinding script

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A2 Staff please complete columns 1-12 of this log, in the event of any unblinding request relating to an ARTIC PC trial participant, and fax to the number right. **FAX ALL ENTRIES TO 023 8000 2380**

ARTIC PC study staff If unblinding requests are received by a member of the ARTIC PC study research team, the researcher should contact A2 immediately to advise them of the request, and then complete columns 1-12 of this log and fax to the number left.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Participant ID	Medicine ID	Patient initials	Request made by (tick box): Clinician, Patient, or Other (please specify)	Name of person making unblinding request	Location or ARTIC PC site of person making request	Contact number of person making request	Reason for unblinding request (please record in full the difference unblinding will make to the patient's management)	Name of person taking the call	Location of person taking the call	Date (dd/mm/yyyy)	Time (24 hr 00:00)	Action taken, for example: Actions Unblinded Not unblinded Trial centre actions Reported to Supplier Other (please specify)	Chief Investigator signature + date	Date (dd/mm/yyyy)
			Clinician ☐ Other ☐ Patient ☐ If other, whom:						A2 ☐ Study centre ☐					
			Clinician ☐ Other ☐ Patient ☐ If other, whom:						A2 ☐ Study centre ☐					
			Clinician ☐ Other ☐ Patient ☐ If other, whom:						A2 ☐ Study centre ☐					

Unblinding script for A2

Good morning/afternoon/evening this is the ARTIC PC unblinding service.

I understand you would like to unblind a patient? Yes No

Could you please answer the following questions:

1. Are you involved in the study ARTIC PC as a GP (general practitioner) recruiting patients? Y N

Info: The other possibility is another physician treating the patient at this moment, but not involved in the study. Parents or guardians of children participating should be advised to contact a medical practitioner if they are concerned about the health of a child.

2. Could you please tell me the date of birth of the patient? dd/mm/yyyy

3. What's the trial medication code we need to unblind for you?

Info: You can find this code on the label present on the medication bottle (first line, 4 digits, for example 1621). **XXXX**

4. What's the reason for unblinding?

Please write down reason..... .....
.....

Info: Possible reasons for unblinding: possible side effect or adverse event on study medication, serious adverse event (SAE), treatment not effective (they would like to start another treatment).

Thank you for your answers. The patient who got the study medication with the trial medication code **XXXX** [*MENTION CODE*], got .....

Option 1: Amoxicillin 50mg/kg for 7 days

Option 2: a placebo.

Circle antibiotic (option 1) or placebo (option 2)

Just to make sure, could you please repeat the treatment the patient got. [*Should be the same as ticked above*]

Thank you for calling and have a nice day/evening.