Ambition Trial Coordinating Centre
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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Trial Management
Work Practice Document 2
Site Training

Title of study	High Dose AMBISOME© on a Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: A Phase III Randomized Controlled Non-inferiority Trial		
Acronym	Ambition-cm – AMBIsome Therapy Induction OptimizatioN		
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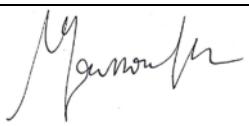
Author(s)	Nabila Youssouf Trial Manager		20/07/2017
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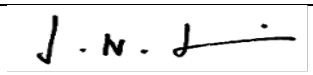
Approved by	Joseph Jarvis CI		20/07/2017

Revision History:		
Version Number	Effective Date	Reason for Change
1.0	20/07/2017	First version

Working Practice Document
Site Training

Purpose

This purpose of this Working Practice Document (WPD) is to describe the process to follow when initiating site investigators to conduct the Ambition trial.

This WPD applies to the Ambition trial conducted by the Ambition Trial Coordinating Centre and will be carried out according to applicable aspects of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) standards.

References

Ambition Phase III Trial Protocol

ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996), accessible at:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Appendices

1. Trial Master File template
2. Investigator Site File template
3. Pharmacy File template
4. Material User Guidance
5. Site Initiation report

Procedure

The person conducting the site initiation (trainer) should have a full understanding of the trial procedures in advance of conducting the initiation. He/she should have been trained directly by the Chief Investigator (CI) either by attendance at an investigators' meeting where the trial procedures were presented or had discussions directly with CI or Trial Manager (TM). In addition, if the trainer is not directly employed by the Sponsor or collaborating organisation, an appropriate agreement/contract must be in place.

The TM should ensure that those delegated as trainers are familiar with the following documents and they have access to all of them:

- Protocol
- Investigators Brochure
- DVD training films
- PowerPoint presentations on CD
- Consent procedure (or country specific approved procedure).

The trainer must confirm with site that they have the following materials in advance of any initiation:

- Investigator's Study File
- Pharmacy File

- Folder containing:
    - Consent Forms x10
    - Patient Information Sheets x10
    - Appointment cards
    - Medical notes labels.

At the start of the site initiation, the trainer should confirm who at the site is in attendance and record.

The trainer should ask if the Investigator has gone through all of the materials sent and the investigator should have the training materials with them during the initiation.

The trial flow chart (found in section 3 of the ISF) guides the investigator through the trial processes and may be a useful tool to refer to during the training.

The investigator should be allowed to ask questions about the ISF, protocol or other materials at the start.

The topics outlined below in sections A-E should then be discussed. The time spent on each subject will vary according to the investigator's experience and understanding and any questions asked.

Within 10 working days of the site initiation, the trainer will complete a Site Initiation Report recording the topics covered, any local requirements or procedures and any actions arising.

A. Discussion of the protocol

Reiterate any country specific issues (e.g. minimum age of adulthood). Confirm this is reflected in the materials sent. Discuss the following, taking into account any questions raised by the investigator earlier.

1. Other treatments for Cryptoccocal Meningitis (CM)
    - Randomisation and the administration of the trial treatment should be done as soon as possible after diagnosis once eligibility is confirmed and consent process followed and alongside the administration of other treatments. Concurrent treatment must not be delayed to participate in the study.
    - The Ambition trial will not affect standard treatment given to patient.

2. Diagnosis of CM
    - The trial team should use standard method for diagnosis used at their hospital
    - Glasgow Coma Scale (GCS) - use of GCS to determine eligibility of the patient will be discussed with the trial team.

3. Eligibility
    - Refer to:
        - The eligibility criteria in the Ambition trial protocol (flowchart)
        - PowerPoint training presentations on CD inside front cover of ISF
        - MOP in ISF section 3
        - Randomisation flowchart and guidance provided to sites as wall posters
    - Confirm the minimum age for adult as per the country-specific protocol, approved by the ethics committee

- Refer to the Inclusion/Exclusion criteria in the protocol. No other exclusion criteria apply but it is always the clinician's judgement and decision whether to include the patient in the trial.

4. Informed consent – ISF section 5
   - Ask the Investigator to explain to you the consent procedure to be used locally. Confirm that this is in line with the ethics committee approval.
   - Discuss the various options for obtaining consent:
     - Next of kin Consent; Relative/Representative Agreement
     - Follow-up consent to be obtained from patient/relative/representative
     - If initial consent not from patient and patient later regains capacity, every effort should be made to also obtain their consent
   - Discuss the different scenarios that might occur and the options for obtaining consent e.g. patient unconscious and no representative available, or what to do if patient has died and consent has not yet been obtained
   - Discuss the capacity of the patient or relative to provide consent and factors that might affect capacity e.g. level of distress, level of consciousness
   - Confirm that the information sheet and consent forms have been sent in all relevant languages
   - Confirm that the original consent form must be kept in the ISF and a copy to be given to the patient/person who gave consent and a copy to be placed in the patient medical records
   - Reiterate the key point that the consent form must be completed, signed and dated by the person giving consent and signed by the person taking consent
   - Reiterate that consent for each patient ***must*** be obtained pre randomisation, signed and dated by person giving consent and person taking consent, and the Principal Investigator (PI), which can be at a later date.
   - Person taking consent must be trained and understand the process
   - Consent forms will be monitored, and feedback provided via a consent monitoring report.

5. Randomisation
   - Ensure the team are familiar and confident to use the database for data entry and randomisation
   - Ensure that the Investigator is aware of the labels provided for labelling the medical records and other documents e.g. medical records label, appointment cards etc

6. Drug administration – ISF section 4
   - Method – discuss the IMP storage guidance located in the ISF and the PowerPoint presentation and the administration instructions contained in each box
   - Discuss when each drug is administered and how

7. Drug accountability – ISF section 13
   - Confirm that the initial supply of IMPs has arrived intact and that the receipt/confirmation has been returned
   - Confirm that in the event a patient is randomised and the trial treatment is not used, the patient is still in the trial. The unused treatment must be documented on the Drug Accountability Log (DAL) and not used for another patient unless agreed otherwise with the Chief Investigator
   - Instruct site to keep all shipping documents and file in the Pharmacy File
   - Confirm that there have been no changes to the IMP Management Risk Assessment that was completed prior to release of IMPs by Sponsor

- Discuss that if there are any changes to IMP storage, the IMP Management Risk Assessment will need to be completed by the Pharmacist for the new storage area

8. Data collection – ISF section 6
   - Ensure investigators know to use the database
   - Confirm that as most data for the trial originates from the patient medical records, these must contain data which match the data reported (can be audited, checked, inspected, reviewed)
   - Complete all sections, blank sections will be queried

9. Adverse events and reporting – ISF section 7
   - Discuss protocol reporting requirements
   - Discuss care of patients who develop an AE
   - AE forms can be completed online or returned by fax or secure email
   - Discuss procedure and reiterate that PI and team need to ensure they are familiar with the procedure.

10. Laboratory procedures – ISF section 17
    - Ensure all laboratory staff are trained in Ambition techniques
    - Ensure equipment (e.g. fridges, incubators) used are suitably calibrated
    - Ensure reagents used are not expired
    - Importance of keeping a log of material, logbook for the samples and stock-bins
    - Ensure that bio-safety cabinets are serviced according to their Manufacturer's Manuals.

B. ISF

11. The ISF is a complete history of the trial at that site
    - Confirm that the Investigator is aware that the ISF and all its contents and the medical records of all randomised patients must be kept for at least five years after the end of the trial.
    - Confirm that the PI is aware that the trial is subject to independent audit and inspection by relevant regulatory authority, and why this is done (covered in GCP training)
    - Emphasise that ISF must be kept up to date, including logs (list of logs to be maintained using materials user guidance e.g. Randomisation log, Screening log, Site Responsibilities Delegation log, DAL)

12. Filing of documents
    - Point out the ISF user guidance

Tasks may be delegated to trial team members – but this must be recorded on 'Site Delegation of Responsibilities Log' – ISF section 19.

C. Recruitment

13. Discuss recruitment target
    - To be decided based on hospital cases and discussions with PI
    - Recruitment will be monitored against this target. Significantly lower than expected recruitment or no recruitment will lead to the trial processes being forgotten and to poor standards.
    - Aim to start recruitment as soon as possible after training session (ideally within 1 week)

14. Local plans for recruitment and data management

- Confirm where the IMP and ISF will be stored. This should be in a secure location in the relevant department, but accessible to the trial team at all times.
- Discuss:
    - Who will have access the IMPs and ISF?
    - How will the PI monitor recruitment and follow-up?
    - Who will be responsible in their absence?
    - Who will recruit patients?
    - Who will do follow-up?
    - Who will enter data?
    - Does someone from Medical Records need to be on the trial team?

D. Training

15. Training the trial team – ISF section 3

- Discuss sources of training materials; training films and presentations (e.g. DVD, ISF, PowerPoint presentations)
- Schedule regular training sessions, especially when there is a change of staff
- Ask if translated posters/pocket cards are needed

16. GCP training for the team

- Ask PI to encourage the whole team to complete the online training, especially those involved in consent and data collection
- Available free of charge on LSHTM website

E. Materials

17. Top-up and ordering / need for other materials

- Explain that:
    - Site to contact the Ambition Trial Coordinating Centre by phone or email if any materials are needed

Training

Each staff member receives or has direct access to applicable Working Practice Documents (WPDs).

Each staff member reviews the applicable WPDs once a year.

All WPD training is documented and tracked in the training log located in the Investigator Site File (ISF)

New staff is trained on applicable WPDs within 30 days of employment and all WPDs within 90 days of employment.

Staff members whose duties fall within this WPD scope are retrained within 14 days of the approval of each WPD revision.

Staff signatures: (signing below indicate that you have read this SOP and understand the material contained in it)

Date	Name (Please print)	Signature