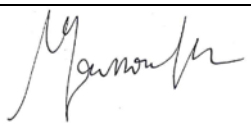
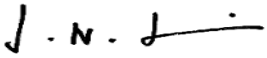
Ambition Trial Coordinating Centre
Private Bag 320, Princess Marina Hospital
Gaborone, Botswana

AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document 4
Adverse Events Reporting

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		
ISRCTN No.:	ISRCTN72509687		
WPD Current version	Version 1.0		
Author(s)	Nabila Youssouf Study Manager		14/10/2018
Reviewer(s)	Sile Molloy Study Manager		28/02/2018
Approved by	Joseph Jarvis CI		14/10/2018

Revision History:		
Version Number	Effective Date	Reason for Change
1.0	14/10/2018	First version

Working Practice Document
Adverse Events Reporting

Purpose

The purpose of this Working Practice Document (WPD) is to describe the procedure to be used by all Investigators and the staff they delegate to do so for the management of any trial related safety event.

This WPD applies to the Ambition trial conducted by the Ambition Trial Coordinating Centre and applies to all participating sites.

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

LSHTM-SOP-008-01 Recording, Managing and Reporting Adverse Events for studies of Investigational Medicinal Products

LSHTM-SOP-012-01 Protocol Violations and Deviations

Appendix

What to report on the EDC

1. Definitions

	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening*

	• Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Is another important medical condition***
Urgent Safety Measure (USM)	A sponsor or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body.

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency. Presence of malaria is not an SAE unless the current infection is life threatening.

2. Assessment and evaluation of Adverse Events during the trial

It is the responsibility of the PI/Study Doctor at each trial site to evaluate each AE for seriousness, causality, severity and expectedness. The CI cannot downgrade the PI's/Study Doctor's assessment. All SAEs must be followed up until a resolution is reached (i.e. recovered, fatal etc.).

2.1 Seriousness

An event is considered serious if it meets one or more of the definitions as outlined in ICH GCP guidelines as described in section 1 of this WPD.

2.2 Causality

The Council for Internal Organisations of Medical Sciences (CIOMS) VI group defines Investigator's causality assessment as vital information and every effort must be made by the PI, using his/her clinical judgement to obtain all the required information to determine whether the AE is related to the trial intervention. The PI is best placed to assess how the subject has changed since baseline (before treatment is administered) and therefore the best person to assess causality. The Investigator should also consult the SmPC document.
If the investigator indicates an unknown causality assessment in the report sent to the TMG, the TMG will have to take the most conservative approach and consider the adverse experience as related to IMP and could warrant expedited reporting.

The CIOMS VI group recommends that PI(s) consider the following criteria before reaching a decision:

- Medical History
- Lack of efficacy/worsening of existing condition
- Study treatment(s)
- Other treatments-concomitant or previous
- Withdrawal of study treatment-especially following study discontinuation/end of study
- Erroneous treatment with study medication (or concomitant)
- Protocol related process
- The CI/PIs evaluation of severity.

When reporting on adverse events, the trial investigator will state whether they believe that the event is causally associated with any of the trial treatments and the strength of the causal relationship. They will also state whether the adverse event was expected and what if any action was taken. The relationship between the drug and the occurrence of each AE will be assessed and recorded using criteria described below:

Where an event is assessed as possibly related, probably related, and definitely related, the event is an AR.

CLASSIFICATION OF ADVERSE EVENTS BY RELATIONSHIP TO STUDY MEDICATION	
UNRELATED:	This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY:	This category applies to those AEs that are judged to be unrelated to the test drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study medication if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered.
POSSIBLY:	This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY:	This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY:	This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if re-challenge occurs); and (4) it follows a known pattern of response to the test drug.

2.3 Expectedness

The PI must evaluate events for expectedness. If the event adds significant information on the specificity or severity of an expected event, it is considered as 'unexpected'. The expectedness of SAE/Rs should be determined according to the SmPC for each product.

- Expected: Reaction previously identified and described in protocol and/or the Summary of Product Characteristics (SmPC).
- Unexpected**:** Reaction not previously described in the protocol or SmPC.

2.4 Intensity

The assessment of intensity will be based on the Investigator's clinical judgement using the following definitions:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

When specific events are assessed for clinical severity (intensity defined as: mild, moderate or severe), severity must not be confused with 'serious' which is a regulatory definition based on subject/event outcome or action criteria.

3. Responsibilities

3.1 Study site responsibilities

All SAEs and Grade III and above AEs must be reported within 24 hours by the PI/Study Doctor by completing the electronic CRF on the Ambition database. This step is of utmost importance as it triggers the automated TMG reporting process (See section 4.1.1 of this WPD.) where necessary.
The investigator should assess the AE for the likelihood that that it is a response to a study drug.
Follow-up of SAEs: In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information is noted on the second section of the AE form and should be completed as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.
An appointed member of the TMG will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities. The causality assessment given by the local investigator cannot be overruled and in the case of disagreement, review by a second TMG member will be requested.

3.2 Responsible personnel

It is the responsibility of the CI and the individual investigators within a trial team to keep records of all AEs that occur in trial subjects as per protocol.
It is the responsibility of the TMG to review all Grade IV and above AEs and SAEs as reported from the site.
The TMG is also responsible for reporting SUSARs to the sponsor and regulatory and ethics bodies and compiling and sending reports to the Sponsor, regulatory and ethics bodies. This may be delegated to the PI at each site.

3.3 Principal Investigator Responsibilities

The Investigator can choose to delegate responsibilities outlined below to other members of his/her team:

a) The investigator should be thoroughly familiar with the appropriate use of the IMP(s), as described in the protocol and other information sources such as the SmPC and the Trial Treatment document.
b) The Investigator must ensure that other research team members are trained in the use of IMP(s). The Investigator must update all other research team members on new information related to IMP(s).
c) The Investigator should be aware that the SmPC has to be updated annually and should request these documents from IMP manufacturer(s) to ensure that yearly updates of IMP information are filed in the Investigator Site File (ISF).
d) Records of all AE/Rs that occur in trial subjects in the medical records (hospital notes) and when applicable on the AE eCRF.
e) The Investigator must assess each event for intensity, causality, expectedness and seriousness.

f) All Grade IV and above AEs and SAE/Rs must be reported to the TMG within 24 hrs of completing the AE eCRF.
All follow-up information should be communicated in follow-up reports until resolution as the information become available.

g) All SUSARs must be reported to the TMG within 24hrs of the Investigator becoming aware of the SUSAR and to regulatory and ethics committees within 7 days if fatal and 15 days if non-fatal.

h) All SAEs that may be reported by Research Nurse and/or Trial Coordinator (including those that occur in urgent situation) should be discussed with Chief Investigator (CI) or Principal Investigator (PI) at site.

i) Clinical Trial subject(s) must be protected at all times and the investigator must sometimes undertake appropriate urgent safety measures immediately. Following such measures, the Investigator must report his/her action to the TMG immediately to enable the TMG to inform the appropriate regulatory and ethical bodies and sponsor within 3 days of any Urgent Safety Measure taken as a result of an AE.

j) A member of the TMG will prepare Safety Reports as requested for the DMC (at least 2 per year) and will send Annual Safety Reports to the regulatory and ethical bodies and Sponsor (LSHTM).

k) The Trial Manager will monitor this pharmacovigilance procedure periodically.

4. Procedures

4.1 When to start recording AE/Rs?

All grade III and above AE/Rs must be recorded from the point that the patient is consented onto the study.

4.1.1 How to record AEs?

a) The AE eCRF must be completed by the investigator (the consultant named on the Signature List and Delegation of Responsibilities Log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed by a member of the site trial team. The responsible investigator should subsequently check the AE eCRF and make changes as appropriate. The initial report must be followed by detailed, follow-up and final reports as appropriate.

b) The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting and why the event is considered serious.

c) The AE eCRF must be completed on the trial database. Once submitted, the co-ordinating centre is alerted of the submission by an automated email to its dedicated pharmacovigilance email address: ambitionReporting@lshtm.ac.uk.

4.1.2 What AEs to record?

The PI should record all Grade III and above events (based on the modified DAIDS Toxicity Tables classifications) on the AE eCRF.

4.1.3 What AEs to report?

Due to the patient population and expected burden of disease, Grade III are recorded in the database only, they do not need reporting to the TMG and competent authorities.
Grade IV and above AEs and SAEs must be reported to the TMG within 24hrs via details entered in the adverse event eCRF (i.e. within 24hrs of the AE eCRF being logged on the database; 48hrs of the site becoming aware of the AE). The reporting process is automatic through the database. Please see Appendix 1 *What to report on the EDC* for a guide to reportable events.

4.1.3 Adverse events – Guidelines on inclusions and exclusions

Adverse events include	Adverse events do not include
a) an exacerbation of a pre-existing illness b) an increase in frequency or intensity of a pre-existing episodic event/condition c) a condition (even though it may have been present prior to the start of the trial) detected after trial drug administration d) continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment e) Any abnormal clinically significant event which occurs after trial drug administration	a) medical or surgical procedures- the condition which leads to the procedure is the adverse event b) pre-existing disease or conditions present before treatment that do not worsen c) situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery d) overdose of medication without signs or symptoms e) the disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

4.1.4 Severity/grading of adverse events

This will be according to the modified DAIDS Toxicity Tables classifications.
Serious adverse events that occur during the pre-randomisation period may be reportable if they occur as a result of a protocol specified intervention or can cause the participant not to be allocated to randomisation treatment.

4.1.5 What should not be reported?

Any AE/Rs which are Grade I, II or III (based on the modified DAIDS Toxicity Tables classifications) will not usually need to be reported.
Given the severity of illness of patients with cryptococcal meningitis, and the frequency of co-morbidities due to their late stage of HIV infection, it is only feasible to routinely report more clinically significant, grade IV and above AEs. Of note however, routine blood monitoring is done for all patients that is available to clinicians looking after the patients in real time, and that will also allow analysis of the most common and important laboratory adverse effects of the study drugs at the grade III and lower levels.
If there is a national requirement to report all AEs, grade III and lower will be reported by the Ambition team according to their local procedures.
Please see Appendix 1 *What to report on the EDC* for a guide to reportable events.

4.2 Follow-up after adverse events

Patients may be either admitted to hospital or seen at intervals to monitor the progress, recovery and investigations of the adverse events. In the event treatment needs to be modified or changed, the PI should inform the Chief Investigators and agree on the new treatment. See Section 3.1 for further details on Follow-up.

4.3 Where to send SAE/SUSAR reports?

AE eCRFs must be completed on the trial database. Once submitted, the co-ordinating centre is alerted of the submission by an automated email to its dedicated pharmacovigilance email address: ambitionReporting@lshtm.ac.uk

A TMG member will complete TMG Review eCRF and return within 48 hours.

5. The TMG Review process

Three rotating members of the TMG will be responsible for evaluating all grade IV and above AEs received for seriousness, expectedness and causality. The causality assessment given by the local investigator cannot be overruled. In the case of disagreement, both opinions will be recorded and a third opinion will be sought through a second TMG reviewer.
Members have 48 hrs to review the reports from the time they receive it.

6. Reporting adverse events to competent authorities

6.1 Reporting to local ethical and regulatory bodies

Reporting to authorities is coordinated by the Ambition Trial Coordinating Centre. All reports are accessible to the team through the database. If anything is unclear the team will email the PI/study doctor to seek clarifications where required.
As there are strict reporting timelines (see table below), it is essential that site staff complete the AE electronic CRF as soon as they become aware of the event.
The Ambition Trial Coordinating Centre team will review the reports and advise the site when to submit to the authorities, ensure those timelines are met. Local submissions may be done by any member of the local Ambition team delegated to do so, under the oversight of the site PI.

Country specific reporting requirements for reportable events are listed below:

Country	Regulatory Body	Ethics Committee
Botswana	Within 7 days	Within 7 days
South Africa	Within 7 days	Within 7 days
Malawi	Within 24hrs	Within 24hrs
Uganda	Within 7 days	Within 7 days
Zimbabwe	Within 7 days; Deaths within 3 days	Within 7 days; Deaths within 3 days

The requirements specified above must be coordinated by the Ambition Trial Coordinating Centre at all times. Failure to comply with this procedure and timelines will require a protocol deviation form to be completed and forwarded to the Ambition Trial Coordinating Centre, as per the Sponsor's SOP-012-01 Protocol Violations and Deviations.
Violations will be reported to Competent Authorities every 2 months whilst deviations will not require onward reporting.

6.2 Reporting to the Sponsor and pharmaceutical company

The Sponsor and LSHTM EC must be notified of any SUSARs received (rgio@lshtm.ac.uk) within 7 days if fatal and 15 days in other cases. This is coordinated by the Ambition Trial Coordinating Centre.

The Gilead Pharmacovigilance team must be notified of all SAEs within 15 days (Safety_FC@gilead.com).
This is coordinated by the Ambition Trial Coordinating Centre.

The Sponsor, LSHTM EC and Gilead must also receive details of SAEs in a bimonthly report. This is coordinated by the Ambition Trial Coordinating Centre.

It is important to maintain subject confidentiality, privacy and adherence to all applicable Data Protection laws on all reports in relation to recording, management and reporting of AEs.

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