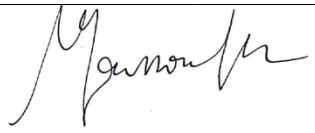
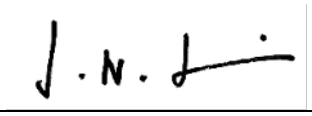
MONITORING PLAN

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		
Sponsor	London School of Hygiene and Tropical Medicine		
ISRCTN No.:			
Chief Investigators	Dr Joseph Jarvis/Prof Tom Harrison		
Funder	The European and Developing Countries Clinical Trials Partnership		
Investigator led study/ Commercial study	Investigator led study	**Multi-centre Trial**	Gaborone, Botswana Kampala, Uganda Lilongwe and Blantyre, Malawi Harare, Zimbabwe Cape Town, South Africa
Author	Nabila Youssouf Trial Manager		29/06/2017
Reviewer	Sile Molly		29/06/2017
Approved by	Joseph Jarvis CI		29/06/2017

Revision History:		
Version Number	Effective Date	Reason for Change
1.0	29/06/2017	First version

SUMMARY OF KEY POINTS OF THE TRIAL

This phase III randomized controlled trial will be conducted at 6 African sites over a 42 month period with a total target recruitment of 850 patients.

Recruiting Sites:
Princess Marina Hospital,
Gaborone, Botswana

Infectious Diseases Insititute,
Kampala, Uganda

Queen Elizabeth Central Hospital,
Blantyre, Malawi

Kamuzu Central Hospital,
Lilongwe, Malawi

Parirenyatwa Central Hospital and Harare Central Hospital,
Harare, Zimbabwe

Mitchells Plain District Hospital and Khayelitsha Hospital,
Cape Town, South Africa

1. OVERVIEW OF MONITORING PLAN

Summary of the planned monitoring.

Type of monitoring	Details	Responsibility
Trial oversight committees	- Trial Management Group (TMG) - Trial Steering Committee (TSC) - Independent Data Monitoring Committee (IDMC) - Trial Implementation & Co-ordinating Committee (TICC)	These committees are composed of a number of qualified members. See details below.
Central Monitoring	- Central Statistical Monitoring (highlight inconsistent/missing data) - SAE/SARs/SUSARs -Monthly Reports - Statistical analyses (identify unusual patterns of data, detect deviations from the protocol)	Statistician/TICC/TMG TMG (review all) See below Data manager /Statistician
On-site monitoring	- Training and setup - Adherence to protocol, GCP & associated regulations - Consent obtained - Eligibility criteria adhered to - Drug supply/storage/administration - Monitor trial data - SAE/SAR/SUSAR reporting - Trial close	Trial Manager will monitor all sites at pre-determined visit dates (see details below) Reports will be sent to the relevant committees for review and to the Sponsor LSHTM/Local Reg body External Audit, as requested
Monitoring reports	-Cumulative monthly reports (including information on recruitment rates, withdrawals, losses to follow-up) - Monthly reports on Grade IV and V AEs/SAEs/SARs/SUSARs - IDMC reports: on request. A compilation of all monthly reports (see above).	Trial manager/Statistician (create) TMG (review) Trial manager/Statistician (create) TMG (review – pooled arms) Trial manager/Statistician (create) IDMC/TSC/TMG/TICC/Sponsor (review) Trial Manager will write monitoring reports following each

	- Reports to be completed following each site visit - Annual Safety Reports	visit and these will be reviewed by TMG and sent to the other committees and Sponsor
Procedures for dealing with issues	- Contact TMG for advice/guidance and highlight all issues in report. - Correction of data where necessary - Protocol deviations log/reports to be downloaded from database monthly and held centrally for all sites. This will document corrective and preventative action as discussed by the TMG	Trial manager/TMG TMG/TCC Reviewed by TMG

2. MONITORING OBJECTIVES

Objectives:

- Verify rights and well-being of the human participants are protected
- Verify written informed consent was obtained prior to each subject's participation in the trial
- To ensure the validity, accuracy and integrity of the data
- Verify conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements.
- To ensure that the essential trial documents are maintained in compliance with ICH GCP and local regulations.
- To verify eligibility criteria are met for all enrolled participants
- To verify drug accountability records, to include receipt, use, return and disposal, are maintained and reconciled throughout the duration of the trial.
- To verify that handling and storage of investigational products are maintained in accordance with the acceptable product characteristics for the duration of the trial
- To verify laboratory procedures, recording of results and storage of samples
- To verify that all Serious Adverse Events (SAEs) and SUSARs (Suspected Unexpected Serious Adverse Reaction) are reported within the time periods required by the protocol to the relevant Ethics committees and local regulations.

3. TRIAL MANAGEMENT/MONITORING BODIES

Four trial oversight committees will be formed in order to monitor the trial over time. The four committees are as follows:

(a) Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the international and local Investigators, trial manager and statistician. The TMG will be responsible for the day-to-day running and management of the trial and will liaise at regular intervals.

(b) Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be constituted. The chairperson will be independent of the running of the trial.

Their terms of reference will defined. They will include:

- To monitor the progress of the trial and provide support and guidance on interim and overall objectives so that the trial is completed successfully.
- To review at regular intervals relevant information from other sources (e.g. other related trials) and recommend changes to strategy as necessary.
- To review safety and ethics and consider the recommendations of the Data Monitoring Committee. The TSC will be resposnisble for implementing 'Urgent Safety Measures'.
- To review requests for major changes to research plans (e.g. addition of sub-studies) and major ammendments to protocol.
- To review and comment on the analytical plan.
- To review publication policy and major publications.

The role of the TSC is to provide overall supervision for the trial and provide advice through its Independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

(c) Independent Data Monitoring Committee (DMC)

There will be an Independent Data Monitoring Committee whose terms of reference will be defined. They will include:

- To review safety data, in particular adverse events, particularly serious adverse events
- To monitor the conduct of the trial with respect to the ethical aspects of the trial
- To recommend to the trial steering committee and chief investigator of the continuation of the trial or early stopping based on safety or ethical data

(d) Trial Implementation and Co-ordinating committee

This committee will be formed at each site and the study Dr/nurse will take a lead role. They will be responsible for:

- Every day running of the trial
- Consenting, screening and enrolling patients according to trial protocol
- The clinical management of each study patient
- Ensuring that procedures and processes are in adherence to trial protocol
- Ensuring that all data is collected and recorded accurately
- Ensuring that all Grade 4 AEs, SAEs and SUSARs are reported within the appropriate time frame
- Ensuring that any issues are reported to the Principal Investigators and co-investigators in a timely manner
- Trial follow-up of 16 weeks from study enrolment
- Monitoring drug storage and supply

Proposed members:

Study members as indicated on the delegation log at each site.

4. CO-ORDINATING SITE MONITORING

The sites will be visited at regular intervals in order to monitor the conduct of the trial. These visits will be made by the Trial Manager/Monitor. The frequency of monitoring visits will be according to need but will be at least after recruitment of the first 10/15 patients and after 50% and 100% of patients (trial closure). If issues arise the frequency of visits will be increased. The Trial Manager will remain on-site for up to 2 weeks after study initiation for intensive monitoring purposes.

	Number of patients required to trigger on-site visit			
Site	**Early visit**	**40%**	**70%**	**100%**
Princess Marina Hospital, Gaborone, Botswana	10/15	36	63	90
Infections Diseases Institute, Kampala, Uganda	10/15	44	77	110
Queen Elizabeth Central Hospital, Blantyre, Malawi	10/15	92	161	230
Kamuzu Central Hospital, Lilongwe, Malawi	10/15	44	77	110
Parirenyatwa Central Hospital, Harare Central Hospital Harare, Zimbabwe	10/15	92	161	230
Mitchells Plain District Hospital, Khayelitsha Hospital Cape Town, South Africa	10/15	32	56	80

Table 1: Number of patients to be recruited at each site triggering a monitoring visit.

Site suitability assessments will be conducted at each site prior to trial initiation. The Trial Manager will visit the sites and ensure that all training has been completed, that drug supply and equipment are in place and that all study staff are up-to-date regarding protocol and procedures.

Both central and on-site monitoring procedures will be put in place as detailed below.

5. CENTRAL MONITORING

A number of monitoring procedures will be conducted off-site:

- Grade IV AEs and above will be reviewed by a member of the TMG as they are reported from each site. All AEs received will be reviewed for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately by the TMG and those that are SUSARs identified and reported to the LSHTM ethics committee and the relevant non-UK authorities (See section 6.2 Serious Adverse Events).

- A cumulative monthly report will be written centrally for each site by the Statistician, and for all sites together, and will include details on recruitment rates, withdrawal and losses to follow-up. Monthly reports on Grade IV AEs, SAEs, SARs and SUSARs will also be written. These reports will be sent to the TMG for review (pooled arm). These reports will be compiled and presented to the IDMC, TSC and the Sponsor for review on request and at least once every 6 months.

- Statistical analyses (identify unusual patterns of data, detect deviations from the protocol) will be performed for Central Statistical Monitoring.

- LSHTM will conduct an audit of the trial and each site will comply with audit requirements for the local regulatory bodies. Subsequent reports will be sent to all committees: TMG/TSC/IDMC/TICC/Sponsor.

6. ON-SITE MONITORING

The Trial Manager will visit the site at the times specified previously and will be responsible for:

- Arranging and confirming appointments of the visits with all relevant staff prior to the visit.

- Conducting visits and providing a written site monitoring report at the agreed time (within 2 weeks) after the visit.

- Ensuring that monitoring activities are being conducted in accordance with the study protocol, with ICH-GCP and with trial working practice documents (WPDs).

6.1 Training and setup

Prior to trial initiation an investigator meeting will be held; each site will be visited and staff training will be completed. Written assurance will be obtained from local investigators that setup is complete prior to study initiation.

- A GCP training session will be run at each site prior to initiation to ensure all study staff are GCP trained. Training on the use of the electronic database system will also be conducted at this time along with training on taking informed consent and on WPDs. Training documents will be signed and dated by the participant and the trainer and will be stored in the training records file in the Investigator Site File (ISF).

- There will be a site visit by the lead Clinican and the Trial Manager/Monitor immediately prior to study initiation to review setup and team understanding of trial procedures. This will include a visit to the site pharmacy to review setup, storage conditions, supplies and procedures. They will also ensure that an emergency drug supply is in place.

- Teleconferences will be arranged if any issues arise so that all investigators are involved in discussions.

- Ensure the Staff Delegation of Duties Record for the study is completed and filed in the ISF prior to start of study. This form will be signed by staff members responsible for each study activity and countersigned by the PI to authorise the staff members to perform study related tasks. A copy of the Staff Delegation of Duties will be collected anf filed in the ISF.

- The "Investigator Site File (ISF)" and the index of essential study documents that need to be maintained for the duration of the study will be explained.

- Copies of CVs and training records from local investigators and study team will be collected and stored in the TMF and ISF.

6.2 During the trial

Each year there will be an Investigators meeting to review trial protocol and procedures.

Monitoring visits will take place according to need but will be at least after recruitment of the first 10/15 patients, and after 40%, 70% and 100% of patients have been recruited at each site and on trial closure. Setup and team understanding of trial procedures will be reviewed. These visits will be conducted by the Trial Manager.

The Trial Manager will remain on-site for up to 2 weeks after study initiation for intensive monitoring purposes. During a trial monitoring visit the following monitoring checks will be conducted:

Monitor understanding of/adherence to trial protocol & procedures at sites:

- The trial monitor will conduct site visits to verify that the local investigator follows the approved protocol and all approved amendment(s), if any.

- Ensure that the Principal Investigator has received the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

- Ensure that the local investigator and the investigator's trial staff are adequately informed about the trial.

- Verify that the local investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the local investigator/institution, and have not delegated these functions to unauthorized individuals.

- Verify that the local investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

Verification of participant existence

- Participant existence will be verified against admittance and clinical records

Participant consent

- All signed consent forms will be collected and stored in the site file.

- Check signed consent forms in clinical records to verify that written informed consent was obtained before each subject's participation in the trial.

- A sample of patients will be chosen for interview on the first monitoring visit to determine their understanding of the trial.

Participant eligibility

- Review eligibility criteria prior to randomisation
- Check eligibility criteria in clinic records to verify that the local investigator is enrolling only eligible subjects.

Trial Supplies

- Verify for the study drugs:
  i. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
  ii. That the study drugs are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
  iii. That subjects are provided with necessary instruction on properly taking study medication.
  iv. That the receipt and use of study drugs at the trial sites are controlled and documented adequately. A standardised drug accountability log will be in place for each pharmacy.
  v. Ensure emergency drug supply is in place.

Laboratory data

- Ensure QCC data is accurately calculated and recorded
- Ensure samples are stored correctly and only those where consent has been given
- Ensure lab supplies sufficient throughout the trial

Trial data

At monitoring visits the data entered in the eCRFs will be checked against available source data by the Trial Manager /Monitor. Data stored will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. (Note that the electronic database system has a number of QC checks in place which will capture possible inconsistencies/missing data in real time). Specific monitoring tasks in relation to trial data will include:

- Check eCRFs are only being completed by authorised persons as delegated in the Staff Delegation of Duties Record. New staff joining the team must receive training in the study protocol and procedures, have GCP training and be signed off by the PI on the Staff Delegation of Duties record
- Check patients' notes
- Check all consent forms
- Check site admissions records
- Check that data collected are consistent with adherence to the trial protocol

- Check that no key data are missing
- Check data appear to be valid
- Check outcome against clinical records
- Check the accuracy and completeness of the eCRF entries, source documents and other trial-related records against each other. In particular:

  i. Check all relevant source data that have been recorded (e.g. from admission records)
  ii. Any dose and/or therapy modifications are well documented for each of the trial subjects.
  iii. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the eCRFs.
  iv. Visits that the subjects fail to make, tests that are not conducted, examinations that are not performed, withdrawals and dropouts are clearly reported as such on the eCRFs.
  v. Inform the local investigator of any eCRF entry error. Any corrections, additions, or deletions made, are dated, explained (if necessary), and initialled by the local investigator or by a member of the investigator's trial staff who is authorized to initial eCRF changes for the investigator. This authorization should be documented in the Staff Delegation of Duties Record.
  vi. Check case notes for adverse events – accuracy of reports and missing reports. Determine whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the REC, the sponsor and regulatory bodies.
  vii. Determine whether the local investigator is maintaining the essential documents (ie check site file).
  viii. Communicate deviations from the protocol, WPDs, GCP, and the applicable regulatory requirements to the local investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

- Review and report recruitment rates, withdrawals and losses to follow-up
  (If lost to follow up every effort will be made (for example with mobile telephone calls and financial help with travelling expenses) to obtain accurate and complete follow-up data for 16 weeks after the start of treatment. If a patient fails to attend, the research nurse will visit the home address and make every effort to persuade the patient to attend and continue antifungal and antiretroviral treatment.)

The Trial Monitor will record significant findings, any deficiencies detected, conclusions and any recommended actions. A report will be written, sent to the TMG, DMC, TSC and the Sponsor and filed in the TMF. The Trial Monitor must ensure that recommended actions are completed by the site team within the time frames stipulated in the monitoring report. Any problems identified will be reviewed by the TMG and remedial action taken as necessary.

Grade IV AEs

- Ensure that Grade IV AEs are being reported within 48 hours by the Local Investigator by completing the SAE eCRF (will be reviewed immediately by one of three nominated members of the TMG).

- Ensure monthly reports on Grade IV AEs are compiled and reviewed.

Serious Adverse Events (SAEs) / SARs / SUSARs

- Ensure that SAEs/SARs/SUSARs are being reported within 48 hours by the Local Investigator by e-mail to the Chief Investigator (Will be reviewed immediately by one of three nominated members of the TMG).

- Ensure that all SAEs/SARs/SUSARs reported were documented with the time and date of reporting

- Ensure that all SAEs are being followed up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised.

- Ensure that SUSARs which are fatal or life-threatening are reported to the appropriate regulatory bodies and local ethics committees. These SUSARs will be reported to the LSHTM ethics committee and to each of the sites ethics and regulatory boards as appropriate by site within 7 days of the Local Investigator becoming aware of the event (non fatal or life threatening SUSARs reported within 15 days).

- Three members of the TMG will be responsible for evaluating all AEs received for seriousness, expectedness and causality. The causality assessment given by the local investigator cannot be overruled and in the case of disagreement, both opinions will be provided in subsequent reports.

7. At the end of the trial

- Site visit to review archiving of trial documents

- All documents will be stored securely and free from environmental harm for a period of 5 years after the end of the study.

- A final trial close out monitoring report will be issued to each site with any outstanding actions that require completion.

8. MONITORING REPORTS

Cumulative monthly reports (including information on recruitment rates, withdrawals, losses to follow-up) will be compiled by the Trial Manager/Statistician and reviewed by the TMG. Monthly reports on Grade IV AEs/SAEs/SARs/SUSARs will be compiled by the Trial manager/Statistician and reviewed by the TMG but the arms will be pooled to ensure blinding of the investigators. If the safety data reviews raise concerns an ad hoc, external, by-arm safety review may be requested.

IDMC reports will be compiled by the Trial Manager/Statistician on request (at least 6 monthly) and will consist of a compilation of all monthly reports (see above).These will also be sent to the TSC and the Sponsor. For each full review, summaries provided to the DMC will be broken down by masked strategy arm. Participants' baseline demographic and health characteristics will be summarized. Review of study conduct will address recruitment rate, premature study discontinuations and their reasons (administrative or loss to follow-up), tracking of potential losses to follow-up, adherence to randomized arm and data completeness. The IDMC will also review participants' safety data and frequency and causes of death.

Annual Safety Reports documenting all Grade IV AEs and above will be compiled by the Trial manager/Statistician and sent to all ethics and regulatory bodies, IDMC, TSC, and the Sponsor for review.

Monitoring reports following on-site visits will be completed by the Trial Manager following each site visit. Visits will take place according to need but will be at least after recruitment of the first 10/15 patients, and after40%, 70% and 100% (trial close) of patients have been recruited at each site. Reports will be written within 2 weeks of the site visit. These reports will be reviewed within 1 month by the Investigator at each site and by the TMG. The reports will also be sent to the TSC, IDMC, TICC and the Sponsor.

Any significant issues/major protocol deviations/serious breaches should also be communicated as soon as aware to the Trial Monitor and sponsors should be notified. A log of protocol deviations will be maintained by trial manager centrally to document issues and corrective/preventative action taken. Any urgent safety measures that need to be implemented due to a serious breach/protocol deviation will be communicated to the ethical committees.

9. PROCEDURES FOR DEALING WITH ISSUES

When an issue is highlighted during monitoring the Monitor should contact the TMG for guidance and include any issue in the subsequent report. Corrections to data will be made as required.

10. QUALIFICATIONS OF MONITORS

In accordance with GCP Section 5.18.2, all monitors will have the appropriate training, experience and education to undertake the task. Specific training for monitors (Trial Monitor and a nominated on-site monitor) will be completed prior to the start of the study and training records will be kept in the Trial Master File.

Each member of the various committees will also have relevant training and experience.