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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 3
Patient enrolment and follow-up

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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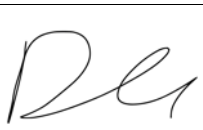
Author(s)	David Lawrence Lead Clinician		08/07/2018
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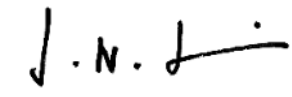
Approved by	Joseph Jarvis CI		08/07/2018

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0	20/07/2017	First version
1.1	08/07/2018	Modification of 5FC dosing to 5kg intervals

Working Practice Document 3: Patient enrolment and follow-up

Purpose

This document describes the process of patient enrolment and follow-up in the Ambition trial.

Scope

This WPD applies to the process of patient enrolment and follow-up

Materials

WPDs 1, 2, 5, 10, 15, 17, 18: Patient screening, Informed patient consent, Individual Study Personnel Responsibilities, Management of raised intracranial pressure, Timing of Evaluations and tests, Management of patients on ARVs >6 months, ECG. Lab WPD 2: QCCs

Patients to be screened by study staff, to fulfil enrolment criteria and give signed consent prior to inclusion in the study (Please refer to WPDs 1 and 2: Patient Screening and Informed Patient Consent).

Patients who do not fulfil study criteria will be excluded from the study (Please refer to WPD: Patient Screening).

1) CONSENT

- Informed consent to be obtained from the patient (or relative if patient unable to give informed consent). Please refer to WPD2: Informed patient consent.

- Copy of consent form to be filed at front of patient medical notes. Original signed copy to be filed in investigator site file (ISF).

- Patient (or next of kin) to be given a copy of the consent form and a study patient information leaflet to keep.

2) HISTORY & EXAMINATION

- Patient inclusion in the study to be documented in patient's hospital notes.

- History and examination to be documented in the 'Patient Medical History' electronic Case Report Form (eCRF) and hospital notes.

- Ward nursing staff and patient's medical team to be informed of patient's inclusion in the study.

- Patient contact details to be filled in on the 'Subject Locator' log on EDC.

3) RANDOMISATION

- Patients will be randomised individually using a computer-generated programme. Randomisation will be stratified by site.

- Study doctor to appropriately randomise patients, according to computer-generated programme and prescribe appropriate treatment on drug chart. Randomisation treatment regimen to be clearly documented in patient's hospital notes using pre-printed labels.

RANDOMISATION

Refer to randomisation procedures document.

- Patients will be randomised individually and randomisation codes will be generated using SAS PROC PLAN via permuted-block randomisation method stratified by site. Block sizes will vary at 4 and 6.

- Randomisation lists will be created for each site by an independent statistician and each list will be housed on the electronic database system (EDC) for that particular site, and will be inaccessible to trial staff except to randomise the next eligible participant.

- Randomised allocation for each trial participant will be provided to trial staff by extracting the next available randomisation allocation, obtained from the randomisation list for that site housed on the database.

- Internally the EDC selects against an electronic randomization list prepared in advance by the Statistician. The EDC guarantees to make the selection in the natural order of the list filtering by study site only. Once a selection is made, the randomization record is tagged with the patient study allocated identifier, date and time of randomization and other EDC system audit values (username, machine name, etc). A tagged record cannot be selected more than once.

- It is impractical to blind the study because of the very high doses of short course L-AmB (currently up to 20 drug vials per dose depending on patient weight) used in the intervention arm, compared to the standard amphotericin B (often only a single vial per patient), given daily, in the control arm. Bias will be minimised by the use of an objective clinical endpoint "all-cause 10-week mortality" as the primary outcome. Laboratory technicians performing EFA will be blinded to study arm. The trial statistician will be blinded regarding the treatment code when developing the statistical analysis plan and writing the statistical analysis programmes, which will be validated and completed using dummy randomisation codes.

4) STUDY DRUG PRESCRIBING

- Patient to be weighed to determine appropriate dose of flucytosine, Ambisome and amphotericin B deoxycholate.

- Patient to be prescribed 1200mg/ day of fluconazole if randomised to single dose Ambisome regimen. This can be given once daily or twice daily in divided doses. If patient cannot swallow, fluconazole can be crushed for nasogastric administration.

- Prescribe flucytosine by weight as follows;

Table 1: Flucytosine dosing schedule

Weight (kg)	Daily dose (mg) 100mg/kg	Number of tablets per day	Suggested schedule of dosing*			
35-39	3500	7	2	2	2	1
40-44	4000	8	2	2	2	2
45-49	4500	9	3	2	2	2
50-54	5000	10	3	2	3	2
55-59	5500	11	3	3	3	2
60-64	6000	12	3	3	3	3
65-69	6500	13	4	3	3	3
70-74	7000	14	4	3	4	3
75-79	7500	15	4	4	4	3
80-84	8000	16	4	4	4	4

*Each site can determine the specific timing of each six hourly dose providing the full quantity is prescribed over 24 hours

- Study Doctor to prescribe study drugs according to randomisation arm and appropriate fluid prehydration, analgesia, co-trimoxazole, and potassium and magnesium supplementation for patients, as required.

- Study Doctor to prescribe study drugs on AMBITION-cm trial drug chart, and any additional medicines on the patient's hospital chart. Write: 'Ambition Trial Patient. FAO Study pharmacist' on hospital drug chart. Inform the study pharmacist of details of patient recruited.

-ECG request form to be completed, if applicable. Please refer to ECG WPD.

5) CANNULATION & PHLEBOTOMY

- Study patient to be cannulated once.

- Routine bloods to be sampled: FBC, U&E and ALT.

- CD4 samples to be also taken on admission, unless results within last three months are available.

- Viral load to be sent if ART exposed and indicated as per national guidance

- Study specific bloods to be sampled: whole blood, plasma and serum for storage, where applicable.

- *Take 1 yellow top and 2 purple top blood tubes for above investigations at baseline*

- *If you are participating in a sub-study please refer to the specific WPD to guide further sample collection.*

6) URINALYSIS

- Pregnancy test to be performed on urine for all women enrolled, if not already performed. If unable to obtain urine for pregnancy test then please perform serum pregnancy test.

7) LUMBAR PUNCTURE/Day 1 LABORATORY WORK

- Study Day 1 lumbar puncture (LP) to be performed if initial diagnostic LP CSF not available or CSF opening pressure (OP) not measured. CSF opening pressure (OP) to be measured on all LPs performed by study team.

Amount of CSF removed and closing pressure to be documented in patient's notes and CRF. Please refer to WPD 11: Management of raised intracranial pressure.

- Sampled CSF – Send in three tubes in total. One will be used for chemistry if not already performed (mimimum of 2 mls) and another for sample storage, and one for microbiology (minimum of 3 mls) which will be used for quantitative cryptococcal culture.

Please refer to Laboratory WPD for quantitative culture methodology.

- *If you are participating in a sub-study please refer to the specific WPD to guide further sample collection.*

8) STUDY DRUG ADMINISTRATION

- Study pharmacist to be informed of patient's recruitment into study so accurate study drug pharmacy records are maintained.

- Study nurse to ensure that study drugs are ordered and administered to the patient according to study protocol.

- Study nurse and pharmacist must ensure there is provision for study drug administration over weekends

Please refer to WPD 5: Individual study personnel responsibilities.

9) INITIAL TWO WEEK PROCEDURE/FOLLOW-UP

-Clinical examination will be performed every day by study nurse and/or doctor up to patient discharge. Patients may be discharged from D7, in which case they will receive close outpatient follow-up with daily calls, blood tests on D10 and D12 and clinical examination with blood tests and LP at D14.

- Chest X-rays will be performed on admission if clinically indicated.

- ECGs will be performed if clinically indicated.

- Blood cell counts and ALT will be taken on Day 1, 7, 14 and at Week 4.

- Creatinine, Urea and electrolytes will be measured on Day 1, 3, 5, 7, 10, 12, 14 and Week 4.

- If a study blood test/LP falls on a weekend, it may be taken or performed on the closest study day, unless the patient's management requires the blood test or LP to be taken/performed and acted upon over the weekend (for example, raised ICP, hypokalemia, rising creatinine, severe anaemia etc.).

- CSF opening and closing pressures will be taken on Day 1, 7, 14, and therapeutically, as required.

- India Ink examination OR Cryptococcal antigen testing will be performed on D1, quantitative fungal culture and organism counts (optional according to possibilities at each site), drug levels and immune parameters will be performed on Day 1, 7, 14.

10) FURTHER FOLLOW-UP

Patients will be followed up after discharge on weeks 4, 6, 8 and 10. The relevant follow up CRF should be filled in at each follow up visit. Follow-up visits will include:

- Physical examination
- ARV initiation between weeks 4 and 6 (usually week 4 follow-up visit), for those not already on ARVs. For patients failing their ARV regimen, consider ARV regimen switch at 4 weeks.

  See WPD 13 – Initiation of ARVS.

  See WPD 17 for management of patients on ARVs >6 months.
- Monitoring of drug adherence and toxicity (both fluconazole and ARVs). Adherence monitoring is best performed by reviewing empty drug packets and should be recorded in patient notes.
- Arranging the next follow up visit

If a patient misses a follow up visit, every effort must be made to locate the patient and encourage re-attendance. Patients' contact details will be recorded on a contact form that will be completed on study enrolment.

If a patient is unwell and presents to the study team outside a scheduled study visit, complete AE form and, as required, organise relevant investigation CRFs (LP, bloods, radiology etc) and arrange hospital admission.

A single telephonic follow-up call will be made at 16 weeks to assess vital status and level of disability.

Please see WPD 15 for a flow chart summarizing follow up and investigations required.

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 are trained on applicable WPDs within 30 days of employment.

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

References

1. **Ambition Trial protocol**
2. **Randomisation procedures**

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

Date	Name (Please print)	Signature