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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 4
Early patient withdrawal following study enrolment

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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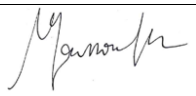
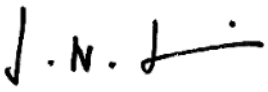
Reviewer(s)	Nabila Youssouf Trial Manager		20/07/2017
Approved by	Joseph Jarvis CI		20/07/2017

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0		First version

Working Practice Document 4:
Early patient withdrawal following study enrolment

Purpose

This document outlines early patient withdrawal following study enrolment for the Ambition trial.

Scope

This WPD applies to early patient withdrawal

Materials

WPD 1 and 3: Patient screening & Patient enrolment & follow up

Protocol Violation CRF

The following criteria/scenarios may result in an enrolled study patient being subsequently excluded from the study:

1) <u>If a patient's blood test results show</u>:

   a) ALT>5 times upper limit of normal (i.e. >200 IU/mL)

   b) PMNs<500x10^6/L

   c) Platelets<50,000x10^6/L

For the above scenarios patients will be withdrawn from the study and treatment of such patients will be in conjunction with routine care, but the study team will provide drugs and monitoring support for amphotericin B therapy, as required, for at least 7 days. A protocol violation CRF does **not** need to be completed.

There is no specific exclusion or inclusion criteria for renal function. Clinicians are advised to use their best judgement whether to randomise a patient with impaired renal function. If they feel that treatment with intravenous fluids is warranted they may start fluconazole and wait to see if the renal function improves. If they feel the patient can have amphotericin then randomise and give at the stated dose with subsequent doses dictated by WPD 8: Toxicity management.

2) <u>Violation of inclusion or exclusion criteria</u>

For example, if it subsequently becomes apparent that a study patient has been treated for cryptococcal meningitis in the past, this patient will be excluded from the present study. The patient will be referred to the relevant healthcare staff for further management. A protocol violation CRF should be completed.

3) Study patient decides to withdraw from the study

Study patients are free to withdraw from the study at any point without providing a reason. Patients who withdraw from the study will receive the routine medical care provided by the site hospital. Patients who withdraw from the study intervention should be asked if we can continue to follow them up to collect data for the study (i.e. 2 and 10 week outcomes and 16-week telephone follow-up). The reasons why we want to continue collecting follow up data should be explained and the patient's right to refuse this will be respected.

The appropriate medical consultant at the site will be informed of the patient's withdrawal from the study and a full summary of the patient's care as part of the study will be handed over to the new medical team. Every effort will be made to ensure a smooth transition of the patient's care.

If the patient is an out-patient, the patient will be referred by the reviewing doctor to the appropriate healthcare facility where the patient can receive appropriate medication, including antiretroviral therapy.

The local Principal Investigator and Chief Investigator will be informed of the patient's decision to withdraw from the study and a patient termination CRF will be completed.

The study team will try to understand the reasons for the patient's withdrawal from the study, document them on the electronic data capture system and discuss withdrawals at the monthly meeting of the TMG.

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 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.

References

1. Declaration of Helsinki, 2013: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ accessed 12th June 2017
2. International Conference on Harmonisation (ICH) Guideline For Good Clinical Practice E6(R1), 1996
3. Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice E6(R2), 2016
4. Ambition Trial Protocol

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

Date	Name (Please print)	Signature