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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 2
Informed patient consent

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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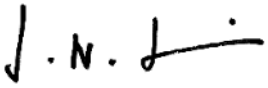
Approved by	Joseph Jarvis CI		20/07/2017

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

Working Practice Document 2: Informed patient consent

Purpose

This document describes the process of consenting patients for the Phase III Ambition Trial

References

Ambition Trial Protocol

Scope

This WPD applies to the process of patient enrolment

Associated materials

Patient information sheet (PIS)

Informed consent form (ICF)

Electronic Data Collection Tool

The following document outlines the procedure required to obtain informed consent from patients prior to inclusion in the Ambition study. Excellent communication with prospective study patients is required. Consenting of patients will be performed by the study nurse and/or doctor delegated to do so by the local investigator.

1) Greet the patient and introduce yourself.

2) Identify a private area (if possible, a side room or draw curtains)

3) Make the patient comfortable, in chair or bed.

4) Assess the patient's mental status. A patient's mental status is abnormal if a patient has a Glasgow Coma Score (GCS) <15 (including confusion and drowsiness), has had a recent seizure resulting in drowsiness/confusion, or displays abnormal behavior such as aggression or delusional beliefs.

   If a patient has an abnormal mental status, consent for trial inclusion must be obtained from the patient's next-of-kin (this should be a family member or legal guardian), as per National Guidance. In countries where a next-of-kin cannot legally provide consent for a patient they will complete an agreement form. If the abnormal mental status resolves after study inclusion, informed consent must be obtained again from the patient themself. The steps below are to be discussed and explained to the patient or next-of-kin, depending on mental status.

5) Explain the definition of Cryptococcal meningitis (CM) as inflammation of the lining of the brain due to infection and that blocked flow of fluid around the brain often causes headache during this infection.

6) Tell the patient that CM is acquired through inhalation and that the patient is not infectious to other people and that CM usually affects people with a weak immune system.

7) Tell the patient about the relationship between CM and CD4 counts. If the patient is known to be HIV+ then explain about CD4 counts. If the patient is not known to be HIV+, propose voluntary HIV test counseling to the patient.

Do not explain this to a next-of-kin if they are unaware of the patient's HIV status.

8) Tell the patient that we are doing a research study into CM to establish effective treatments that are well tolerated and can be used safely in Africa.

9) Tell the patient, that if he/she agrees to be part of the study and is eligible, that he/she will be a hospital in-patient for at least seven days and possibly up to two weeks.

10) Tell the patient that he/she will get one of two possible treatment options:

a. Liposomal Amphotericin B (Ambisome) 10 mg/kg at day 1 (single dose)

+ Fluconazole 1200 mg/day for 14 days

+ Flucytosine 100 mg/kg/d for 14 days

b. Amphotericin B deoxycholate 1 mg/kg/day for 7days (standard dose, "control arm")

+ Flucytosine 100 mg/kg/d for 7 days then fluconazole 1200 mg/day for 7 days

11) Tell the patient that blood tests will be taken every 2 days to check for abnormalities. Explain what a lumbar puncture (LP) is and that LPs will be done on days 1, 7 and 14 as part of the study. More frequent LPs may be required to relieve possible raised intracranial pressure (ICP), thus relieving headache symptoms.

12) If you are working at a site which is participating in a sub-study, explain that sub-study to the patient.

a. In Blantyre: see WPD 19: PK/PD, WPD 20: qPCR, WPD 21: Semi-quantitative CrAg titer

b. In Gaborone: see WPD 20: qPCR and WPD 21: Semi-quantitative CrAg titer

13) Explain to the patient that we will follow them up for a period of 16 weeks after study inclusion. Explain patients will be in hospital for at least one week but probably longer to receive antifungal therapy, and for the management of raised ICP which is a common complication of CM.

14) Explain to the patient that they will receive antiretrovirals (ARVs) for HIV infection.

Do not explain this to a next of kin if they are not aware of the patient's HIV status.

15) Explain to the patient that participation in the study is voluntary.

16) Tell the patient about the alternative to inclusion in the study, which is management by the site hospital i.e. standard hospital treatment.

17) Explain how randomization works: all patients get one of the two treatment regimens described above and all patients will get fluconazole as maintenance therapy, after day 14.

18) Tell the patient about the benefits of the study: benefit of care from dedicated specialist study nurse and doctor, including closer monitoring for side effects, the possibility of greater activity of Ambisome, transport money for follow up visit, longer follow up period, specialist follow up.

19) Tell the patient about possible risks associated with the study:

    a. **Adverse drug reactions** – low salts in the blood (low magnesium and potassium), kidney damage, reduction in red blood cells (anaemia), nausea, vomiting; pain around insertion site.

       Explain that these are all usually reversible. Explain that all study drugs are well known and have been used for many years, however all reactions will be monitored carefully and treated by study staff. Explain that it is also possible that high doses of Ambisome may be more toxic than standard doses. However, extensive experience, often in very sick patients on chemotherapy, suggests that high doses of Ambisome are well tolerated. The data from our earlier study suggests that high dose Ambisome is no more toxic than standard therapy, and may be less toxic. Tell the patient that to minimize any risk of toxicity we will closely monitor them for side effects in hospital.

    b. **Ineffective induction therapy** - tell the patient that it is possible that single high dose Ambisome may not be enough for effective treatment.

       To ensure all study participants get effective treatment we will monitor the clearance of infection very closely.

    c. **Lumbar Punctures** - by taking part in the study they will probably receive more lumbar punctures than they would during routine treatment. Lumbar punctures are very safe procedures when performed correctly by experienced doctors. Frequent lumbar punctures have also been shown to improve outcomes in HIV-associated cryptococcal meningitis. Serious complications are rare. Soreness of the back and headaches may occur. In many patients with cryptococcal meningitis, lumbar punctures relieve the associated headache. Great care will be taken to ensure the risks are as low as possible.

20) Ask if the patient has any questions and answer them appropriately.

21) Tell the patient that if they choose to be included in the study that they retain the right to withdraw from the study at any point. Patients who withdraw from the study will be referred to their local health service provider.

22) Explain that if the patient consents to study inclusion that they may choose to allow their samples (blood and spinal fluid) to be used in future studies and that these samples may be stored for a period

of up to 5 years either locally or outside of the country. Agreeing to samples being stored for research purposes is optional, and does not affect the patient's ability to participate in the main trial. It may be the case that a specific consent form for the storage of samples is in place in your country.

IF THE PATIENT CONSENTS TO THE TRIAL BUT NOT TO HAVING THEIR SAMPLES STORED THIS MUST BE DOCUMENTED AND THAT PATIENT'S SAMPLES MARKED AS "NOT TO BE STORED"

23) Explain that if the patient consents to study inclusion that they may choose to allow their samples (blood and spinal fluid) to be used in future studies, whereby genetic tests will be performed to greater understand why some people become more unwell with CM. Agreeing for samples to undergo genetic testing is optional, and does not affect the patient's ability to participate in the main trial. It may be the case that a specific consent form for the storage of samples is in place in your country.

IF THE PATIENT CONSENTS TO THE TRIAL AND TO HAVE SAMPLES STORED BUT NOT TO HAVING THEIR SAMPLES UNDERGO GENETIC TESTING THIS MUST BE DOCUMENTED AND THAT PATIENT'S SAMPLES MARKED AS "NOT TO UNDERGO GENETIC TESTING"

IF THE PATIENT CONSENTS TO THE TRIAL BUT NOT TO HAVE SAMPLES STORED AND NOT TO HAVING THEIR SAMPLES UNDERGO GENETIC TESTING THIS MUST BE DOCUMENTED AND THAT PATIENT'S SAMPLES MARKED AS "NOT TO UNDERGO STORAGE OR GENETIC TESTING"

24) Explain confidentiality to the patient: everything stays between the patient, study doctor and study nurse. Names are entered as a separate, encrypted part of the database that is not accessible to the daily database user. Data is anonymized with only a patient identification number used for daily database usage.

25) (i) If the patient consents to partake in the study ask them to write their name on the appropriate line on the consent form and then sign and date.

(ii) If the patient is illiterate, an impartial witness (which may be next of kin or a member of hospital staff) should write the patient's name and date, and the patient can then use a thumb print to sign. The witness should then write their own name, sign and date (on the witness line of the form).

(iii) If the next-of-kin is illiterate, and patient is not competent, the witness should write the name and date for the patient and next of kin, next of kin should give thumb print and witness should complete their own section of the form.

(iv) The patient's name ***must*** be written on the form in all instances, by the patient if competent and witness if not. Remember to reconsent the patient on recovery from abnormal mental status: this will be prompted by the database. A new form should be used and filed away with the old form, again giving a copy to the patient. Complete a file note to explain events where a patient is not re- consented e.g. in cases where the patient dies prior to re-consenting.

26) Give the patient a copy of the consent form and the patient information sheet as well as the contact details for the study doctor and nurse. Ensure the patient has sufficient time to make a decision regarding potential inclusion in the study.

27) Original signed consent forms must be kept by the investigator and documented in the electronic case report form eCRF, a copy given to the participant or family, and a copy placed in the participant's medical notes.

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SUMMARY OF INFORMED CONSENT PROCEDURES for AMBITION TRIAL

IF	AND/BUT	THEN	Meaning
GCS = 15	Patient is literate.	Get direct consent from patient.	Patient writes their own name and date on consent form
GCS = 15	Patient is illiterate OR too weak to write.	Thumbprint and witness is needed.	Patient provides the thumbprint and impartial witness writes both the patient's name and their own name on the appropriate lines.
GCS <15	Next-of-kin is literate.	Seek next-of-kin consent*	Next-of-kin signs both their name and the patient's name. They must also document their relationship to the patient on the consent forms.
GCS <15	Next-of-kin is illiterate.	Next-of-kin should give thumb print.	The witness should write the name and date for the patient and next of kin, and witness should complete their own section of the form.

Please note that all patients who initially were consented using a surrogate should be re-consented when mental status is regained such they give direct consent for their participation in the study.

*as per National Guidance

Important Notes:

- All consent forms must have a signature, date AND time of consent by the person performing the consenting process, this must be done before study related procedures
- Patients should use their full names (first, middle, last) whenever possible when signing consent forms
- Study staff CANNOT serve as witness or surrogate for patients
- Study staff CANNOT write patient's name on behalf of patient

  Ensure that specific consent for storage has been sought and the relevant part of the consent form is completed

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 SOP and understand the material contained in it)

Date	Name (Please print)	Signature