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High dose fluconazole with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitiscryptococcal meningitis

Submission date	Recruitment status	[_] Prospectively registered
11/02/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
20/03/2008	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
05/01/2010	Infections and Infestations	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
MRC (UK) ref: 76201; 1.0

Study information

Scientific Title
A randomised controlled clinical trial to evaluate high dose fluconazole with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis

Study objectives
As of 27/02/2009 this record was updated to include the second phase Step 2 within this record. Ethics approval was extended to include this phase. All additions to this record regarding Step 2 can be found in the relevant field under the title Step 2. The titles for Step 2 are as follows:
Step 2 public title: High dose fluconazole with short course amphotericin B, with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis
Step 2 scientific title: A randomised controlled clinical trial to evaluate high dose fluconazole with short course amphotericin B, with or without flucytosine in the treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis

Please also note that the anticipated start and end dates for Step 2 are as follows:
Step 2 anticipated start date: 01/03/2009
Step 2 anticipated end date: 01/01/2010

At the time of registration, the initial trial dates reflected Step 1 of this trial, and therefore these have been amended to include the Step 2 dates as above; the initial end date (for Step 1) was 18/02/2009.

Step 1 hypothesis:
Addition of flucytosine to fluconazole will lead to more rapid sterilisation of cerebrospinal fluid (CSF) in cryptococcal meningitis.

Step 2 hypotheses:
1. In the presence of a short course of amphotericin B, the addition of flucytosine to fluconazole (1200 mg/d) will lead to more rapid sterilisation of cerebrospinal fluid (CSF) in cryptococcal meningitis
2. A short course of amphotericin B will avoid toxicity observed in longer courses of amphotericin B.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Malawi National Health Sciences Research Committee approved on the 8th November 2007 (Step 2 amendment: 17th February 2009)
2. Wandsworth LREC (covering St Georges University of London UK) approved on the 8th January 2008 (Step 2 amendment: 13th February 2009)
3. Institutional review board (IRB) University of North Carolina at Chapel Hill approved on the 29th November 2007 (Step 2 amendment pending as of 26/02/2009)

Study design
Randomised open-labelled controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Cryptococcal meningitis/ HIV

Interventions
Step 1:
1. Fluconazole 1,200 mg/d for two weeks
2. Fluconazole 1,200 mg/d plus flucytosine 100 mg/kg/d for two weeks
After two weeks all patients receive fluconazole 800 mg/d.

Step 2:
1. Amphotericin B 1 mg/kg daily for 7 days plus fluconazole 1200 mg/d (started concurrently) for 2 weeks
2. Amphotericin B 1 mg/kg daily for 7 days, plus fluconazole 1200 mg/d, plus flycytosine 100 mg /kg/day (started concurrently) for 2 weeks
After two weeks all patients receive fluconazole 800 mg/d.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Fluconazole, flucytosine

Primary outcome measure
Early fungicidal activity (rate of clearance of infection) of alternative regimens over the first two weeks of therapy.

Secondary outcome measures
1. Clinical and laboratory side effects
2. Mortality at 2 and 10 weeks

Overall study start date
18/02/2008

Completion date
01/01/2010

Eligibility

Key inclusion criteria
1. Patients greater than 18 years, either sex
2. A first episode of cryptococcal meningitis

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
80

Key exclusion criteria
1. Alanine aminotransferase (ALT) greater than five times the upper limit of normal
2. Pregnancy or lactation
3. Previous serious reaction to study drugs
4. Taking systemic anti-fungals
5. Polymorphonuclear leukocytes (PMNs) less than 500 x 10^6/L
6. Platelets less than 50,000 x 10^6/L
7. Concomitant medication that is contraindicated with any study drugs
8. Already on antiretroviral therapy (ART)

STEP 2 additional criteria:
9. Initial creatinine greater than 2.5 mg/dl

Date of first enrolment
18/02/2008

Date of final enrolment
01/01/2010

Locations

Countries of recruitment
Malawi

United Kingdom

Study participating centre
Cranmer Terrace
London
United Kingdom
SW17 ORE

Sponsor information

Organisation
St George's University of London (UK)

Sponsor details
Cranmer Terrace
London
United Kingdom
SW17 ORE

Sponsor type
University/education

Website
http://www.sgul.ac.uk

ROR
https://ror.org/040f08y74

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council (UK) (grant ID: 76201)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype

National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2010		Yes	No