

# Effect trial: Treatment of cryptococcal antigen-positive patients identified through screening using fluconazole plus flucytosine vs fluconazole alone

<b>Submission date</b> 10/02/2021	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 04/03/2021	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 24/07/2025	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Over the last 10 years, many more people living with HIV in Africa have been able to start antiretroviral treatment (ART). However, about one-third of people living with HIV only seek care when they have advanced HIV disease (when their CD4 count falls below 200 cells/ $\mu$ l). The frequency of infections such as cryptococcal meningitis in this group is high. Cryptococcal meningitis, caused by a fungus, is the commonest form of meningitis in sub-Saharan Africa, resulting in about 180,000 deaths per year globally with over 75% of these occurring in sub-Saharan Africa.

Over half of the patients diagnosed with cryptococcal meningitis die within 10 weeks in sub-Saharan Africa, a death rate similar to Ebola virus disease. Fortunately, cryptococcal disease can be diagnosed earlier, before the development of life-threatening meningitis, using a simple blood test to detect a part of the fungal cell called cryptococcal antigen (CrAg). Studies have shown that 70% of people testing positive for CrAg in blood would progress to develop meningitis or die without a diagnosis if they are not given antifungal treatment. Routine screening for CrAg among people presenting to HIV centres, combined with oral antifungal (fluconazole) treatment for those who screen CrAg-positive, can therefore decrease the risk of cryptococcal meningitis and death. CrAg screening has now been recommended in the national HIV guidelines of 28 countries and screening programmes are being rolled out across sub-Saharan Africa.

However, there is now also evidence showing that CrAg-positive patients who are treated with fluconazole alone have a 2.5 to 3 times higher chance of dying compared to people with similar CD4 counts who test CrAg-negative, despite receiving this antifungal treatment. Up to 40% of people testing blood CrAg-positive may have asymptomatic (subclinical) cryptococcal meningitis diagnosed at the time of the screening test; these people need a combination of antifungal medicines to treat meningitis. Yet many patients decline the procedure to diagnose meningitis (lumbar puncture) and are thus not treated appropriately for meningitis.

Recent studies have shown that combined oral treatment of fluconazole plus flucytosine for 2 weeks is safe, has few unwanted side effects and works as well as the standard of 2 weeks of

intravenous amphotericin B plus flucytosine for people treated in hospital with symptomatic cryptococcal meningitis. This study aims to compare how well this oral combination of fluconazole plus flucytosine works compared to fluconazole alone (the current recommended treatment) in reducing 6-month mortality in asymptomatic people with advanced HIV disease and a CrAg-positive blood test in Tanzania, South Africa and Vietnam.

#### Who can participate?

HIV-infected adults (>18 years old) identified through routine laboratory screening at participating centres as CrAg-positive in blood and who are also cerebrospinal fluid CrAg-negative or who decline a lumbar puncture.

#### What does the study involve?

Eligible participants are randomly allocated to be treated with either fluconazole (1200 mg) plus flucytosine OR fluconazole (1200 mg) alone for 14 days. Fluconazole (800 mg daily) will be given to all participants for a further 8 weeks and fluconazole 200 mg/d thereafter as per national guidelines. Participants who are treated as outpatients will be seen in clinic on day 1 and 14 and contacted on days 3 and 9 by telephone for adherence counselling and at 1, 2.5 (10 weeks), 4 and 6 months to determine survival status. Mortality (death rates) will be compared between the two groups.

#### What are the possible risks and benefits of participating?

The ultimate goal of this project is to reduce mortality due to HIV-associated cryptococcal disease by ensuring universal access to affordable, safe, and effective treatment. If a combination therapy of fluconazole and flucytosine is shown to be safe and more effective than fluconazole alone, results from this study would lead to evidence-based changes in regional and international treatment guidelines, and provide an effective and practical treatment, which could be administered to outpatients, with the potential to prevent a significant number of HIV-related deaths.

Risks associated with the oral combination of fluconazole and flucytosine are expected to be low, with little toxicity observed for CM patients in a recent phase III randomised controlled trial (ACTA trial) treated with the same combination. However, the risk-benefit for flucytosine in asymptomatic out-patients is not defined, and flucytosine can be associated with neutropenia. Toxicity in study participants will be closely monitored with adjustments made as necessary and adverse events regularly reported to the Data Monitoring Committee.

An additional potential risk is a lack of adherence to the medications due to an increased daily pill count for the first 14 days. Participants will be counselled on the importance of adherence and will be seen face-to-face twice during induction phase treatment (on day 1 and 14) and called by telephone on days 3 and 9 to encourage adherence to medication and discuss any issues. As the intervention is given over the first 2 weeks, a pill count will be performed on day 14. If significant issues are identified for some participants, patient advocates (including CM survivors) will be asked to assist.

#### Where is the study run from?

1. Mycology Division, WITS Health Consortium (Based at the National Institute for Communicable Diseases) (South Africa)
2. St George's University of London (UK)

#### When is the study starting and how long is it expected to run for?

November 2020 to August 2026

#### Who is funding the study?

The study is funded through the Joint Global Health Trials (JGHT) Scheme with funding from the

UK - Department of Health and Social Care (DHSC), the Foreign, Commonwealth & Development Office (FCDO), the Medical Research Council (MRC), Wellcome and National Institute for Health Research (NIHR).

Who is the main contact?

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2. Dr Síle Molloy

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3. Michelle Eriksson

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### **Study website**

<https://witsmycology.co.za/projects/EFFECT/index.html>

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Dr Síle Molloy

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### **Type(s)**

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### **Contact name**

Prof Nelesh Govender

### **ORCID ID**

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South Africa

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**Type(s)**  
Scientific

**Contact name**  
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## **Additional identifiers**

**EudraCT/CTIS number**  
Nil known

**IRAS number**

**ClinicalTrials.gov number**  
Nil known

**Secondary identifying numbers**  
JRES 2020.0308

## **Study information**

**Scientific Title**  
Fluconazole plus flucytosine vs fluconazole alone for cryptococcal antigen-positive patients identified through screening: a phase III randomised controlled trial

**Acronym**  
EFFECT - Efficacy of Flucytosine and Fluconazole as Early Cryptococcal Treatment

**Study objectives**  
Pre-emptive combination treatment of fluconazole plus flucytosine for 2 weeks will be more efficacious in reducing 6-month all-cause mortality than standard treatment of fluconazole alone among CrAg-positive HIV-infected adults

**Ethics approval required**  
Old ethics approval format

**Ethics approval(s)**

1. Approved 22/01/2021, St George's, University of London (SGUL) Research Ethics Committee (Joint Research and Enterprise Services, Ground Floor, Jenner Wing, St. George's, University of London, Cranmer Terrace, London, SW17 0RE, UK; +44 (0)208 266 6073; sgulrec@sgul.ac.uk), ref: 2020.0308
2. Approved 21/07/2021, National Institute for Medical Research (NIMR) REC (PO Box 9653, Dar es Salaam, Tanzania; +255 22 2121 400; ethics@nimr.or.tz), no ref provided
3. Approved 12/08/2021, University of Cape Town Faculty of Health Sciences Human REC (Room G50, Old Main Building, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa; +27 (021) 650 5184; hrec-enquiries@uct.ac.za), ref: 274/2021
4. Approved 21/05/2021, University of the Witwatersrand Human REC (Suite 189, Private Bag x2600, Houghton, Johannesburg 2021, South Africa; +27 (0)11 275 9200; HREC-Medical.ResearchOffice@wits.ac.za), ref: 210305
5. Approved 22/07/2022, University of KwaZulu-Natal Biomedical REC (UKZN Research Office, Govan Mbeki Building, Westville Campus, University Drive, Durban 4001, South Africa; +27 (031) 260 1074; brec@ukzn.ac.za; ref: BREC/00002777/2021
6. Approved 30/06/2021, Walter Sisulu University Health Research Ethics and Biosafety Committee (Academic Health Services Complex of the Eastern Cape, Postgraduate Research and Training, Faculty of Health Sciences, Walter Sisulu University, Private Bag X1, WSU, South Africa 5117; +27 (0)47 502 2100; ggeorge@wsu.ac.za), ref: 067/2021

## **Study design**

Open-label multicentre phase III randomized 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 contact details to request a participant information sheet

## **Health condition(s) or problem(s) studied**

Asymptomatic cryptococcal antigen (CrAg)-positive individuals with advanced HIV infection

## **Interventions**

Individual randomisation using SAS PROC PLAN via a permuted-block randomisation method stratified by site. Block sizes will vary.

1. Fluconazole 1200 mg/day plus flucytosine 25 mg/kg four times daily PO (intervention arm) for 2 weeks
2. Fluconazole alone 1200 mg/day PO (standard dose 'control arm') for 2 weeks

All participants will then receive fluconazole 800 mg/day to 10 weeks, and fluconazole 200 mg /day thereafter for a minimum of 12 months as per national guidelines. ART will be commenced on day 14 as per current international (WHO) and national guidelines.

## **Intervention Type**

Drug

## **Phase**

Phase III

## **Drug/device/biological/vaccine name(s)**

Flucytosine, fluconazole

## **Primary outcome measure**

All-cause mortality, measured using patient medical records and interviews, at 6 months after randomisation

## **Secondary outcome measures**

Current secondary outcome measures as of 24/07/2025:

1. Time to all-cause mortality within first 6 months measured using patient medical records and interviews, at 6months.
2. All-cause mortality at 10 weeks measured using patient medical records and interviews, at 10 weeks
3. Time to all-cause mortality within first 10 weeks measured using patient medical records and interviews, at 10 weeks
4. Cryptococcal meningitis-free survival to 6-months measured using patient medical records, to 6 months
5. Incidence rate of symptomatic laboratory-confirmed cryptococcal meningitis, measured using patient medical records, measured to 6 months
6. Crypto-related mortality at 6-months measured using patient medical records, to 6 months
7. Tolerability and safety: proportions of patients developing clinical and laboratory-defined grade III/IV adverse events measured using patient medical records and interviews at 6 months
8. Efficacy outcomes by baseline CrAg titre and semi-quantitative assay score at 10 weeks and 6 months
9. Rate of disability at 6 months measured using patient medical records and interviews at 6 months
10. Health service costs per life-year saved, measured using participant and health service provider interviews, at 6 months

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Previous secondary outcome measures:

1. Time to all-cause mortality, measured using patient medical records and interviews, within the first 6 months
2. All-cause mortality, measured using patient medical records and interviews, at 10 weeks
3. Cryptococcal meningitis-free survival, measured using patient medical records, to 6 months
4. Incidence rate of symptomatic laboratory-confirmed cryptococcal meningitis, measured using patient medical records, over 6 months

5. Tolerability and safety: proportions of patients developing clinical and laboratory-defined grade III/IV adverse events measured using patient medical records and interviews up to 21 days
6. Efficacy outcomes by baseline CrAg titre and semi-quantitative assay score at 10 weeks and 6 months
7. Health service costs per life-year saved, measured using participant and health service provider interviews, over 6 months

**Overall study start date**

09/11/2020

**Completion date**

31/08/2026

## Eligibility

**Key inclusion criteria**

1. Consecutive patients aged >18 years
2. HIV-seropositive
3. CD4 count of <100 cells/ $\mu$ l
4. Serum/plasma Cryptococcal antigen (CrAg) test positive within the last 14 days
5. Cerebrospinal fluid (CSF) CrAg test negative or lumbar puncture not done (declined)
6. Willing to participate in the study

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

600

**Key exclusion criteria**

Current exclusion criteria:

Initial exclusion criteria:

1. Prior episode of cryptococcal meningitis
2. Pregnancy (confirmed by urine or serum pregnancy test) or breastfeeding
3. Previous serious reaction to flucytosine or fluconazole
4. Already taking high-dose fluconazole treatment (800-1200 mg/day) for  $\geq 1$  week
5. Contraindicated concomitant medications including cisapride and the class of antihistamines including terfenadine
6. HIV-seronegative
7. Clinical symptoms/ signs of symptomatic meningitis at any time since CrAg screening, i.e. a progressively severe headache OR a headache and marked nuchal rigidity OR a headache and

vomiting OR seizures OR a Glasgow Coma Scale (GCS) score of <15

8. Jaundice

9. CSF positive for cryptococcal meningitis (i.e. positive microscopy with India Ink, culture, or CrAg test) at any time between the CrAg test and screening for eligibility, while the patient remained without clinical symptoms/ signs of meningitis as described in 7 (late withdrawal criterion)

Late exclusion criteria: (after randomisation and day 1 visit)

10. DAIDS grade 4 abnormalities of platelets, neutrophil count or creatinine level on baseline bloods:

10.1. Platelets <25,000 x 10<sup>6</sup>/l

10.2. Neutrophils <400 x10<sup>6</sup>/l

10.3. Creatinine > 3.5x upper limit of normal (with standardised ULN of 114 µmol/l, this includes any creatinine level ≥400 µmol/l)

11. Microbiological evidence of CM on CSF if full CSF results not present at randomisation (e.g. screening CSF CrAg negative but culture on same sample later returns positive for CM)

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Previous exclusion criteria:

1. Prior episode of Cryptococcal meningitis

2. Pregnancy (confirmed by urine or serum pregnancy test) or breastfeeding

3. Previous serious reaction to flucytosine or fluconazole

4. Already taking high-dose fluconazole treatment (800-1200 mg/day) for ≥1 week

5. Contraindicated concomitant medications including cisapride and the class of antihistamines including terfenadine

6. HIV-seronegative

7. Clinical symptoms/ signs of symptomatic meningitis at any time since CrAg screening, i.e. a progressively severe headache OR a headache and marked nuchal rigidity OR a headache and vomiting OR seizures OR a Glasgow Coma Scale (GCS) score of <15

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**Date of first enrolment**

08/05/2022

**Date of final enrolment**

31/10/2025

## Locations

**Countries of recruitment**

South Africa

Tanzania

Viet Nam



**Study participating centre**

**Khayelitsha Site B Clinic and Mitchell's Plain Hospital**

Cnr Walter Sisulu & Steve Biko Road

Khayelitsha

Cape Town

South Africa

7784

**Study participating centre**

**Chris Hani Baragwanath Academic Hospital**

26 Chris Hani Rd

Diepkloof 319-lq

Johannesburg

South Africa

1864

**Study participating centre**

**Helen Joseph Hospital**

Rossmore

Johannesburg

South Africa

2092

**Study participating centre**

**Klerksdorp/Tshepong Hospital**

Jouberton

Klerksdorp

South Africa

2574

**Study participating centre**

**King Edward VIII Hospital**

Sydney Rd

Umbilo

Durban

South Africa

4013

**Study participating centre**

**Harry Gwala Regional Hospital (formerly Edendale Hospital)**

89 Selby Msimang Rd

Plessislaer  
Pietermaritzburg  
South Africa  
3201

**Study participating centre**

**Livingstone Hospital**  
Lindsay Rd, Industrial  
Gqeberha  
South Africa  
6020

**Study participating centre**

**Amana Regional Referral Hospital**  
Uhuru St, Ilala  
Dar es Salaam  
Tanzania  
-

**Study participating centre**

**Mwananyamala Regional Referral Hospital**  
Kinondoni  
Dar es Salaam  
Tanzania  
-

**Study participating centre**

**Temeke Regional Referral Hospital**  
Temeke  
Dar es Salaam  
Tanzania  
-

**Study participating centre**

**Dora Nginza Hospital**  
Spondo St  
Gqeberha  
South Africa  
6020

# Sponsor information

## Organisation

St George's, University of London

## Sponsor details

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## Sponsor type

University/education

## Website

<http://www.sgul.ac.uk/>

## ROR

<https://ror.org/040f08y74>

# Funder(s)

## Funder type

Research organisation

## Funder Name

Wellcome Trust

## Alternative Name(s)

Wellcome, WT

## Funding Body Type

Private sector organisation

## Funding Body Subtype

Trusts, charities, foundations (both public and private)

## Location

United Kingdom

**Funder Name**

Medical Research Council

**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

**Funder Name**

Department of Health and Social Care

**Alternative Name(s)**

Department of Health & Social Care, DH

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

**Funder Name**

National Institute for Health Research

**Alternative Name(s)**

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

**Funder Name**

Foreign, Commonwealth and Development Office

**Alternative Name(s)**

Foreign, Commonwealth & Development Office, Foreign, Commonwealth & Development Office, UK Government, FCDO

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

## Results and Publications

**Publication and dissemination plan**

1. Planned publication of the protocol
2. Planned publication of the results in a high-impact peer-reviewed journal

**Intention to publish date**

31/08/2026

**Individual participant data (IPD) sharing plan**

The current data sharing plans for the current study are unknown and will be made available at a later date.

**IPD sharing plan summary**

Data sharing statement to be made available at a later date