

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

**AMBisome Therapy Induction Optimisation (AMBITION):
High dose Ambisome for Cryptococcal Meningitis Induction
Therapy in sub-Saharan Africa: Economic Evaluation
Protocol for a Randomised Controlled Trial Based
Equivalence Study**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026288
Article Type:	Protocol
Date Submitted by the Author:	24-Aug-2018
Complete List of Authors:	<p>Ponatshego, Ponego; Botswana-Harvard AIDS Institute Partnership, Clinical Trials Unit Lawrence, David; Botswana-Harvard AIDS Institute Partnership, Clinical Trials Unit; London School of Hygiene and Tropical Medicine Department of Clinical Research Youssof, Nabila; London School of Hygiene and Tropical Medicine, EPH; Botswana-Harvard AIDS Institute Partnership Molloy, Sile; St. George's University of London Alufandika, melanie; Malawi-Liverpool-Wellcome Trust Clinical Research Centre Bango, Funeka; Institute of Infectious Diseases and Molecular Medicine Boulware, David R.; Univ Minnesota Chawinga, Chimwemwe; Lilongwe Medical Relief Trust (UNC Project) Dziwani, Eltas; Malawi-Liverpool-Wellcome Trust Clinical Research Centre Gondwe, Ebbie; Malawi-Liverpool-Wellcome Trust Clinical Research Centre Hlupeni, Admire; University of Zimbabwe College of Health Sciences Hosseinipour, Mina C.; Kamuzu Cent Hosp Kanyama, Cecilia; Lilongwe Medical Relief Trust (UNC) Project Meya, David; Makerere University Mosepele, Mosepele; Botswana-Harvard AIDS Institute Partnership Muthoga, Charles; Botswana-Harvard AIDS Institute Partnership Muzoora, Conrad; Makerere University Mwandumba, Henry; Liverpool School of Tropical Medicine; Malawi Liverpool Wellcome Trust Clinical Research Programme Ndhlovu, Chiratidzo; University of Zimbabwe College of Health Sciences Rajasingham, Radha; University of Minnesota sayed, sumaya; Institute of Infectious Diseases and Molecular Medicine Shamu, Shepherd; University of Zimbabwe College of Health Sciences Tsholo, Katlego; Botswana-Harvard AIDS Institute Partnership Tugume, Lillian ; Makerere University Williams, Darlisha; Makerere University Maheswaran, Hendramoorthy; University of Warwick Warwick Medical School Shiri, Tinevimbo; Liverpool School of Tropical Medicine BOYER-CHAMMARD, Timothée; Institut Pasteur Loyse, Angela; St George's University of London</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	<p>Chen, T; Liverpool School of Tropical Medicine, Department of Clinical Sciences Wang, Duolao; Liverpool School of Tropical Medicine Lalloo, David; Malawi Liverpool Wellcome Trust Clinical Research Centre; Liverpool School of Tropical Medicine Meintjes, Graeme; University of Cape Town, Medicine Jaffar, Shabbar; Liverpool School of Tropical Medicine Harrison, Thomas; St George's University of London Jarvis, Joseph; Botswana-Harvard AIDS Institute Partnership; London School of Hygiene and Tropical Medicine Niessen, Louis; Liverpool School of Tropical Medicine, Health Economics; University of Warwick, Dept of Health Sciences</p>
<p>Keywords:</p>	<p>HEALTH ECONOMICS, HIV & AIDS < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES, Clinical trials < THERAPEUTICS</p>

SCHOLARONE™
Manuscripts

1
2
3 **AMBisome Therapy Induction Optimisation (AMBITION): High dose Ambisome for Cryptococcal**
4
5 **Meningitis Induction Therapy in sub-Saharan Africa: Economic Evaluation Protocol for a**
6
7 **Randomised Controlled Trial Based Equivalence Study.**
8
9

10 Ponego Ponatshego (pponatshego@bhp.org.bw)^{1*}

11
12
13 David S Lawrence (david.s.lawrence@lshtm.ac.uk)^{1,2+*},

14
15
16 Nabila Youssouf (nabila.youssouf@lshtm.ac.uk)^{1,2},

17
18
19 Síle L. F. Molloy (smolloy@sgul.ac.uk)³,

20
21
22 Melanie Alufandika (malufandika@mlw.mw)⁴,

23
24
25 Funeka Bango (funeka.bango@hiv-research.org.za)⁵,

26
27
28 David R. Boulware (boulw001@umn.edu)^{6,7},

29
30
31 Chimwemwe Chawinga (cchawinga@unclilongwe.org)⁸,

32
33
34 Eltas Dziwani (eltas.nyirenda@live.com)⁴,

35
36
37 Ebbie Gondwe (egondwe@mlw.mw)⁴,

38
39
40 Admire Hlupeni (ahlupeni@gmail.com)⁹,

41
42
43 Mina C. Hosseinipour (mina_hosseinipour@med.unc.edu)⁸,

44
45
46 Cecilia Kanyama (ckanyama@gmail.com)⁸,

47
48
49 David B. Meya (david.meya@gmail.com)⁶,

50
51
52 Mosepele Mosepele (mosepele.mosepele@gmail.com)¹,

1
2
3 Charles Muthoga (chmuthoga@gmail.com)¹,
4

5
6 Conrad Muzoora (conradmuzoora@yahoo.com)⁶,
7

8
9 Henry C. Mwandumba (henry.mwandumba@lstmed.ac.uk)^{4,10},
10

11
12 Chiratidzo E. Ndhlovu (mascen@mweb.co.zw)⁹,
13

14
15 Radha Rajasingham (radha@umn.edu)⁶,
16

17
18 Sumaya Sayed (sumaya.sayed@uct.ac.za)⁵,
19

20
21 Shepherd Shamu (shamushe@yahoo.com)⁹,
22

23
24 Katlego Tsholo (katlego.tsholo@yahoo.ie)¹,
25

26
27 Lillian Tugume (lilliantugume18@gmail.com)⁶,
28

29
30 Darlisha Williams (darlisha@gmail.com)⁶,
31

32
33 Hendramoorthy Maheswaran (H.Maheswaran@warwick.ac.uk)¹¹,
34

35
36 Tinevimbo Shiri (tinevimbo.shiri@lstmed.ac.uk)¹⁰,
37

38
39 Timothée Boyer-Chammard (timothee.boyer-chammard@pasteur.fr)¹²,
40

41
42 Angela Loyse (aloyse@sgul.ac.uk)³,
43

44
45 Tao Chen (tao.chen@lstmed.ac.uk)¹⁰,
46

47
48 Duolao Wang (doulao.wang@lstmed.ac.uk)¹⁰,
49

50
51 David G Lalloo (david.lalloo@lstmed.ac.uk)^{4,10},
52

1
2
3 Graeme Meintjes (graemein@mweb.co.za)⁵,
4

5
6 Shabbar Jaffar (shabbar.jaffar@lstmed.ac.uk)¹⁰,
7

8
9 Thomas S Harrison (tharriso@sgul.ac.uk)³
10

11
12 Joseph N Jarvis (joseph.jarvis@lshtm.ac.uk)^{1,2*} and
13

14
15 Louis Niessen (louis.niessen@lstmed.ac.uk)^{10*}
16
17

18
19 ¹ Botswana-Harvard AIDS Institute Partnership, Gaborone, Botswana
20

21
22 ² Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of
23
24 Hygiene and Tropical Medicine, London, UK
25

26
27 ³ Research Centre for Infection and Immunity, St George's University of London, London, UK
28

29
30 ⁴ Malawi-Liverpool-Wellcome Trust Clinical Research Centre, Blantyre, Malawi
31
32

33
34 ⁵ Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town,
35
36 South Africa
37

38
39 ⁶ Infectious Diseases Institute, Makerere University, Kampala, Uganda
40

41
42 ⁷ Department of Medicine, University of Minnesota, Minneapolis, MN, USA
43
44

45
46 ⁸ Lilongwe Medical Relief Trust (UNC Project), Lilongwe, Malawi
47

48
49 ⁹ Department of Medicine, University of Zimbabwe College of Health Sciences, Parirenyatwa
50
51 Hospital, Harare, Zimbabwe
52

53
54 ¹⁰ Department of Clinical Sciences and International Public Health, Liverpool School of Tropical
55
56 Medicine, Liverpool, UK
57

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

¹¹ Population Evidence and Technologies, University of Warwick, Coventry, UK

¹² Molecular Mycology Unit and National Reference Centre for Invasive Mycoses, Institut Pasteur, Paris, France

[†]Corresponding author: david.s.lawrence@lshtm.ac.uk +267 7652 4122

* Equal contribution

Word count: 3894

For peer review only

ABSTRACT

Introduction: Cryptococcal meningitis is responsible for around 15% of all HIV-related deaths globally. Conventional treatment courses with amphotericin-B require prolonged hospitalisation and are associated with multiple toxicities and poor outcomes. A phase II study has shown that a single high-dose of liposomal amphotericin may be comparable to standard treatment. We propose a phase III clinical endpoint trial comparing single, high-dose liposomal amphotericin with the WHO recommended first line treatment at six sites across five countries. An economic analysis is essential to support wide-scale implementation.

Methods and Analysis: Country-specific economic evaluation tools will be developed across the five country settings. Details of patient and household out of pocket expenses and any catastrophic healthcare expenditure incurred will be collected via interviews from trial patients. Health service patient costs and related household expenditure in both arms will be compared over the trial period in a probabilistic approach, using Monte Carlo bootstrapping methods. Costing information and number of life years survived will be used as the input to a decision-analytic model to assess the cost-effectiveness of a single, high-dose liposomal amphotericin to the standard treatment. In addition, these results will be compared to a historical cohort from another clinical trial.

Ethics and Dissemination: The AMBITION trial has been evaluated and approved by the London School of Hygiene and Tropical Medicine, University of Botswana, Malawi National Health Sciences, University of Cape Town, Mulago Hospital and Zimbabwe Medical Research Council research ethics committees. All participants will provide written informed consent or if lacking capacity will have consent provided by a proxy. The findings of this economic analysis, part of the AMBITION trial, will be disseminated through peer-reviewed publications and at international and country-level policy meetings.

Trial Registration: ISRCTN: 7250 9687 Date of Registration: 13/07/2017

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This economic analysis will provide evidence to inform policy decisions about the use of a more expensive medication in cryptococcal meningitis.
- This analysis will provide data that may justify initiatives to increase the availability of a more expensive medication in cryptococcal meningitis
- This approach will enable the development and application of country-level costing tools across five African country settings which can be re-utilised for future studies and contribute to capacity building in the region.
- The study is taking place at six large referral hospitals across five countries in East and Southern Africa and the results might not be representative or generalisable to remote rural areas or settings in other countries.

INTRODUCTION

Cryptococcal Meningitis (CM) is a severe fungal infection of the brain which occurs in advanced HIV infection. It is estimated that there are roughly 220,000 cases of CM globally per year with 73% of these occurring in sub-Saharan Africa. Annual global deaths are estimated at 181,000 and CM is responsible for approximately 15% of all AIDS-related deaths(1).

The current recommended first line treatment for CM is amphotericin B deoxycholate (AmBd). AmBd is associated with multiple drug-induced toxicities including anaemia, impaired renal function, and electrolyte abnormalities. AmBd is also difficult to administer, requiring hospitalization for 7 to 14 days of intravenous infusions, depending on which oral antifungal it has been paired with. In addition, treatment outcomes are poor with acute mortality at 10-weeks ranging from 30-55% (2).

The use of a liposomal form of amphotericin called Ambisome (hereafter referred to as L-AmB) is associated with reduced drug induced-toxicities when compared to conventional AmBd(3). The long tissue half-life and effective penetration into the brain tissue of L-AmB has prompted research into the effectiveness of treatment with short courses of high-dose L-AmB(4). The AMBisome Therapy Induction Optimisation (AMBITION) phase II clinical trial conducted in Botswana and Tanzania found that a single, high-dose of 10mg/kg L-AmB was well tolerated and led to a non-inferior reduction in fungal burden in cerebrospinal fluid when compared to standard 14-day courses of 3mg/kg L-AmB(5). This dosing strategy is now being taken to a clinical endpoint trial.

The phase III AMBITION trial is a phase III open label randomised control non-inferiority trial to compare single, high-dose L-AmB treatment to the WHO first-line recommended regimen of a 7-day course of AmBd based treatment in avoiding all-cause mortality in HIV-associated CM (Figure 1)(6). Eligible patients will be randomised to receive either:

- 1
- 2
- 3 1. L-AmB 10 mg/kg day 1 given with 14-days of fluconazole 1200mg/day and flucytosine
- 4 100mg/kg/day (single dose) or
- 5
- 6
- 7 2. Amphotericin B deoxycholate 1 mg/kg/d for 7-days given with 7-days of flucytosine
- 8 100mg/kg/day followed by 7-days of fluconazole 1200mg/day (control arm).
- 9
- 10

11 After the 2-week induction phase all patients will receive fluconazole 800 mg/day to 10 weeks and
12 200 mg/day thereafter. ART will be commenced 4 to 6 weeks after initiation of antifungal therapy.
13
14 The trial will enrol 850 patients across six sites in five countries in Africa: Gaborone, Botswana (90);
15
16 Blantyre (230) and Lilongwe (110), Malawi; Cape Town, South Africa (80); Kampala, Uganda (110)
17
18 and Harare, Zimbabwe (230). All participants will be invited to take part in the economic evaluation
19
20 study.
21
22
23

24
25 The use of L-AmB has potential implications for both clinical outcomes and healthcare costs. The
26
27 widespread availability of L-AmB has previously been limited by the high cost of therapy: currently
28
29 the internationally listed price is \$85 per 50mg vial compared to \$8 per 50mg vial of AmBd. The
30
31 listed cost per patient of the medication for the single dose arm in this trial will be \$996 versus \$132
32
33 for the control arm. However, the impact of a potentially more clinically effective intervention that is
34
35 associated with fewer drug-induced toxicities and a reduced length of hospital stay may offset this
36
37 expense. An argument for widening access to L-AmB could be strengthened further if the price of
38
39 the drug can be negotiated with the manufacturer, Gilead, as is the case with the same drug as part
40
41 of the expanded access programme for visceral leishmaniasis.
42
43
44

45
46 We plan an economic analysis to estimate the cost consequences and the cost-effectiveness of
47
48 short-course L-AmB treatment, compared to the control arm, in five individual country settings
49
50 across sub-Saharan Africa. The findings will also be compared to a historical cohort from the recently
51
52 completed Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial. The ACTA trial
53
54 recruited patients in Cameroon, Malawi, Tanzania and Zambia and compared treatment outcomes
55
56
57
58
59

1
2
3 among individuals receiving one of five different treatment regimens, including the control arm used
4 in the AMBITION trial (7). The purpose of this comparison is to identify any change in costs over
5 time, any gross variation in health service costs between the AMBITION and ACTA cohorts, and to
6 enable comparison of the cost-effectiveness of the short course L-AmB with the other regimens
7 tested in ACTA.
8
9
10
11
12

13
14 The hypotheses are that the short course treatment:
15

- 16
17
18 1. Will show a zero-net societal cost change or that there will be societal cost savings from the
19 short L-AmB treatment and an equivalent or increased effectiveness of the treatment
20 reducing mortality over a patient life time. Will be cost-effective in terms of life years saved
21 over a patient lifetime when compared to historical cohorts who received different
22 combination treatment regimens in a recently completed clinical trial.
23
24
25
26
27
28

29 These analyses will aim to provide the economic evidence to support wide-scale implementation of
30 short-course L-AmB treatment across sub-Saharan settings.
31
32
33
34
35
36
37

38 **OBJECTIVES:**

39
40
41 The main objective of the economic analysis is to assess the cost-effectiveness of single, high-dose L-
42 AmB compared to the control arm treatment regimen for HIV associated CM across the five country
43 settings in six sites.
44
45
46
47

48 **Secondary Objectives:**

- 49
50
51 • To assess the cost-consequences from the societal and health service perspective of single,
52 high-dose L-AmB compared to the control arm across the five country settings.
53
54
55
56 • To assess the total health service costs per patient at each country site.
57
58
59

- To assess out-of-pocket expenses incurred by patients and households at all trial sites.
- To assess the percentage of catastrophic household expenditure experienced by patients at each trial site.
- To compare the total societal costs per patient and cost-effectiveness of a single, high-dose L-AmB with historical cohorts that received different treatment regimens within the ACTA trial.

METHODS AND ANALYSIS

Study Design

The study is a prospective economic evaluation from the societal perspective – including both health service and patient related perspectives - comparing the costs and effectiveness of the two interventions at each of the six trial sites across the five country settings. The two key components of this study are the collection of data concerning personal expenditure on health and the development of country costing tools which will be applied to data concerning health-service costs collected within the trial.

Household expenditure

To estimate the societal costs at the patient and household level, they or their representatives will be interviewed at two points in time: within the first five days of randomisation and at their final face-to-face follow-up at week 10. The questionnaires, based on those used in the ACTA trial and further developed for this study, are designed to estimate their personal healthcare expenditure in the four weeks leading up to enrolment and during the trial (Table 1). In addition, the out-of-pocket

1
2
3 health care expenditure by the individual and their household, loss of income incurred due to illness,
4
5 and loss of labour time of the patients themselves and their carers will be collected using methods
6
7 adopted in trials of a similar nature(8).
8
9

10 **Table 1: Structure of the health economics questionnaire for the AMBITION study.**
11
12

- | |
|---|
| <ul style="list-style-type: none">• Personal health expenditure including on consultations, medication, travel time and costs• Relative and/or household health expenditure in relation to the patient's condition• The duration and severity of the illness episode• Loss of productivity and time off work for both patient and relative/s• Profession and educational attainment of patient• Profession and educational attainment of the person who earns the highest income (if not the patient)• Access to social security, welfare support and health insurance• Household expenditure on food, utilities, rent and large purchases such as cars, furniture and electrical items to assess the socio-economic status of the household• The need for temporary loans or the sale of assets to fund health care and other costs in relation to the illness episode• The level of disability and care needs of the patient |
|---|
- 13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45 The interview questions will preferably be asked directly to the patient. If the patient is confused or
46 has reduced consciousness due to CM, a relative or next-of-kin may provide proxy consent for them
47 to enrol in the trial. It is unlikely that this person will be fully aware of the patient's financial
48 situation and in these cases, it may be necessary to wait for the patient to recover before asking
49 them directly. In cases where patients have prolonged confusion or are felt to have a poor prognosis
50 then these questions can be asked of the proxy. Data will be collected by study doctors and nurses
51
52
53
54
55
56
57
58
59
60

1
2
3 and entered into the trial Electronic Data Capture (EDC) system: a uniform database to be utilised
4
5 across all sites. An interview guide for those collecting data from patients will ensure that nuances
6
7 and country specific idioms are acknowledged.
8
9

10 The above methods have been developed through an iterative process. Initially the lead Health
11
12 Economist, who led on the ACTA cost-effectiveness analysis, and members of the Trial Management
13
14 Group developed the data collection tools and integrated these into the wider trial EDC. This was
15
16 later refined following a one-week meeting of health economists and study team members from
17
18 across the AMBITION sites held in Blantyre, Malawi in November 2017. This provided the
19
20 opportunity for experts working in this field and individuals who will collect data from patients to
21
22 improve these tools by collecting and entering data from fabricated patients. Feedback was then
23
24 integrated into both the data collection methods and the EDC and shared for final approval across
25
26 the AMBITION consortium until a consensus was reached.
27
28
29
30
31
32

33 **Country-specific costing approaches**

34
35
36 Presently, each site has differing levels of experience with conducting economic analyses and has
37
38 varied access to validated country costing tools. As stated, the preparation of the trial included a
39
40 one-week workshop with at least two team members from each site to assess the face-validity and
41
42 completeness of the questionnaire, to practise electronic data entry of the completed questionnaire,
43
44 carrying costing computations, and to increase the knowledge and understanding of economic
45
46 evaluation.
47
48
49

50 Botswana Harvard AIDS Institute Partnership (BHP): Gaborone, Botswana.
51
52

53 BHP will use a micro-costing approach to estimate CM treatment in Botswana from a single health
54
55 provider's perspective, in this case, from the Ministry of Health and Wellness perspective. The total
56
57
58
59

1
2
3 of related costs i.e. patient-specific treatment cost and 'hotel costs' to cover CM treatment will be
4
5 determined as per the 2016 Botswana HIV Treatment Guidelines(9). All costs of pharmaceuticals will
6
7 be taken from the listed tender prices at the Central Medical Stores which procure stock and
8
9 distribute pharmaceuticals and healthcare commodities to all government healthcare facilities. This
10
11 package will provide an estimate of 'patient specific' costs of uncomplicated CM. 'Hotel costs' will
12
13 determine the necessary hospital, staffing, capital and infrastructure requirements as the patient is
14
15 admitted over a seven-day period. Data will be obtained from Princess Marina Hospital which is the
16
17 biggest and main referral hospital in Botswana. Staff salaries will be taken from the Government of
18
19 Botswana salary scales for health professionals. By combining this treatment costing data with the
20
21 meningitis burden data generated through a previously completed audit we will also generate an
22
23 estimate of the total current costs to the Botswana health service of treating CM. The data will
24
25 complement the 'Estimated resource needs for key health interventions offered under Botswana's
26
27 Essential Health Services Plan (2013-2018)(10)' that project the cost of all health programs, including
28
29 the treatment of CM, from 2013 to 2018 and will also be used as a reference for the next version of
30
31 this document to be published in 2019.
32
33
34
35
36
37
38

39 Malawi Liverpool Wellcome Trust Clinical Research Centre: Blantyre, Malawi.
40
41

42 Standardised national health costing data is not available in Malawi. An existing costing tool which
43
44 was developed for a HIV testing study will be adapted(11). Patient-related health care costs will be
45
46 obtained from the Central Medical Stores Trust, the only supplier mandated to supply government
47
48 health facilities in Malawi. Personnel costs will be refined by referencing the Malawi government
49
50 salary structures and payroll and estimating the proportion of health personnel time taken in the
51
52 clinical care of the patient, as well as allowance costs for patients working out of working hours.
53
54
55
56
57
58
59
60

1
2
3 Programme-related costs will be adapted using the results from recent costing studies within the
4
5 Queen Elizabeth Central Hospital(11).
6
7
8
9

10
11 University of North Carolina Project: Lilongwe, Malawi.
12
13

14 Most of costing data for Lilongwe will be obtained using the same methods as that outlined above
15
16 for Blantyre. In addition, local programme-related costs will be estimated and projected through a
17
18 local costing study within the Kamuzu Central Hospital. This adaptation will be based on existing
19
20 local costing data as part of the Driving Reduced AIDS-associated Meningo-encephalitis (DREAMM)
21
22 study which will be shared with the AMBITION consortium.
23
24
25
26
27
28

29 University of Cape Town: Cape Town, South Africa.
30
31

32 There are currently no costing tools for primary data collection for disease specific costing of CM
33
34 treatment in South Africa. A costing tool will be developed from validated disease specific costing
35
36 tools for the South African context(12). Costs from the health service (Department of Health)
37
38 perspective will be collected using the ingredients costing approach and captured in an Excel
39
40 spreadsheet. The quantity of resources used to treat CM in each study arm will be estimated from
41
42 the trial and patient records. Prices for these treatment related ingredients will be obtained from
43
44 the various service providers within the Department of Health that are responsible for offering the
45
46 products and services. Specific activities by staff will be identified and estimated through the review
47
48 of routinely collected time sheets. Human resource costs as well as recurrent and capital costs will
49
50 be allocated using hospital expenditure and financial records as well as records from the Provincial
51
52 Department of Health. The average cost of each treatment component will be calculated by
53
54 multiplying the quantity of resources used by the unit price. From this we can calculate the cost per
55
56
57
58
59
60

1
2
3 case of CM treated by multiplying the average cost by the number of times a particular cost has
4
5 been incurred.
6
7
8
9

10
11 Infectious Diseases Institute: Kampala, Uganda.
12
13

14 Though there is a high burden of CM in Uganda, the costs associated with treatment have not been
15 formally outlined in a costing tool. Previous research describing the costs of treatment used
16 informally gathered estimates for treatment and management of the disease based on reports from
17 various sources including local pharmacies, laboratories and the Ugandan Ministry of Health(13).
18 The Uganda team will create a systematic costing tool for CM. This tool will consider the costs of
19 treatment as well as the costs borne by the patients being treated. The creation of this tool will
20 involve input from the Ministry of Health as well as the major suppliers of medications. We will
21 engage these organizations and other key stakeholders to ascertain the current costs of meningitis
22 treatment and develop a costing tool which can be adjusted in the future should costs change.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

38 University of Zimbabwe School of Health Sciences: Harare, Zimbabwe.
39
40

41 Clinical cost data will be collected alongside the clinical trial using micro-costing methodologies. The
42 economic evaluation will be done from the societal perspective to enable the study to assess the
43 overall household economic impact of CM and will enable us to determine the patient and provider
44 unit costs. This study is powered enough to detect both country specific clinical and economic
45 differences. Direct patient level clinical activity data such as drugs, staff time, diagnostics, pathology
46 and radiology will be collected alongside the trial and relevant unit costs determined using the study
47 protocol. In other cases, prices for drugs, diagnostic and radiology tests will be collected from the
48 National Pharmaceutical Company of Zimbabwe, national reference diagnostic and radiology
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 laboratories, and from consultations with experts. Indirect and overhead costs such as management
4
5 and administration costs, utilities and other capital costs for in-patient days will be determined using
6
7 data from Parirenyatwa Hospital, Harare financial records, the WHO Choice Database and from
8
9 previous clinical trials that took place at the proposed site(14).
10

11 12 **Data collection and data management**

13
14
15 Data collected and validated using the EDC system will be stored in an electronic database that is
16
17 protected using a scheme of authentication and encryption. Paper documents, such as clinical notes
18
19 and administrative documentation will be kept in a secure location and held for 5 years after the end
20
21 of the trial. During this period, all data should be accessible to the competent or equivalent
22
23 authorities, the Sponsor and other relevant parties with suitable notice. Security of electronic
24
25 records and data is a significant concern. All components of the distributed data systems will use
26
27 authentication and encryption to render subject identity and personal health information unusable,
28
29 unreadable, or indecipherable to unauthorized individuals. Full Drive Encryption will be
30
31 implemented at the hardware layer of all devices storing protected health information. A three-
32
33 factor scheme will be used to authenticate users through the hardware layer to the application layer
34
35 where personal health information is available. The applications will have user profiles to control
36
37 access to certain data and reports. The application and database layers will use a combination of
38
39 hashing and encryption for sensitive and personal data. Mobile devices and the staff operating them
40
41 will not be equipped with the encryption keys to decrypt selected sensitive data fields.
42
43
44
45
46
47
48

49 **Confidentiality**

50
51
52 The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki
53
54 2008, the principles of Good Clinical Practice and applicable national regulations. We plan to follow
55
56
57
58
59

1
2
3 the principles of the UK Data Protection Act (DPA) regardless of the countries where the trial is being
4
5 conducted. Consent forms will be stored under the supervision of each local primary investigator in
6
7 a secured office and accessible to trial staff only. The database will not hold personal details as
8
9 participants are identified by their study number throughout the trial.
10

11 **Data analysis**

12
13
14
15 As outlined above, information on resource use and number of units used will be collected at
16
17 patient-level through the EDC, as part of the trial, and through additional separate country costing
18
19 studies. To validate and refine the data collection process an interim analysis will take place after the
20
21 first 20 patients have been recruited.
22

23
24
25 Upon closure of the study full data analysis will commence. Firstly, an empirical cost-consequence
26
27 analysis will take place, using empirical individual patient data on societal resource use and unit cost
28
29 based on the results from the costing studies(16). Both societal and health care perspectives are
30
31 chosen, and health service patient costs including household costs, treatment cost and
32
33 hospitalisations in both arms will be compared over the trial period in a probabilistic approach, using
34
35 Monte Carlo bootstrapping methods. To handle the heterogeneity of the trial population in within
36
37 trial evaluation, we will derive a benefit value for each patient from the observed costs and effects
38
39 and then construct a regression model with treatment variable and collected explanatory variables.
40
41 Next, the costing information and number of life years' survival will be used in a decision-analytic
42
43 model to assess the cost-effectiveness of the single, high-dose arm against the control arm and also
44
45 against other combination treatment regimens from the ACTA trial. Results will be presented using
46
47 incremental cost-effectiveness ratios and cost-effectiveness acceptability curves generated by
48
49 Monte Carlo bootstrapping methods. This approach avoids the stochastic fallacy and will determine
50
51 if a single, high-dose L-AmB will be as or even more cost-effective compared to the current WHO
52
53 recommended first-line treatment.
54
55
56
57
58
59
60

1
2
3 An existing model will be adapted based on Jarvis et al., using the treatment sub-model (Figure
4 2)(17). The Markov model has a monthly cycle length, running the model for 12 cycles to calculate
5 annual costs and annual life years. We will supplement the model to be able to extrapolate data
6 beyond the period of observed follow-up. The Markov modelling framework allows for the synthesis
7 of data from secondary sources, like mortality risk from other causes and excess mortality risks(13).
8 It also allows for probabilistic sensitivity analyses. The other country teams will be able to use an
9 adapted model to enter their country specific data and costing information as well as estimated
10 survival figures, while using the pooled effectiveness information. In this way, each country will
11 arrive at valid country-specific economic estimates.
12
13
14
15
16
17
18
19
20
21
22

23 We will follow the CHEERS appraisal guidelines on economic evaluation(18). As our study is an
24 equivalence study using empirical data in a model-based analysis these guidelines we will also
25 include good modelling practice approaches(19).
26
27
28
29

30 We anticipate the development of five different country-specific costing tools for CM which can be
31 used to compose two five-country manuscripts concerning the cost-consequence of CM across sites
32 as well as the cost-effectiveness of the intervention across sites. In addition, individual country-level
33 publications will be allowed, using the whole five-country trial data base, complemented with local
34 more detailed country-level costing studies.
35
36
37
38
39
40

41 We intend to use these findings to provide an economic argument for the adoption of single, high-
42 dose L-AmB in low and middle-income countries and to help influence guidelines and policy. Another
43 important component of this study is capacity building across the African sites through the delivery
44 of a health economics course and the ongoing mentoring of individuals and teams at each of the
45 sites.
46
47
48
49
50
51

52 53 **ETHICS AND DISSEMINATION** 54 55 56 57 58 59 60

1
2
3 The Research Ethics Committee of the London School of Hygiene and Tropical Medicine have
4 approved the AMBITION trial protocol v2.1 07.11.17 which outlines this economic analysis (Ref
5 14355). Approval has also been granted by the following: University of Botswana Office of Research
6 and Development (UBR/RES/IRB/BIO/042), Botswana Ministry of Health and Wellness Health
7 Research and Development Division (HPDME:13/18/1), Princess Marina Hospital Research and Ethics
8 Committee (PMH 5/79(407-1-2017), University of Cape Town Human Research Ethics Committee
9 (642/2017), Malawi National Health Sciences Research Committee (1907), Mulago Hospital Research
10 and Ethics Committee (MHREC 1297) and the Medical Research Council of Zimbabwe
11 (MRCZ/A/2263). Any amendments will be submitted and approved by each ethics committee. All
12 participants will provide written informed consent or if lacking capacity will have consent provided
13 by a proxy. The findings of this economic analysis, which is embedded into the AMBITION trial, will
14 be disseminated through peer-reviewed publications and at international and country-level policy
15 meetings.

34 **DISCUSSION AND CONCLUSION**

35
36
37 This phase III clinical endpoint trial comparing single, high-dose liposomal amphotericin to the
38 control arm treatment at six sites across five counties will provide valuable information on the
39 comparative effectiveness with existing and other proposed strategies. This will be based on the
40 effectiveness of simplified treatment strategies as well on the possibly increased safety. The
41 proposed economic analysis of the equivalence trial for the Malawi situation will allow for a realistic
42 comparison with settings where there is very limited coverage of appropriate treatment of CM in
43 people with HIV. The estimates from other trial settings will help to document the generalizability of
44 our findings. The economic information will be essential in the support of wide-scale

1
2
3 implementation strategies and the formulation and testing of alternative delivery modes in all
4
5 comparable sub Saharan setting.
6
7

8 A clinically effective and safer treatment for CM in sub-Saharan Africa could have a dramatic impact
9
10 on HIV-associated mortality in the region. This economic analysis is essential to help justify any
11
12 policy change towards increasing the availability of more expensive medication if is proven to be
13
14 cost-effective. This process will enable the development of country-specific costing tools across five
15
16 African sites which can be utilised for future studies and will build capacity in the region.
17
18

19
20 **Authors Contributions:** PP and DSL jointly wrote the manuscript. DSL created the data collection
21
22 tools for the study. NY and SM have provided critical input into the data collection tools and
23
24 manuscript. DB, MH, CK, DM, MM, CM, HM, and CN are site investigators. MA, FB, CC, ED, EG, AH,
25
26 CM, RR, SS, LT, KT and DW are individuals responsible for the health economics sub-study at the
27
28 sites who have contributed to the refining of the data collection tools. TC, and DW are statisticians
29
30 for the study. TS and HM are health economists. TBC is international clinical adviser to the study. AL
31
32 is an expert adviser. DGM, GM and SJ provided expert input into the conceptualisation and design of
33
34 the broader study and this sub-study. TH and JNJ conceived and designed the broader study and are
35
36 the co-principal investigators. LN leads the Health Economics sub-study and has provided oversight
37
38 of the entire process. All authors read and approved the final manuscript.
39
40
41
42
43
44

45 **Funding:** The study is jointly funded through the European Developing Countries Clinical Trials
46
47 Partnership (EDCTP), the Swedish International Development Cooperation Agency (SIDA), and the
48
49 Wellcome Trust / Medical Research Council (UK) / UKAID Joint Global Health Trials.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Competing Interests:** JNJ and TSH were the recipients of a Gilead Investigator Initiated Award
4
5 (completed). TSH has received speaker fees from Gilead Sciences and Pfizer.
6
7

8 Figure 1. Economic Evaluation Flow Diagram: Trial Entry, Randomisation, Treatment and follow-up.
9

10
11 Figure 2. Simplified Markov model structure to evaluate the CM treatment(17).
12
13
14
15
16
17
18
19
20

21 REFERENCES

- 22
23
24 1. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of
25 disease of HIV-associated cryptococcal meningitis: an updated analysis. *The Lancet Infectious*
26 *diseases*. 2017;17(8):873-81.
27
28
29
30
31 2. Jarvis JN, Harrison TS. Forgotten but not gone: HIV-associated cryptococcal meningitis. *The*
32 *Lancet Infectious diseases*. 2016;16(7):756-8.
33
34
35
36
37 3. Hamill RJ, Sobel JD, El-Sadr W, Johnson PC, Graybill JR, Javaly K, et al. Comparison of 2 doses
38 of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-
39 associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and
40 safety. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of*
41 *America*. 2010;51(2):225-32.
42
43
44
45
46
47
48 4. Lestner J, McEntee L, Johnson A, Livermore J, Whalley S, Schwartz J, et al. Experimental
49 *Models of Short Courses of Liposomal Amphotericin B for Induction Therapy for Cryptococcal*
50 *Meningitis*. *Antimicrobial agents and chemotherapy*. 2017;61(6).
51
52
53
54
55
56
57
58
59
60

- 1
2
3 5. Jarvis J, Leeme T, Molefi M, Chofle AA, Bidwell G, Tsholo K, et al. Short Course High-dose
4 Liposomal Amphotericin B for HIV-associated Cryptococcal Meningitis: A phase-II Randomized
5 Controlled Trial. CID. 2018;published online June 26, 2018.
6
7
8
9
- 10 6. WHO. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in
11 HIV-infected adults, adolescents and children. Geneva: World Health Organisation; 2018 March
12 2018.
13
14
15
- 16 7. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. Antifungal
17 Combinations for Treatment of Cryptococcal Meningitis in Africa. The New England journal of
18 medicine. 2018;378(11):1004-17.
19
20
21
22
23
- 24 8. Campbell SJ, Osei-Atweneboana MY, Stothard R, Koukounari A, Cunningham L, Armoo SK, et
25 al. The COUNTDOWN Study Protocol for Expansion of Mass Drug Administration Strategies against
26 Schistosomiasis and Soil-Transmitted Helminthiasis in Ghana. Trop Med Infect Dis. 2018;3(1):10.
27
28
29
30
31
- 32 9. Handbook of the Botswana 2016 Integrated HIV Clinical Care Guidelines. Botswana: Republic
33 of Botswana Ministry of Health; 2016.
34
35
36
37
- 38 10. Menon V, Iyer P, Mosime W. Estimated resource needs for key health interventions offered
39 under Botswana's Essential Health Services Plan (2013-2018). Washington, DC: Futures Group,
40 Health Policy Project.; 2014.
41
42
43
44
- 45 11. Maheswaran H, Petrou S, MacPherson P, Choko AT, Kumwenda F, Lalloo DG, et al. Cost and
46 quality of life analysis of HIV self-testing and facility-based HIV testing and counselling in Blantyre,
47 Malawi. BMC medicine. 2016;14:34.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 12. Hendriks ME, Kundu P, Boers AC, Bolarinwa OA, Te Pas MJ, Akande TM, et al. Step-by-step
4 guideline for disease-specific costing studies in low- and middle-income countries: a mixed
5 methodology. *Global health action*. 2014;7:23573.
6
7
8
9
10 13. Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis
11 treatment strategies in resource-limited settings: a cost-effectiveness analysis. *PLoS medicine*.
12 2012;9(9):e1001316.
13
14
15 14. Medina Lara A, Kigozi J, Amurwon J, Muchabaiwa L, Nyanzi Wakaholi B, Mujica Mota RE, et
16 al. Cost effectiveness analysis of clinically driven versus routine laboratory monitoring of
17 antiretroviral therapy in Uganda and Zimbabwe. *PLoS One*. 2012;7(4):e33672.
18
19
20
21
22 15. Organization WH. Making choices in health: WHO guide to cost-effectiveness analysis. Tan-
23 Torres Edejer T, editor2003.
24
25
26
27
28
29
30 16. Span MM, TenVergert EM, van der Hilst CS, Stolk RP. Noninferiority testing in cost-
31 minimization studies: Practical issues concerning power analysis. *International journal of technology*
32 *assessment in health care*. 2006;22(2):261-6.
33
34
35
36
37 17. Jarvis JN, Harrison TS, Lawn SD, Meintjes G, Wood R, Cleary S. Cost effectiveness of
38 cryptococcal antigen screening as a strategy to prevent HIV-associated cryptococcal meningitis in
39 South Africa. *PloS one*. 2013;8(7):e69288.
40
41
42
43
44
45 18. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated
46 Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of
47 the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force.
48 *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes*
49 *Research*. 2013;16(2):231-50.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

19. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics*. 2006;24(4):355-71.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

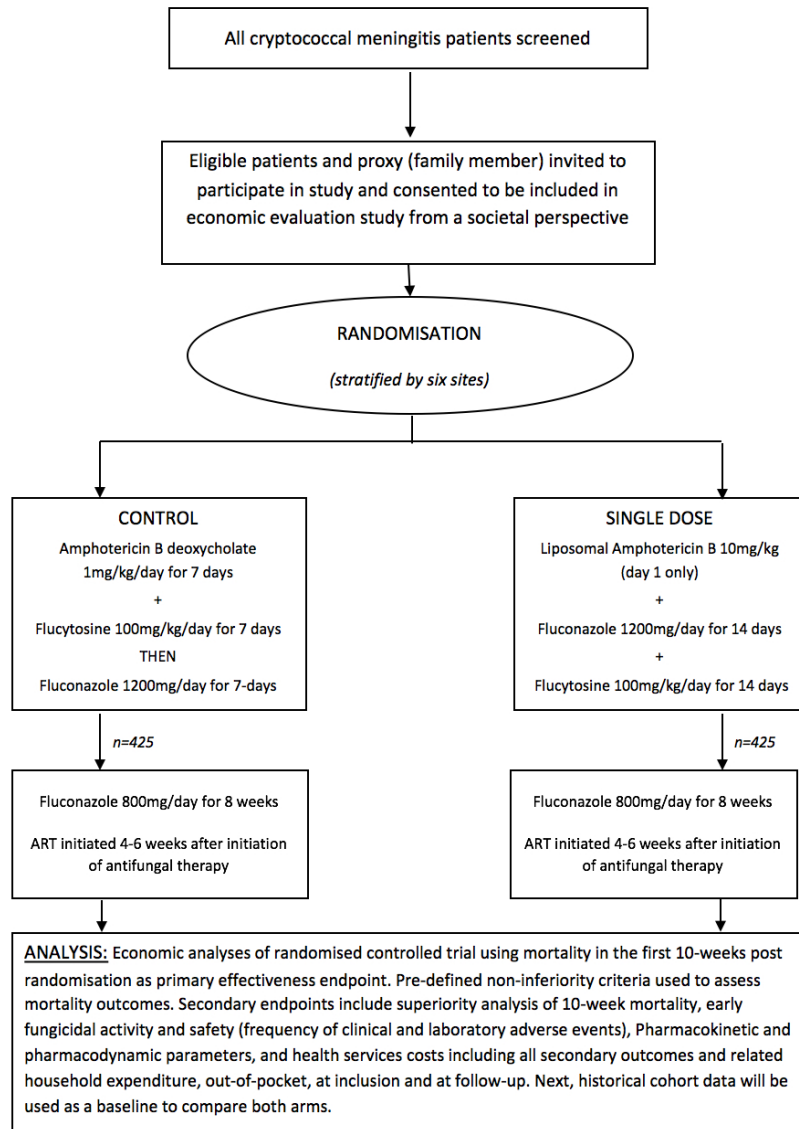


Figure 1. Economic Evaluation Flow Diagram: Trial Entry, Randomisation, Treatment and follow-up.

177x231mm (144 x 144 DPI)

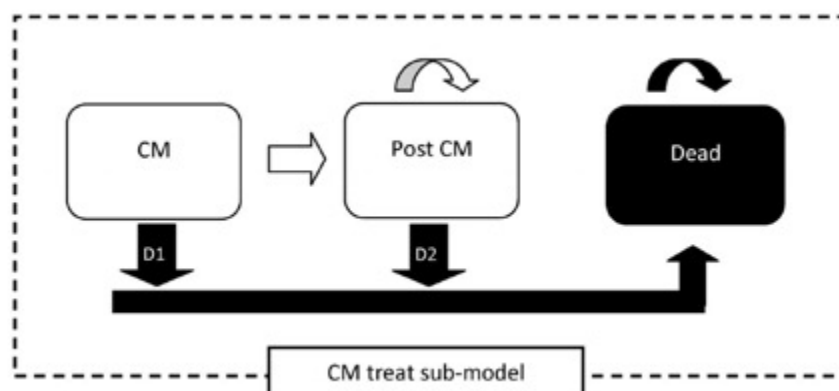


Figure 2. Simplified Markov model structure to evaluate the CM treatment(17).

159x73mm (72 x 72 DPI)

BMJ Open

**AMBIsome Therapy Induction Optimisation (AMBITION):
High dose Ambisome for Cryptococcal Meningitis Induction
Therapy in sub-Saharan Africa: Economic Evaluation
Protocol for a Randomised Controlled Trial Based
Equivalence Study**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026288.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Jan-2019
Complete List of Authors:	<p>Ponatshego, Ponego; Botswana-Harvard AIDS Institute Partnership, Clinical Trials Unit Lawrence, David; Botswana-Harvard AIDS Institute Partnership, Clinical Trials Unit; London School of Hygiene and Tropical Medicine Department of Clinical Research Youssof, Nabila; London School of Hygiene and Tropical Medicine, EPH; Botswana-Harvard AIDS Institute Partnership Molloy, Sile; St. George's University of London Alufandika, melanie; Malawi-Liverpool-Wellcome Trust Clinical Research Centre Bango, Funeka; Institute of Infectious Diseases and Molecular Medicine Boulware, David R.; Univ Minnesota Chawinga, Chimwemwe; Lilongwe Medical Relief Trust (UNC Project) Dziwani, Eltas; Malawi-Liverpool-Wellcome Trust Clinical Research Centre Gondwe, Ebbie; Malawi-Liverpool-Wellcome Trust Clinical Research Centre Hlupeni, Admire; University of Zimbabwe College of Health Sciences Hosseinipour, Mina C.; Kamuzu Cent Hosp Kanyama, Cecilia; Lilongwe Medical Relief Trust (UNC) Project Meya, David; Makerere University Mosepele, Mosepele; Botswana-Harvard AIDS Institute Partnership Muthoga, Charles; Botswana-Harvard AIDS Institute Partnership Muzoora, Conrad; Makerere University Mwandumba, Henry; Liverpool School of Tropical Medicine; Malawi Liverpool Wellcome Trust Clinical Research Programme Ndholvu, Chiratidzo; University of Zimbabwe College of Health Sciences Rajasingham, Radha; University of Minnesota sayed, sumaya; Institute of Infectious Diseases and Molecular Medicine Shamu, Shepherd; University of Zimbabwe College of Health Sciences Tsholo, Katlego; Botswana-Harvard AIDS Institute Partnership Tugume, Lillian ; Makerere University Williams, Darlisha; Makerere University Maheswaran, Hendramoorthy; University of Warwick Warwick Medical School Shiri, Tinevimbo; Liverpool School of Tropical Medicine BOYER-CHAMMARD, Timothée; Institut Pasteur Loyse, Angela; St George's University of London</p>

	Chen, T; Liverpool School of Tropical Medicine, Department of Clinical Sciences Wang, Duolao; Liverpool School of Tropical Medicine Lalloo, David; Malawi Liverpool Wellcome Trust Clinical Research Centre; Liverpool School of Tropical Medicine Meintjes, Graeme; University of Cape Town, Medicine Jaffar, Shabbar; Liverpool School of Tropical Medicine Harrison, Thomas; St George's University of London Jarvis, Joseph; Botswana-Harvard AIDS Institute Partnership; London School of Hygiene and Tropical Medicine Niessen, Louis; Liverpool School of Tropical Medicine, Health Economics; University of Warwick, Dept of Health Sciences
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Health economics, HIV/AIDS, Pharmacology and therapeutics
Keywords:	HEALTH ECONOMICS, HIV & AIDS < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES, Clinical trials < THERAPEUTICS, cryptococcal meningitis

SCHOLARONE™
Manuscripts

1
2
3 **AMBIsome Therapy Induction Optimisation (AMBITION): High dose Ambisome for Cryptococcal**
4 **Meningitis Induction Therapy in sub-Saharan Africa: Economic Evaluation Protocol for a**
5 **Randomised Controlled Trial Based Equivalence Study.**
6
7
8
9
10
11

12 Ponego Ponatshego (pponatshego@bhp.org.bw)^{1*}

13
14 David S Lawrence (david.s.lawrence@lshtm.ac.uk)^{1,2†*},

15
16 Nabila Youssouf (nabila.youssouf@lshtm.ac.uk)^{1,2},

17
18 Síle F. Molloy (smolloy@sgul.ac.uk)³,

19
20 Melanie Alufandika (malufandika@mlw.mw)⁴,

21
22 Funeka Bango (funeka.bango@hiv-research.org.za)⁵,

23
24 David R. Boulware (boulw001@umn.edu)^{6,7},

25
26 Chimwemwe Chawinga (cchawinga@unclilongwe.org)⁸,

27
28 Eltas Dziwani (eltas.nyirenda@live.com)⁴,

29
30 Ebbie Gondwe (egondwe@mlw.mw)⁴,

31
32 Admire Hlupeni (ahlupeni@gmail.com)⁹,

33
34 Mina C. Hosseinipour (mina_hosseinipour@med.unc.edu)⁸,

35
36 Cecilia Kanyama (ckanyama@gmail.com)⁸,

37
38 David B. Meya (david.meya@gmail.com)⁶,

39
40 Mosepele Mosepele (mosepele.mosepele@gmail.com)¹,

41
42 Charles Muthoga (chmuthoaga@gmail.com)¹,

43
44 Conrad Muzoora (conradmuzoora@yahoo.com)⁶,

45
46 Henry C. Mwandumba (henry.mwandumba@lstmed.ac.uk)^{4,10},

47
48 Chiratidzo E. Ndhlovu (mascen@mweb.co.zw)⁹,

49
50 Radha Rajasingham (radha@umn.edu)⁶,

1
2
3 Sumaya Sayed (sumaya.sayed@uct.ac.za)⁵,
4
5
6 Shepherd Shamu (shamushe@yahoo.com)⁹,
7
8 Katlego Tsholo (katlego.tsholo@yahoo.ie)¹,
9
10
11 Lillian Tugume (lilliqntugume18@gmail.com)⁶,
12
13
14 Darlisha Williams (darlisha@gmail.com)⁶,
15
16 Hendramoorthy Maheswaran (H.Maheswaran@warwick.ac.uk)¹¹,
17
18
19 Tinevimbo Shiri (tinevimbo.shiri@lstmed.ac.uk)¹⁰,
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Timothée Boyer-Chammard (timothee.boyer-chammard@pasteur.fr)¹²,
Angela Loyse (aloyse@sgul.ac.uk)³,
Tao Chen (tao.chen@lstmed.ac.uk)¹⁰,
Duolao Wang (doulao.wang@lstmed.ac.uk)¹⁰,
David G Laloo (david.laloo@lstmed.ac.uk)^{4,10},
Graeme Meintjes (graemein@mweb.co.za)⁵,
Shabbar Jaffar (shabbar.jaffar@lstmed.ac.uk)¹⁰,
Thomas S Harrison (tharriso@sgul.ac.uk)³,
Joseph N Jarvis (joseph.jarvis@lshtm.ac.uk)^{1,2*} and
Louis Niessen (louis.niessen@lstmed.ac.uk)^{10*}

1. Botswana-Harvard AIDS Institute Partnership, Gaborone, Botswana
2. Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK
3. Research Centre for Infection and Immunity, St George's University of London, London, UK
4. Malawi-Liverpool-Wellcome Trust Clinical Research Centre, Blantyre, Malawi
5. Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town,

1
2
3 South Africa
4

- 5 6. Infectious Diseases Institute, Makerere University, Kampala, Uganda
6
7 7. Department of Medicine, University of Minnesota, Minneapolis, MN, USA
8
9 8. Lilongwe Medical Relief Trust (UNC Project), Lilongwe, Malawi
10
11 9. Department of Medicine, University of Zimbabwe College of Health Sciences, Parirenyatwa
12 Hospital, Harare, Zimbabwe
13
14 10. Department of Clinical Sciences and International Public Health, Liverpool School of Tropical
15 Medicine, Liverpool, UK
16
17 11. Population Evidence and Technologies, University of Warwick, Coventry, UK
18
19 12. Molecular Mycology Unit and National Reference Centre for Invasive Mycoses, Institut Pasteur,
20 Paris, France
21
22
23
24
25

26
27 † Corresponding author: david.s.lawrence@lshtm.ac.uk +267 7652 4122
28

29 *Equal contribution
30
31
32
33
34

35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Word count: 4050

ABSTRACT

Introduction: Cryptococcal meningitis is responsible for around 15% of all HIV-related deaths globally. Conventional treatment courses with amphotericin-B require prolonged hospitalisation and are associated with multiple toxicities and poor outcomes. A phase II study has shown that a single high-dose of liposomal amphotericin may be comparable to standard treatment. We propose a phase III clinical endpoint trial comparing single, high-dose liposomal amphotericin with the WHO recommended first line treatment at six sites across five countries. An economic analysis is essential to support wide-scale implementation.

Methods and Analysis: Country-specific economic evaluation tools will be developed across the five country settings. Details of patient and household out of pocket expenses and any catastrophic healthcare expenditure incurred will be collected via interviews from trial patients. Health service patient costs and related household expenditure in both arms will be compared over the trial period in a probabilistic approach, using Monte Carlo bootstrapping methods. Costing information and number of life years survived will be used as the input to a decision-analytic model to assess the cost-effectiveness of a single, high-dose liposomal amphotericin to the standard treatment. In addition, these results will be compared to a historical cohort from another clinical trial.

Ethics and Dissemination: The AMBITION trial has been evaluated and approved by the London School of Hygiene and Tropical Medicine, University of Botswana, Malawi National Health Sciences, University of Cape Town, Mulago Hospital and Zimbabwe Medical Research Council research ethics committees. All participants will provide written informed consent or if lacking capacity will have consent provided by a proxy. The findings of this economic analysis, part of the AMBITION trial, will be disseminated through peer-reviewed publications and at international and country-level policy meetings.

Trial Registration: ISRCTN: 7250 9687 Date of Registration: 13/07/2017

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This economic analysis will provide evidence to inform policy decisions about the use of a more expensive medication in cryptococcal meningitis.
- This analysis will provide data that may justify initiatives to increase the availability of a more expensive medication in cryptococcal meningitis
- This approach will enable the development and application of country-level costing tools across five African country settings which can be re-utilised for future studies and contribute to capacity building in the region.
- The study is taking place at six large referral hospitals across five countries in East and Southern Africa and the results might not be representative or generalisable to remote rural areas or settings in other countries.

INTRODUCTION

Cryptococcal Meningitis (CM) is a severe fungal infection of the brain which occurs in advanced HIV infection. It is estimated that there are roughly 220,000 cases of CM globally per year with 73% of these occurring in sub-Saharan Africa. Annual global deaths are estimated at 181,000 and CM is responsible for approximately 15% of all AIDS-related deaths(1).

The current recommended first line treatment for CM is amphotericin B deoxycholate (AmBd). AmBd is associated with multiple drug-induced toxicities including anaemia, impaired renal function, electrolyte abnormalities and infusion related reactions which make it unsafe to administer in high doses. AmBd is also difficult to administer, requiring hospitalization for 7 to 14 days of intravenous infusions, depending on which oral antifungal it has been paired with. In addition, treatment outcomes are poor with acute mortality at 10-weeks ranging from 30-55%(2). The use of a liposomal form of amphotericin called Ambisome (hereafter referred to as L-AmB) is associated with reduced drug induced-toxicities when compared to conventional AmBd(3). The long tissue half-life and effective penetration into the brain tissue of L-AmB has prompted research into the effectiveness of treatment with short courses of high-dose L-AmB(4). The AMBisome Therapy Induction Optimisation (AMBITION) phase II clinical trial conducted in Botswana and Tanzania found that a single, high-dose of 10mg/kg L-AmB was well tolerated and led to a non-inferior reduction in fungal burden in cerebrospinal fluid when compared to standard 14-day courses of 3mg/kg L- AmB(5). This dosing strategy is now being taken to a clinical endpoint trial.

The phase III AMBITION trial is a phase III open label randomised control non-inferiority trial to compare single, high-dose L-AmB treatment to the WHO first-line recommended regimen of a 7-day course of AmBd based treatment in avoiding all-cause mortality in HIV-associated CM (Figure 1)(6, 7). Eligible patients will be randomised to receive either:

1. L-AmB 10 mg/kg day 1 given with 14-days of fluconazole 1200mg/day and flucytosine 100mg/kg/day

1
2
3 (single dose) or
4

- 5 2. Amphotericin B deoxycholate 1 mg/kg/d for 7-days given with 7-days of flucytosine 100mg/kg/day
6 followed by 7-days of fluconazole 1200mg/day (control arm).
7
8
9

10
11 After the 2-week induction phase all patients will receive fluconazole 800 mg/day to 10 weeks and
12 200 mg/day thereafter. ART will be commenced 4 to 6 weeks after initiation of antifungal therapy.
13
14 The trial will enroll 850 patients across six sites in five countries in Africa: Gaborone, Botswana (90);
15 Blantyre (230) and Lilongwe (110), Malawi; Cape Town, South Africa (80); Kampala, Uganda (110)
16 and Harare, Zimbabwe (230). All participants will be invited to take part in the economic evaluation
17 study.
18
19
20
21
22
23
24

25
26 The use of L-AmB has potential implications for both clinical outcomes and healthcare costs. The
27 widespread availability of L-AmB has previously been limited by the high cost of therapy: currently
28 the internationally listed price is \$85 per 50mg vial compared to \$8 per 50mg vial of AmBd. The
29 listed cost per patient of the medication for the single dose arm in this trial will be \$996 versus \$132
30 for the control arm. However, the impact of a potentially more clinically effective intervention that is
31 associated with fewer drug-induced toxicities and a reduced length of hospital stay may offset this
32 expense. An argument for widening access to L-AmB has been strengthened since, in September
33 2018, Gilead announced as part of the expanded access preferential pricing programme for visceral
34 leishmaniasis to include cryptococcal meningitis. While the normal cost in other countries varies
35 from US\$80 to US\$400, the drug will now be available for US\$16.25 in 116 low and middle-income
36 countries(8). This could have a dramatic impact on mortality(9).
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51
52 We plan an economic analysis to estimate the cost consequences and the cost-effectiveness of
53 short-course L-AmB treatment, compared to the control arm, in five individual country settings
54 across sub-Saharan Africa. The findings will also be compared to a historical cohort from the recently
55 completed Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial. The ACTA trial
56
57
58
59
60

1
2
3 recruited patients in Cameroon, Malawi, Tanzania and Zambia and compared treatment outcomes
4
5 among individuals receiving one of five different treatment regimens, including the control arm used
6
7 in the AMBITION trial(10). The purpose of this comparison is to identify any change in costs over
8
9 time, any gross variation in health service costs between the AMBITION and ACTA cohorts, and to
10
11 enable comparison of the cost-effectiveness of the short course L-AmB with the other regimens
12
13 tested in ACTA(11).
14
15

16
17
18 The hypotheses are that the short course treatment:

- 19
20
21 1. Will show a zero-net societal cost change or that there will be societal cost savings from the short L-
22
23 AmB treatment and an equivalent or increased effectiveness of the treatment reducing mortality
24
25 over a patient life time.
26
27 2. Will be cost-effective in terms of life years saved over a patient lifetime when compared to historical
28
29 cohorts who received different combination treatment regimens in a recently completed clinical
30
31 trial.
32
33
34

35 These analyses will aim to provide the economic evidence to support wide-scale implementation of
36
37 short-course L-AmB treatment across sub-Saharan settings.
38
39
40

41 **OBJECTIVES:**

42
43 The main objective of the economic analysis is to assess the cost-effectiveness of single, high-dose L-
44
45 AmB compared to the control arm treatment regimen for HIV associated CM across the five country
46
47 settings in six sites.
48
49
50

51 **Secondary Objectives:**

- 52
53
54 • To assess the cost-consequences from the societal and health service perspective of single, high-
55
56 dose L-AmB compared to the control arm across the five country settings.
57
58 • To assess the total health service costs per patient at each country site.
59
60

- To assess out-of-pocket expenses incurred by patients and households at all trial sites.
- To assess the percentage of catastrophic household expenditure experienced by patients at each trial site.
- To compare the total societal costs per patient and cost-effectiveness of a single, high-dose L-Amb with historical cohorts that received different treatment regimens within the ACTA trial.

METHODS AND ANALYSIS

Study Design

The study is a prospective economic evaluation from the societal perspective – including both health service and patient related perspectives - comparing the costs and effectiveness of the two interventions at each of the six trial sites across the five country settings. The two key components of this study are the collection of data concerning personal expenditure on health and the development of country costing tools, which will be applied to data concerning health-service costs collected within the trial.

Household expenditure

To estimate the societal costs at the patient and household level, they or their representatives will be interviewed at two points in time: within the first five days of randomisation and at their final face-to-face follow-up at week 10. The questionnaires, based on those used in the ACTA trial and further developed for this study, are designed to estimate their personal healthcare expenditure in the four weeks leading up to enrolment and during the trial. A summary of the questions included in the questionnaire are presented in Table 1. In addition, the out-of-pocket health care expenditure by the individual and their household, loss of income incurred due to illness, and loss of labour time of the patients themselves and their carers will be collected using methods adopted in trials of a similar nature(12).

Table 1: Structure of the health economics questionnaire for the AMBITION study.

- Personal health expenditure including on consultations, medication, travel time and costs
- Relative and/or household health expenditure in relation to the patient's condition
- The duration and severity of the illness episode
- Loss of productivity and time off work for both patient and relative/s
- Profession and educational attainment of patient
- Profession and educational attainment of the person who earns the highest income (if not the patient)
- Access to social security, welfare support and health insurance
- Household expenditure on food, utilities, rent and large purchases such as cars, furniture and electrical items to assess the socio-economic status of the household
- The need for temporary loans or the sale of assets to fund health care and other costs in relation to the illness episode
- The level of disability and care needs of the patient

The interview questions will preferably be asked directly to the patient. If the patient is confused or has reduced consciousness due to CM, a relative or next-of-kin may provide proxy consent for them to enroll in the trial. It is unlikely that this person will be fully aware of the patient's financial situation and in these cases, it may be necessary to wait for the patient to recover before asking them directly. In cases where patients have prolonged confusion or are felt to have a poor prognosis then these questions can be asked of the proxy. Data will be collected by study doctors and nurses and entered into the trial Electronic Data Capture (EDC) system: a uniform database to be utilised across all sites. An interview guide for those collecting data from patients will ensure that nuances and country specific idioms are acknowledged.

1
2
3 The above methods have been developed through an iterative process. Initially the lead Health
4 Economist, who led on the ACTA cost-effectiveness analysis, and members of the Trial Management
5 Group developed the data collection tools and integrated these into the wider trial EDC. This was
6 later refined following a one-week meeting of health economists and study team members from
7 across the AMBITION sites held in Blantyre, Malawi in November 2017. This provided the
8 opportunity for experts working in this field and individuals who will collect data from patients to
9 improve these tools by collecting and entering data from fabricated patients. Feedback was then
10 integrated into both the data collection methods and the EDC and shared for final approval across
11 the AMBITION consortium until a consensus was reached.
12
13
14
15
16
17
18
19
20
21
22
23

24 **Country-specific costing approaches**

25 Presently, each site has differing levels of experience with conducting economic analyses and has
26 varied access to validated country costing tools. As stated, the preparation of the trial included a
27 one-week workshop with at least two team members from each site to assess the face-validity and
28 completeness of the questionnaire, to practice electronic data entry of the completed questionnaire,
29 carrying costing computations, and to increase the knowledge and understanding of economic
30 evaluation. In each country, resource use data will be collected using an ingredients-based approach.
31 The data on individual resource use will be collected from all participants onto case-report forms.
32 Overhead costs, including costs of admissions and laboratory tests, will be collated from the hospitals'
33 financial and utilisation documents.
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 Botswana Harvard AIDS Institute Partnership (BHP): Gaborone, Botswana

49 BHP will use a micro-costing approach to estimate CM treatment in Botswana from a single health
50 provider's perspective, in this case, from the Ministry of Health and Wellness perspective. The total
51 of related costs i.e. patient-specific treatment cost and 'hotel costs' to cover CM treatment will be
52 determined as per the 2016 Botswana HIV Treatment Guidelines(13). All costs of pharmaceuticals
53 will be taken from the listed tender prices at the Central Medical Stores, which procure stock and
54
55
56
57
58
59
60

1
2
3 distribute pharmaceuticals and healthcare commodities to all government healthcare facilities. This
4 package will provide an estimate of 'patient specific' costs of uncomplicated CM. 'Hotel costs' will
5 determine the necessary hospital, staffing, capital and infrastructure requirements as the patient is
6 admitted over a seven-day period. Data will be obtained from Princess Marina Hospital, which is the
7 biggest, and main referral hospital in Botswana. Staff salaries will be taken from the Government of
8 Botswana salary scales for health professionals. By combining this treatment costing data with the
9 meningitis burden data generated through a previously completed audit we will also generate an
10 estimate of the total current costs to the Botswana health service of treating CM. The data will
11 complement the 'Estimated resource needs for key health interventions offered under Botswana's
12 Essential Health Services Plan (2013-2018)' that project the cost of all health programs, including the
13 treatment of CM, from 2013 to 2018 and will also be used as a reference for the next version of this
14 document to be published in 2019(14).

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31 Malawi Liverpool Wellcome Trust Clinical Research Centre: Blantyre, Malawi.

32 Standardised national health costing data is not available in Malawi. An existing costing tool which
33 was developed for a HIV testing study will be adapted(15). Patient-related health care costs will be
34 obtained from the Central Medical Stores Trust, the only supplier mandated to supply government
35 health facilities in Malawi. Personnel costs will be refined by referencing the Malawi government
36 salary structures and payroll and estimating the proportion of health personnel time taken in the
37 clinical care of the patient, as well as allowance costs for patients working out of working hours.
38 Programme-related costs will be adapted using the results from recent costing studies within the
39 Queen Elizabeth Central Hospital(15).

40
41
42
43
44
45
46
47
48
49
50
51
52 University of North Carolina Project: Lilongwe, Malawi.

53 Most of costing data for Lilongwe will be obtained using the same methods as that outlined above
54 for Blantyre. In addition, local programme-related costs will be estimated and projected through a
55 local costing study within the Kamuzu Central Hospital. This adaptation will be based on existing
56
57
58
59
60

1
2
3 local costing data as part of the Driving Reduced AIDS-associated Meningo-encephalitis (DREAMM)
4
5 study, which will be shared with the AMBITION consortium.
6
7
8

9
10 University of Cape Town: Cape Town, South Africa.

11
12 There are currently no costing tools for primary data collection for disease specific costing of CM
13
14 treatment in South Africa. A costing tool will be developed from validated disease specific costing
15
16 tools for the South African context(16). Costs from the health service (Department of Health)
17
18 perspective will be collected using the ingredients costing approach and captured in an Excel
19
20 spreadsheet. The quantity of resources used to treat CM in each study arm will be estimated from
21
22 the trial and patient records. Prices for these treatment related ingredients will be obtained from
23
24 the various service providers within the Department of Health that are responsible for offering the
25
26 products and services. Specific activities by staff will be identified and estimated through the review
27
28 of routinely collected time sheets. Human resource costs as well as recurrent and capital costs will
29
30 be allocated using hospital expenditure and financial records as well as records from the Provincial
31
32 Department of Health. The average cost of each treatment component will be calculated by
33
34 multiplying the quantity of resources used by the unit price. From this we can calculate the cost per
35
36 case of CM treated by multiplying the average cost by the number of times a particular cost has
37
38 been incurred.
39
40
41
42
43

44 Infectious Diseases Institute: Kampala, Uganda.

45
46 Though there is a high burden of CM in Uganda, the costs associated with treatment have not been
47
48 formally outlined in a costing tool. Previous research describing the costs of treatment used
49
50 informally gathered estimates for treatment and management of the disease based on reports from
51
52 various sources including local pharmacies, laboratories and the Ugandan Ministry of Health(17).
53
54 The Uganda team will create a systematic costing tool for CM. This tool will consider the costs of
55
56 treatment as well as the costs borne by the patients being treated. The creation of this tool will
57
58 involve input from the Ministry of Health as well as the major suppliers of medications. We will
59
60

1
2
3 engage these organizations and other key stakeholders to ascertain the current costs of meningitis
4 treatment and develop a costing tool which can be adjusted in the future should costs change.
5
6
7
8
9

10 University of Zimbabwe School of Health Sciences: Harare, Zimbabwe.

11 Clinical cost data will be collected alongside the clinical trial using micro-costing methodologies. The
12 economic evaluation will be done from the societal perspective to enable the study to assess the
13 overall household economic impact of CM and will enable us to determine the patient and provider
14 unit costs. This study is powered enough to detect both country specific clinical and economic
15 differences. Direct patient level clinical activity data such as drugs, staff time, diagnostics, pathology
16 and radiology will be collected alongside the trial and relevant unit costs determined using the study
17 protocol. In other cases, prices for drugs, diagnostic and radiology tests will be collected from the
18 National Pharmaceutical Company of Zimbabwe, national reference diagnostic and radiology
19 laboratories, and from consultations with experts. Indirect and overhead costs such as management
20 and administration costs, utilities and other capital costs for in-patient days will be determined using
21 data from Parirenyatwa Hospital, Harare financial records, the WHO Choice Database and from
22 previous clinical trials that took place at the proposed site(18, 19).
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 **Data collection and data management**

40 Data collected and validated using the EDC system will be stored in an electronic database that is
41 protected using a scheme of authentication and encryption. Paper documents, such as clinical notes
42 and administrative documentation will be kept in a secure location and held for 5 years after the end
43 of the trial. During this period, all data should be accessible to the competent or equivalent
44 authorities, the Sponsor and other relevant parties with suitable notice. Security of electronic
45 records and data is a significant concern. All components of the distributed data systems will use
46 authentication and encryption to render subject identity and personal health information unusable,
47 unreadable, or indecipherable to unauthorized individuals. Full Drive Encryption will be
48 implemented at the hardware layer of all devices storing protected health information. A three-
49 factor scheme will be used to authenticate users through the hardware layer to the application layer
50
51
52
53
54
55
56
57
58
59
60

1
2
3 where personal health information is available. The applications will have user profiles to control
4 access to certain data and reports. The application and database layers will use a combination of
5 hashing and encryption for sensitive and personal data. Mobile devices and the staff operating them
6
7 will not be equipped with the encryption keys to decrypt selected sensitive data fields.
8
9
10

11 12 13 14 **Confidentiality**

15
16 The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki
17 2008, the principles of Good Clinical Practice and applicable national regulations. We plan to follow
18 the principles of the UK Data Protection Act (DPA) regardless of the countries where the trial is
19 being conducted. Consent forms will be stored under the supervision of each local primary
20 investigator in a secured office and accessible to trial staff only. The database will not hold personal
21 details as participants are identified by their study number throughout the trial.
22
23
24
25
26
27
28
29
30

31 **Data analysis**

32
33 As outlined above, information on resource use and number of units used will be collected at
34 patient-level through the EDC, as part of the trial, and through additional separate country
35 costing studies. To validate and refine the data collection process, an early analysis will take place
36 at each site after ten patients have completed the ten-week study follow-up period.
37
38
39
40
41
42
43

44 Upon closure of the study full data analysis will commence. Firstly, an empirical cost-consequence
45 analysis will take place, using empirical individual patient data on societal resource use and unit cost
46 based on the results from the costing studies(20). Both societal and health care perspectives are
47 chosen, and health service patient costs including household costs, treatment cost and
48 hospitalisations in both arms will be compared over the trial period in a probabilistic approach, using
49 Monte Carlo bootstrapping methods. To handle the heterogeneity of the trial population in within
50 trial evaluation, we will derive a benefit value for each patient from the observed costs and effects
51 and then construct a regression model with treatment variable and collected explanatory variables.
52
53
54
55
56
57
58
59
60

1
2
3 Next, the costing information and number of life years' survival will be used in a decision-analytic
4 model to assess the cost-effectiveness of the single, high-dose arm against the control arm and also
5 against other combination treatment regimens from the ACTA trial. A Markov model has been chosen
6 as it allows to explicitly account for passage of time to calculate time dependent costs and life years of
7 the remaining life span. Results will be presented using incremental cost-effectiveness ratios and
8 cost-effectiveness acceptability curves generated by Monte Carlo bootstrapping methods. This
9 approach avoids the stochastic fallacy and will determine if a single, high-dose L-AmB will be as or
10 even more cost-effective compared to the current WHO recommended first-line treatment. An
11 existing model will be adapted based on Jarvis et al., using the treatment sub-model (Figure 2)(21).
12 The Markov model has a monthly cycle length, running the model for 12 cycles to calculate annual
13 costs and annual life years. We will supplement the model to be able to extrapolate data beyond the
14 period of observed follow-up. The Markov modelling framework also allows for the synthesis of data
15 from secondary sources, like mortality risk from other causes and excess mortality risks(17). It also
16 allows for probabilistic sensitivity analyses. We are going to use non-parametric bootstrapping to
17 assess uncertainties, and both deterministic and probabilistic sensitivity analyses to examine the impact
18 of all relevant parameters on the incremental cost-effectiveness ratio. The other country teams will be
19 able to use an adapted model to enter their country specific data and costing information as well as
20 estimated survival figures, while using the pooled effectiveness information. In this way, each
21 country will arrive at valid country-specific economic estimates.

22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46 We will follow the CHEERS appraisal guidelines on economic evaluation(22). As our study is an
47 equivalence study using empirical data in a model-based analysis these guidelines we will also
48 include good modelling practice approaches(23).
49
50
51

52
53
54 We anticipate the development of five different country-specific costing tools for CM which can be
55 used to compose two five-country manuscripts concerning the cost-consequence of CM across sites
56 as well as the cost-effectiveness of the intervention across sites. In addition, individual country-level
57
58
59
60

1
2
3 publications will be allowed, using the whole five-country trial data base, complemented with local
4
5 more detailed country-level costing studies.
6
7
8

9
10 We intend to use these findings to provide an economic argument for the adoption of single, high-
11
12 dose L-AmB in low and middle-income countries and to help influence guidelines and policy. Another
13
14 important component of this study is capacity building across the African sites through the delivery
15
16 of a health economics course and the ongoing mentoring of individuals and teams at each of the
17
18 sites.
19

20 21 22 **Patient and Public Involvement**

23
24 For the primary AMBITION clinical trial, a number of the sites have well developed community
25
26 groups and are experienced in engaging local communities when undertaking such studies. These
27
28 groups were consulted prior to trial implementation, and they will be consulted regularly during trial
29
30 conduct. To engage the wider community, we will work with community groups, HIV patient groups
31
32 and local Ministries of Health to provide information about the trial, disseminate the results, and to
33
34 develop health education materials aimed at dispelling the current beliefs around meningitis, and
35
36 encouraging early care-seeking.
37
38
39
40
41

42 **ETHICS AND DISSEMINATION**

43
44 The Research Ethics Committee of the London School of Hygiene and Tropical Medicine have
45
46 approved the AMBITION trial protocol v2.1 07.11.17 which outlines this economic analysis (Ref
47
48 14355). Approval has also been granted by the following: University of Botswana Office of Research
49
50 and Development (UBR/RES/IRB/BIO/042), Botswana Ministry of Health and Wellness Health
51
52 Research and Development Division (HPDME: 13/18/1), Princess Marina Hospital Research and
53
54 Ethics Committee (PMH 5/79(407-1-2017), University of Cape Town Human Research Ethics
55
56 Committee (642/2017), Malawi National Health Sciences Research Committee (1907), Mulago
57
58 Hospital Research and Ethics Committee (MHREC 1297) and the Medical Research Council of
59
60

1
2
3 Zimbabwe (MRCZ/A/2263). Any amendments will be submitted and approved by each ethics
4 committee. All participants will provide written informed consent or if lacking capacity will have
5 consent provided by a proxy. The findings of this economic analysis, which is embedded into the
6 AMBITION trial, will be disseminated through peer-reviewed publications and at international and
7 country-level policy meetings.
8
9
10
11
12

13 14 15 16 **DISCUSSION AND CONCLUSION**

17
18 This phase III clinical endpoint trial comparing single, high-dose liposomal amphotericin to the
19 control arm treatment at six sites across five counties will provide valuable information on the
20 comparative effectiveness with existing and other proposed strategies. This will be based on the
21 effectiveness of simplified treatment strategies as well on the possibly increased safety. The
22 proposed economic analysis of the equivalence trial for the Malawi situation will allow for a realistic
23 comparison with settings where there is very limited coverage of appropriate treatment of CM in
24 people with HIV. The estimates from other trial settings will help to document the generalizability of
25 our findings. The economic information will be essential in the support of wide-scale
26 implementation strategies and the formulation and testing of alternative delivery modes in all
27 comparable sub-Saharan setting.
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 A clinically effective and safer treatment for CM in sub-Saharan Africa could have a dramatic impact
43 on HIV-associated mortality in the region. This economic analysis is essential to help justify any
44 policy change towards increasing the availability of more expensive medication if is proven to be
45 cost-effective. This process will enable the development of country-specific costing tools across five
46 African sites, which can be utilised for future studies and will build capacity in the region.
47
48
49
50
51

52
53
54 **Authors Contributions:** PP and DSL jointly wrote the manuscript with contribution on the methodology
55 from TS, LN, TH and JNJ. PP is a study doctor in Gaborone, Botswana. DSL is the international lead
56 clinician for the trial and created the initial data collection tools for this sub-study. NY is the trial manager
57
58
59
60

1
2
3 and SFM is the trial epidemiologist and both have provided critical input into the data collection tools,
4 electronic data capture system and this manuscript. DB, MH, CK, DM, MM, CM, HM, and CN are principal
5 investigators at each of the sites and will oversee the development of costing tools and the collection of
6 data at each site. MA, FB, CC, ED, EG, AH, CM, RR, SS, LT, KT and DW are all study team members or
7 affiliated academics who attended the Ambition health economics course and are the focal individuals
8 for the health economics study at their respective sites, as well as contributing to the refining of the data
9 collection tools and the country specific sections of this manuscript. TC, and DW are statisticians for the
10 study and have contributed to the database function of the electronic data capture system. TS and HM
11 are health economists who have contributed to the development of the methodology and TS will perform
12 the early reviews of data and the overall data analysis with DSL. TBC is an international clinical adviser
13 and a monitor who performs data checks for the study. AL, DGL, GM and SJ provided expert input into
14 the conceptualisation and design of both the broader study and this health economics study, particularly
15 in terms of adopting a societal perspective. TH and JNJ conceived and designed the broader study and are
16 the co-principal investigators. LN leads the health economics study and has provided oversight of the
17 entire process. All authors read, critiqued and approved the final manuscript.

18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37 **Funding:** The study is jointly funded through the European Developing Countries Clinical Trials
38 Partnership (EDCTP), the Swedish International Development Cooperation Agency (SIDA), and the
39 Wellcome Trust / Medical Research Council (UK) / UKAID Joint Global Health Trials.

40
41
42
43
44
45
46 **Competing Interests:** JNJ and TSH were the recipients of a Gilead Investigator Initiated Award
47 (completed). TSH has received speaker fees from Gilead Sciences and Pfizer.

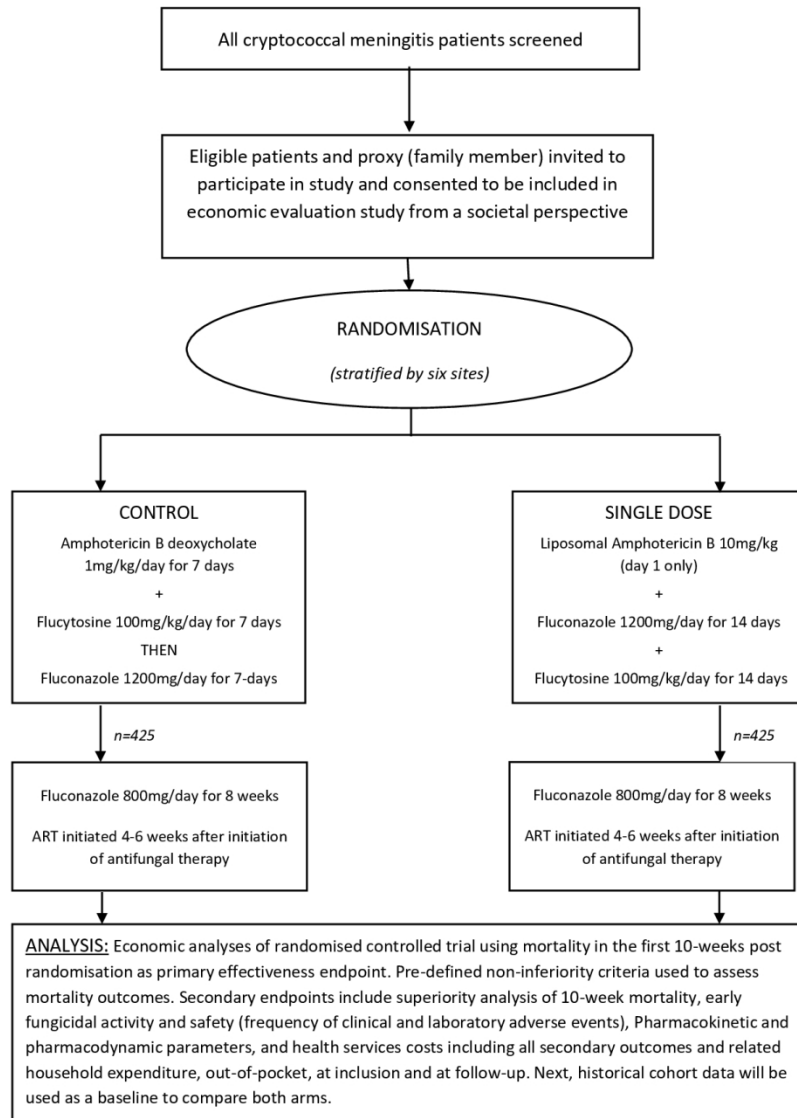
48
49
50
51
52 Figure 1. Economic Evaluation Flow Diagram: Trial Entry, Randomisation, Treatment and follow-up.

53
54 Figure 2. Simplified Markov model structure to evaluate the CM treatment(21).

REFERENCES

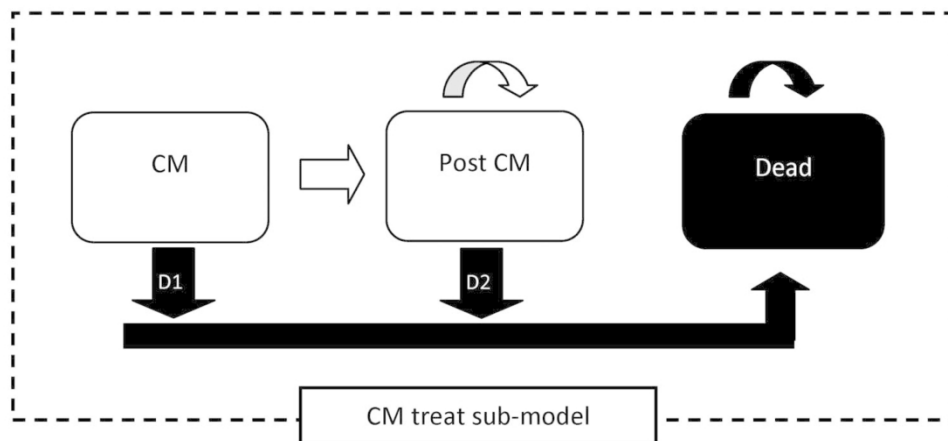
1. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *The Lancet Infectious diseases*. 2017;17(8):873-81.
2. Jarvis JN, Harrison TS. Forgotten but not gone: HIV-associated cryptococcal meningitis. *The Lancet Infectious diseases*. 2016;16(7):756-8.
3. Hamill RJ, Sobel JD, El-Sadr W, Johnson PC, Graybill JR, Javaly K, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2010;51(2):225-32.
4. Lestner J, McEntee L, Johnson A, Livermore J, Whalley S, Schwartz J, et al. Experimental Models of Short Courses of Liposomal Amphotericin B for Induction Therapy for Cryptococcal Meningitis. *Antimicrobial agents and chemotherapy*. 2017;61(6).
5. Jarvis J, Leeme T, Molefi M, Chofle AA, Bidwell G, Tsholo K, et al. Short Course High-dose Liposomal Amphotericin B for HIV-associated Cryptococcal Meningitis: A phase-II Randomized Controlled Trial. *CID*. 2018;published online June 26, 2018.
6. WHO. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organisation; 2018 March 2018.
7. Lawrence DS, Youssouf N, Molloy S, Alanio A, Alufandika M, Boulware DR, et al. AMBIsome Therapy Induction Optimisation (AMBITION): High Dose Ambisome for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: Study Protocol for a Phase 3 Randomised Controlled Non-Inferiority Trial. *Trials*. 2018;In Press.
8. Gilead Sciences Announces Steep Discounts for Ambisome to Treat Cryptococcal Meningitis in Low - and Middle-Income Countries [press release]. Internet, September 7th 2018 2018.
9. Lawrence DS, Boyer-Chammard T, Jarvis JN. Emerging concepts in HIV-associated cryptococcal meningitis. *Current opinion in infectious diseases*. 2019;32(1):16-23.
10. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. *The New England journal of medicine*. 2018;378(11):1004-17.
11. Chen T, Lakhi S, Chanda D, Mwaba P, Molloy S, Gheorghe A, et al. ACTA Trial Team. Health care costs and deaths prevented by ACTA trial treatments for cryptococcal meningitis: A comparison between 5 induction strategies in sub Saharan Africa. 22nd International AIDS Conference; 2018; Amsterdam2018.
12. Campbell SJ, Osei-Atweneboana MY, Stothard R, Koukounari A, Cunningham L, Armoo SK, et al. The COUNTDOWN Study Protocol for Expansion of Mass Drug Administration Strategies against Schistosomiasis and Soil-Transmitted Helminthiasis in Ghana. *Trop Med Infect Dis*. 2018;3(1):10.
13. Wellness MoHa. Handbook of the Botswana 2016 Integrated HIV Clinical Care Guidelines. Gaborone, Botswana; 2016.
14. Menon V, Iyer P, Mosime W. Estimated resource needs for key health interventions offered under Botswana's Essential Health Services Plan (2013-2018). Washington, DC; 2014.
15. Maheswaran H, Petrou S, MacPherson P, Choko AT, Kumwenda F, Lalloo DG, et al. Cost and quality of life analysis of HIV self-testing and facility-based HIV testing and counselling in Blantyre, Malawi. *BMC medicine*. 2016;14:34.
16. Hendriks ME, Kundu P, Boers AC, Bolarinwa OA, Te Pas MJ, Akande TM, et al. Step-by-step guideline for disease-specific costing studies in low- and middle-income countries: a mixed methodology. *Global health action*. 2014;7:23573.
17. Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis. *PLoS medicine*. 2012;9(9):e1001316.

- 1
2
3 18. Medina Lara A, Kigozi J, Amurwon J, Muchabaiwa L, Nyanzi Wakaholi B, Mujica Mota RE, et
4 al. Cost effectiveness analysis of clinically driven versus routine laboratory monitoring of
5 antiretroviral therapy in Uganda and Zimbabwe. *PloS one*. 2012;7(4):e33672.
6
7 19. WHO. Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva: World
8 Health Organisation; 2003.
9 20. Span MM, TenVergert EM, van der Hilst CS, Stolk RP. Noninferiority testing in cost-
10 minimization studies: Practical issues concerning power analysis. *International journal of technology*
11 *assessment in health care*. 2006;22(2):261-6.
12 21. Jarvis JN, Harrison TS, Lawn SD, Meintjes G, Wood R, Cleary S. Cost effectiveness of
13 cryptococcal antigen screening as a strategy to prevent HIV-associated cryptococcal meningitis in
14 South Africa. *PloS one*. 2013;8(7):e69288.
15 22. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated
16 Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of
17 the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force.
18 *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes*
19 *Research*. 2013;16(2):231-50.
20 23. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-
21 analytic modelling in health technology assessment: a review and consolidation of quality
22 assessment. *PharmacoEconomics*. 2006;24(4):355-71.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Economic Evaluation Flow Diagram: Trial Entry, Randomisation, Treatment and follow-up.

117x155mm (300 x 300 DPI)



Simplified Markov model structure to evaluate the CM treatment.