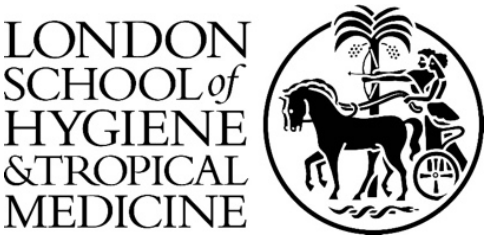

THE LIVED EXPERIENCE OF PARTICIPANTS IN AN AFRICAN RANDOMISED TRIAL

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DECLARATION OF OWN WORK

I, David Stephen Lawrence, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Background: The AMBITION-cm trial aimed to define a novel treatment approach for HIV-associated cryptococcal meningitis. I aimed to explore inclusion and representation in trials for cryptococcal meningitis, and to critically interpret qualitative data around clinical trials for life-threatening illnesses. I then used ethnographic methods to explore the lived experience of those involved in the AMBITION-cm trial.

Methods: I systematically searched research databases and performed a meta-analysis of clinical trials for cryptococcal meningitis, and a critical interpretive synthesis of qualitative data collected from participants in trials from life-threatening illnesses. I embedded an ethnographic study within AMBITION-cm in Botswana and Uganda, utilising in-depth interviews and direct observations and analysed data thematically.

Results: In the meta-analysis, 39 papers were included. Trials had evolved with the epidemiology of cryptococcal meningitis, however severe and relapse cases were underrepresented, as were female researchers and researchers from LMICs in authorship. Twenty-two papers were included in the critical interpretive synthesis to produce a synthetic construct describing how the life-threatening illness overwhelmingly impacts decision-making. Eighty-nine individuals were recruited into the ethnographic study. Pathways to care were extremely convoluted and I identified multiple recommendations for improvement. Participants had a complex decision-making process to navigate, and decisions were made based on a therapeutic expectation from the trial. The AMBITION-cm regimen was acceptable to patients and providers.

Conclusions: Trials for cryptococcal meningitis are typically conducted in line with the epidemiology of the disease however some groups are under-represented. There are significant gaps in routine healthcare systems for people living with advanced HIV. Challenges in managing cryptococcal meningitis may be averted by the convenience and acceptability of the AMBITION-cm regimen. The life-threatening nature of an illness has a critical impact on the experience of enrolling into a trial and the decision to enrol in AMBITION-cm was based on a therapeutic expectation.

PREFACE

This thesis is presented in a research paper style. The Background is followed by two Methods sections. Each Methods section contains considerably more detail than was typically presented in the research papers. The first Methods section relates to two systematic reviews and is followed by the two resultant review papers. The second Methods section relates to an ethnographic study and is followed by four research papers. The first is a protocol paper and this is followed by a summary of the recruitment into this PhD study, the AMBITION-cm trial results, and then three results papers. Each of the three results papers are prefaced by linking pages which aim to create a cohesive narrative. This thesis therefore includes a total of six research papers: three of which have been published with the remaining three submitted for publication, including one which is in press. Each of the six research papers are prefaced with an overview, including brief summaries of the results and their implications, the publication status, and contribution of other researchers. The research papers are followed by a discussion, conclusion, and an appendix containing the relevant supplementary material for each research paper followed by additional relevant publications.

ACKNOWLEDGEMENTS

The greatest thanks go to the individuals who participated in this study who gave up their time and shared their personal experiences, particularly those who were recovering from cryptococcal meningitis and who had already given so much to the AMBITION-cm trial. Thanks to all of those who worked on the trial, who gave up their evenings, weekends, and nights to care for participants, particularly Siphokazi, an excellent nurse and fierce advocate who is dearly missed. Your acts of selflessness and dedication have inspired me to become a better doctor and a kinder person.

I would never have moved to Gaborone had it not been for Fiona Cresswell, my long-suffering work wife, who convinced me to apply for the job working on AMBITION-cm, and who, along with Liam and the children, hosted me in Kampala on countless occasions. Without your encouragement I may never have met Joe Jarvis who took a chance on me and entrusted me with this important role, taking me under his wing and teaching me all there is to know about clinical trials, camping in the Kalahari, and everything in between. Through Joe I met Chelsea, Miles, and Nick who kept me sane and grounded, particularly during my final year in Gaborone, and showed us all the corners of Botswana. Joe encouraged me to play to my strengths and pursue this PhD and our long discussions in the office helped to shape every piece of this work.

I never thought I would meet someone who replied to emails faster than me. Let alone someone who would take on a potential PhD student they had never heard of who, very subtly, asked for advice on a research idea in the hope of finding a supervisor. Thanks to Janet Seeley for supervising this thesis, introducing me to her wide network of social scientists, and

listening to my long, rambling streams of consciousness as I tried to form coherent arguments when analysing data. Janet introduced me to Agnes who is an exceptional colleague and now a great friend, and to Georgina whose warm, caring nature encouraged participants to share their stories. Thanks to David Meya for supporting this study in Kampala and for demonstrating all the qualities of a true leader, and the entire team at the Infectious Diseases Institute, particularly Laura Nsangi who was always available to help with a favour (or three).

Thanks to Tom Harrison for the continued mentorship and dependable positivity. Thanks to the National Institute for Health and Care Research (UK) who funded my research expenses and to the European Developing Countries Clinical Trials Partnership (EDCTP), the Swedish International Development Cooperation Agency (SIDA) and the Wellcome Trust / Medical Research Council (UK) / UKAID Joint Global Health Trials for funding AMBITION-cm and my salary.

Life in Gaborone was never dull. Thanks to the entire team in the AMBITION-cm office for the warm welcome, showing me around Gabs, and for all the runs, parties, and braais. Nametso, Katlego, Ponego, Siamisang, Norah, Kwana, and Miss Fifs made me feel like one of the family, and Tshepo continues to be a dependable sounding board. Thanks to the community of activists in Gaborone who welcomed me into their networks and taught me so much. Neo and Lebo, without your hard work, determination, and humour we never would have finished data collection and Ken, Mos, Mo, Alex, James, and Becky, you all made life during the pandemic bearable, maybe even fun at times.

Friends overseas were never far away and always had an ear to lend or a sofa to spare. Thanks to Enoch for inspiring me, Dom and Emma for your enduring friendship, Rishi for your guidance and cheerleading skills, and Moe for your boundless optimism. Thanks to my family, and most of all, thanks to Chris.

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AHD	Advanced HIV Disease
AMBITION-cm	AMBIsome Therapy Induction OptimisatioN
ART	Antiretroviral Therapy
BHP	Botswana Harvard AIDS Institute Partnership
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CM	Cryptococcal Meningitis
COVID-19	Coronavirus Disease 2019
CrAg	Cryptococcal Antigen
DSD	Differentiated Service Delivery
EDCTP	European and Developing Countries Clinical Trials Partnership
GCS	Glasgow Coma Scale
HICs	High-Income Countries
HIV	Human Immunodeficiency Virus
IDI	In-depth Interview
L-AmB	Liposomal Amphotericin B
LMICs	Low- and Middle-Income Countries
LSHTM	London School of Hygiene and Tropical Medicine
NIHR	National Institute for Health and Care Research
PLWH	People Living with HIV
sSA	sub-Saharan Africa
SRHR	Sexual and reproductive health and rights

CHAPTER ONE: BACKGROUND

Preamble

In 2017 I moved to Gaborone, Botswana to become the lead clinician for a large multi-site trial called AMBIsome Therapy Induction OptimisatioN (AMBITION-cm). AMBITION-cm aimed to define a novel treatment regimen for HIV-associated cryptococcal meningitis, hereafter referred to as cryptococcal meningitis, a potentially fatal complication of advanced HIV disease (AHD) and the second leading cause of all AIDS-related mortality. The trial became my life for five years, and still is to an extent. This role was an incredible opportunity to build on my clinical training in HIV medicine, my burgeoning interest in research, and my experience working in sub-Saharan Africa. In addition, the trial provided a rich context to continue my postgraduate training in medical anthropology. The concept of this thesis emerged naturally over the course of my first year working on AMBITION-cm, as I immersed myself in the trial and the research context. The value of an anthropological perspective became evident for a number of reasons I will discuss here. Of course, how to frame the research questions and the specific methods required to answer them did not come quite so naturally however I was fortunate to be surrounded by mentors who could help me with that.

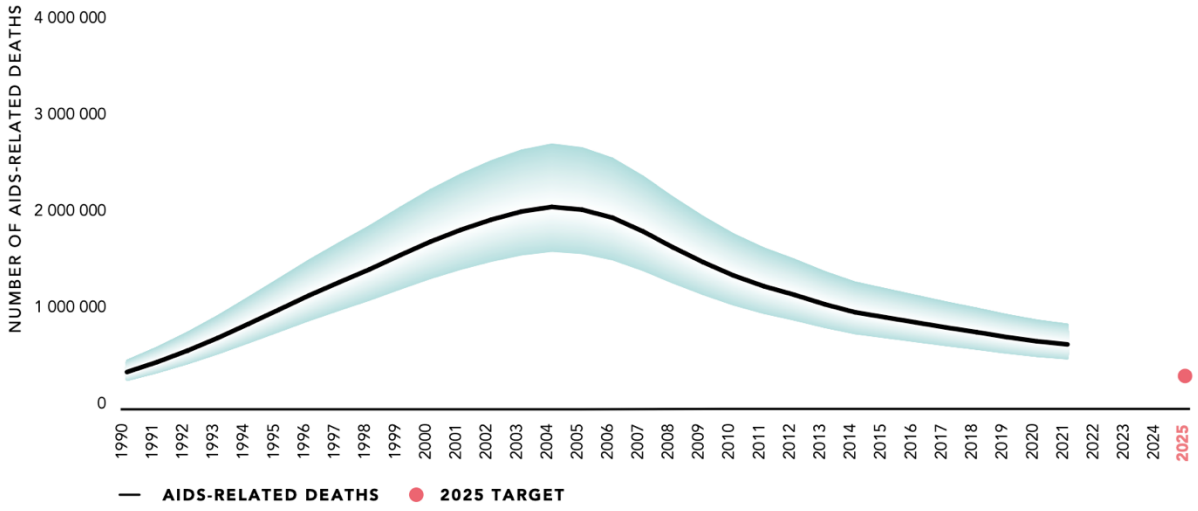
Within this background chapter I will summarise extensive epidemiological data which demonstrate the burden and persistence of AHD in sub-Saharan Africa and how devastating cryptococcal meningitis has been, and continues to be, among this group. I will also summarise the limited qualitative methods research conducted around cryptococcal meningitis to date. Then I will present an overview of AMBITION-cm and outline the aspects of the trial which prompted me to conduct this research before discussing more broadly the

bioethical issues around clinical trials for life-threatening illnesses. I will conclude by presenting my research aim and objectives.

The continued burden of Advanced HIV Disease

An estimated 650,000 people died from AIDS-related complications in 2021 (UNAIDS, 2022). This figure is a 68% reduction from the peak of 2.1 million people who died in 2004 (UNAIDS, 2004), however over the last decade the rate of decline has decreased significantly (Figure 1). In 2020 UNAIDS set a target to reduce annual AIDS deaths to below 250,000 by 2025 (UNAIDS, 2020) but if current trends continue 460,000 people are projected to die of AIDS-related causes in that year. These deaths occur primarily in people living with HIV (PLWH) who have advanced HIV disease (AHD) and a CD4 count of less than 200cells/µL. People with AHD are particularly vulnerable to potentially fatal opportunistic infections such as tuberculosis and cryptococcal meningitis, as well as malignancies such as cervical cancer and lymphoma (Egger et al., 2002).

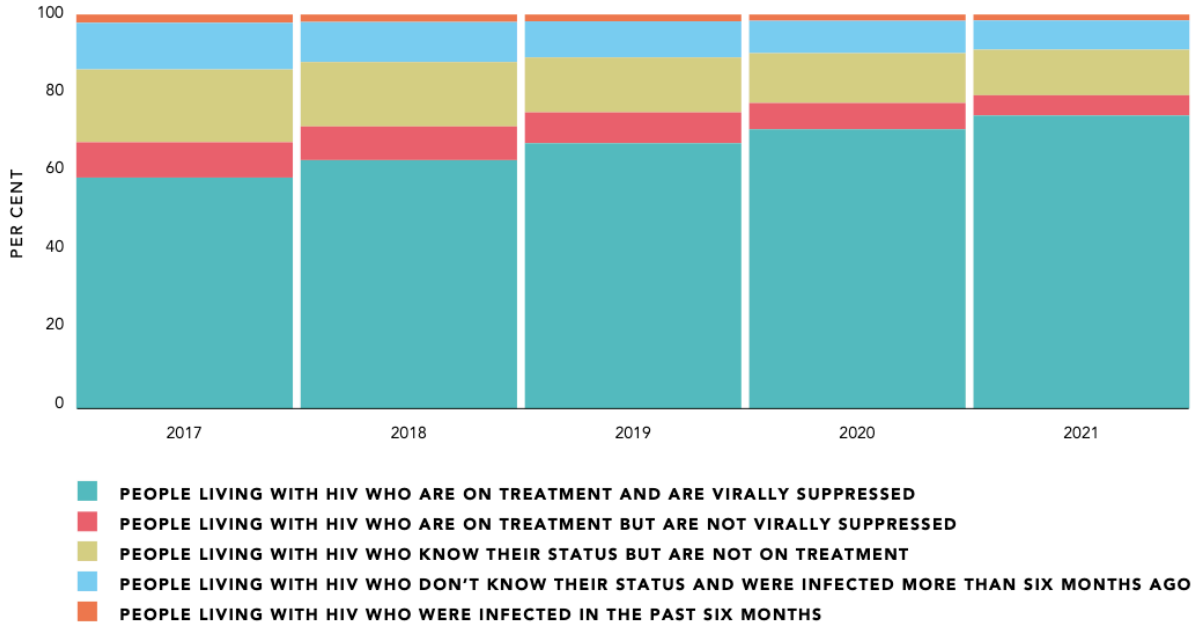
Figure 1: Number of AIDS-related deaths globally from 1990-2021 and the UNAIDS 2025 target (UNAIDS, 2022).



There remains a relatively constant population of people living with HIV who are diagnosed with AHD (Carmona et al., 2018). This is an extremely heterogeneous population but can be crudely categorised into two groups.

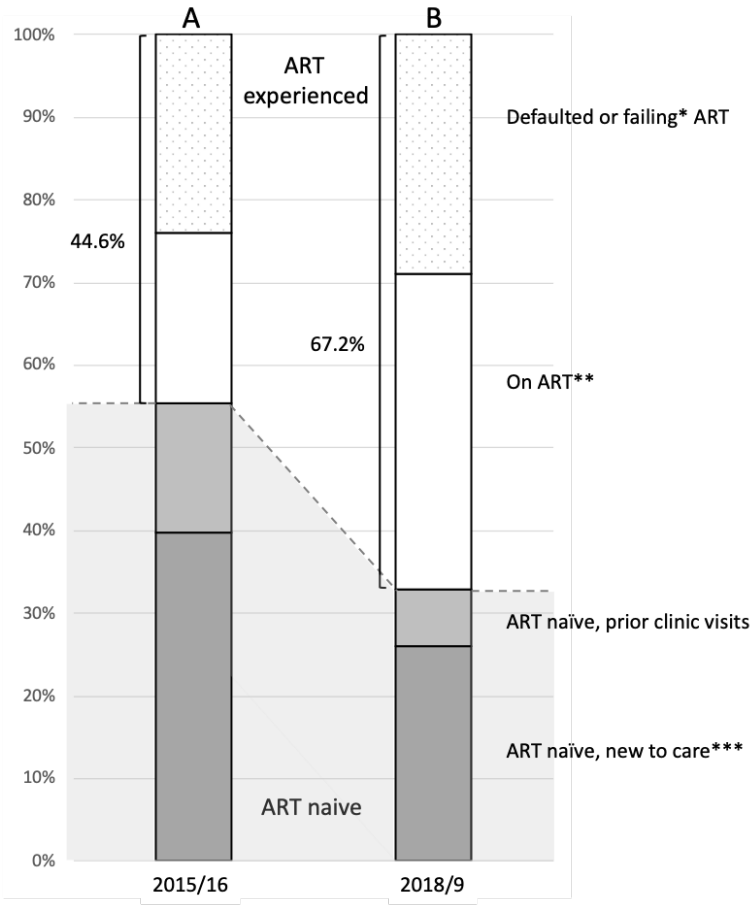
The first are individuals who have AHD upon initial diagnosis of HIV, indicating that a considerable length of time has lapsed between acquiring HIV and undergoing testing. These individuals who are living with undiagnosed HIV infection are in essence part of the first 90 outlined in the UNAIDS 90-90-90 targets which were first launched in 2014 (UNAIDS, 2014). There has been extensive research conducted to explore reasons as to why individuals may not test for HIV. Briefly, these include healthcare provider factors such as availability of testing in terms of location, time, and modality as well as healthcare worker attitudes and fears around stigma and confidentiality (Hlongwa et al., 2019; Meyerson et al., 2021). Individual factors include knowledge around HIV; a low perception of risk of HIV acquisition; feeling healthy; stigma, and fear (MacPhail et al., 2009; Mitchell et al., 2010). In general, this group of people who are living with undiagnosed HIV infection is falling globally as shown in Figure 2 below which demonstrates that in southern and eastern Africa the proportion of PLWH who were unaware of their status, depicted by the combined blue and orange bars, has been decreasing over time (UNAIDS, 2022). Although the number of new diagnoses may be decreasing, recent data from South Africa (Carmona et al., 2018), Nigeria (Otubu et al., 2022), and Botswana (Leeme et al., 2021) indicate that roughly 32.9%, 47.6% and 24.8% of people have AHD at diagnosis. We can therefore expect there will still be a constant, albeit potentially falling, proportion of people with AHD who are those with newly diagnosed HIV.

Figure 2: HIV testing and treatment cascade among adults (aged 15+ years) in eastern and southern Africa, 2017-2021 (UNAIDS, 2022).



The second group are more heterogeneous and are individuals who have been previously diagnosed with HIV and develop AHD over time. These individuals may never have linked to care and are therefore antiretroviral therapy (ART) naïve or they may have had challenges with ART toxicity and intolerance, difficulties with adherence, and drug resistance. Data suggest that this is an increasingly large proportion of people with AHD and that it is not uncommon for individuals to move 'backwards' along the care cascade and develop AHD in the process. For example, our data from Botswana and presented in Figure 3 below found that between 2015-16, 40% of all individuals with a CD4 count <100 cells/µL were new to care compared to 26% in 2018-19 (Lawrence et al., 2021c). These data indicate that the epidemiology of AHD is changing, with more ART-experienced PLWH presenting which, in general, makes their clinical management more challenging than those who are ART-naïve as complex decisions are required around ART prescribing (Alufandika et al., 2020).

Figure 3: ART status of individuals presenting with very advanced HIV disease (CD4 count ≤100 cells/μL) in Gaborone, Botswana, prior to universal treatment in 2015/16 (A) and following the introduction of universal antiretroviral therapy in 2018/19 (B).



The stubborn epidemiology of cryptococcal meningitis

HIV-associated cryptococcal meningitis is the second leading cause of AIDS-related mortality (Rajasingham et al., 2022). As with AHD, the burden of cryptococcal meningitis persists and the most recent Global Burden of Disease estimates have indicated that although the number of annual cases globally has reduced from an estimated 223,100 (95% CI 150,600 – 282,400) to 152,000 (111,000 – 185,000) between 2014 and 2020, the proportion of all AIDS-related mortality attributed to cryptococcal meningitis has increased from 15% to 19%. Recent programmatic data from South Africa and Botswana indicate that the number of cases has stayed relatively constant in recent years (Osler et al., 2018; Tenforde et al., 2017).

Cryptococcal meningitis primarily affects people with very advanced HIV disease, typically with a CD4 count less than 100 cells/µL (Lawrence et al., 2019). Meningitis is the most serious manifestation of cryptococcal disease, which is caused by *Cryptococcus spp,* a ubiquitous fungus that enters the lungs through inhalation of spores. In immunocompetent individuals this exposure rarely leads to any disease or impact on health, however among individuals with severely weakened immune systems, such as those with AHD, the fungus can spread throughout the body, including to the brain. This spread is a state called cryptococcal antigenaemia and can be detected by a point of care blood test called a cryptococcal antigen (CrAg) (Jarvis et al., 2009). Screening the blood of people with AHD provides the opportunity to identify the presence of *Cryptococcus* in the blood and attempt to avert its onward spread, and many high-prevalence countries have national CrAg screening programmes, although these are implemented variably (Greene et al., 2021).

Cryptococcal meningitis can also develop shortly after ART initiation, often within several weeks but sometimes up to six months later, as an unmasking Immune Reconstitution Inflammatory Syndrome (IRIS). In this situation the ART stimulates immune recovery which then leads to a previously undiagnosed or subclinical infection being 'unmasked' by a large inflammatory reaction (Lawrence et al., 2019). A similar phenomenon can occur if ART is initiated when someone is already suffering from clinical cryptococcal meningitis and has not received adequate antifungal therapy in what is termed a paradoxical IRIS, in which the initiation of ART leads to worsening or a recurrence of symptoms. To avert this, ART is initiated 4-6 weeks after antifungal therapy (Boulware et al., 2014). Similarly, if an ART regimen needs to be switched around the time someone is diagnosed with cryptococcal meningitis this is also delayed for 4-6 weeks (Alufandika et al., 2020).

If meningitis does occur, the prevailing symptom is headache, and this can be followed by a myriad of other symptoms including confusion, seizures, and coma. Left untreated, cryptococcal meningitis is uniformly fatal. Death can arise from the direct impact of the fungus on the brain but also from impedance of the normal flow of fluid around the brain which leads to raised intracranial pressure and can result in coning, in which the brainstem is pushed down through the base of the skull. Cryptococcal meningitis must be diagnosed with a lumbar puncture in which a needle is inserted into the bottom of the spinal column to obtain cerebrospinal fluid and the same procedure is also warranted, often daily, to reduce raised intracranial pressure.

Progress in outcomes from cryptococcal meningitis

Outcomes among individuals diagnosed with cryptococcal meningitis have historically been very poor. For a long time, the oral antifungal fluconazole was the mainstay of treatment, and this drug was widely available but associated with roughly 70% of patients dying within a year (Gaskell et al., 2014; Longley et al., 2008; Nussbaum et al., 2010; Rothe et al., 2013). Outcomes can be improved when fluconazole is given in combination with a 14-day course of an intravenous antifungal called amphotericin B deoxycholate, however this drug is notoriously toxic and prolonged courses can cause renal impairment and anaemia (Bicanic et al., 2015). In clinical trial settings the mortality at ten weeks with this treatment regimen is roughly 40% (Beardsley et al., 2016; Molloy et al., 2018) but in the real world this figure is closer to 50% (Azzo et al., 2018). Observational data consistently demonstrate that outcomes in cryptococcal meningitis trials are better than when using the same drugs in routine care (Tenforde et al., 2020), a point we shall return to later.

There have been significant advances in recent years following a landmark trial which demonstrated that mortality rates below 30% were possible. The Advancing Cryptococcal Treatments for Africa trial found that shorter, seven-day courses of amphotericin B deoxycholate could be administered if the oral antifungal was changed from fluconazole to flucytosine (Molloy et al., 2018). In this trial, with this regimen, the mortality at 10 weeks was 24%, a significant improvement, with the explanation being that the flucytosine had a stronger antifungal effect which justified shorter courses of amphotericin B and reduced the associated toxicity. ACTA ultimately led to the World Health Organisation (WHO) in 2017 updating their guidelines for the management of cryptococcal meningitis in resource-limited settings (WHO, 2018).

Despite the improvement in outcomes observed in the ACTA trial, and the move towards novel, shorter courses of intravenous treatment for cryptococcal meningitis (Moeng et al., 2020), the preferred regimen still contained one-week of amphotericin B deoxycholate. However, even one week of amphotericin B deoxycholate was associated with toxicities and administering and monitoring seven days of intravenous amphotericin posed logistical challenges in many clinical settings. An alternative formulation of amphotericin was available. Liposomal amphotericin (L-AmB, AmBisome, Gilead Sciences Inc) was commonly prescribed for 14-days to treat cryptococcal meningitis in high-income countries (HICs) and was known to be associated with fewer toxicities (Nelson et al., 2011; Saag et al., 2000). However, L-AmB was expensive and required a large cumulative dose if given over 14 days, but it was hypothesised that its high tolerability could potentially make it possible to administer a single, high-dose of treatment for cryptococcal meningitis.

The AMBITION-cm trial

Liposomal amphotericin had been recognised as being potentially well suited for use in short-course induction treatment for cryptococcal meningitis as it can be given at high doses, owing to lower rates of drug-induced toxicity (Adler-Moore et al.; Groll et al.; Hamill et al., 2010), a long tissue half-life (Adler-Moore et al.; Groll et al.; Gubbins et al., 2009; Hope et al., 2012; O'Connor et al., 2013), and effective penetration into brain tissue (Adler-Moore et al.; Groll et al.; Vogelsinger et al., 2006). The concept of single, high-dose treatment with L-AmB had been established in the treatment of another neglected tropical diseases, visceral leishmaniasis (Sundar et al., 2010), and pharmacokinetic data from animal models and humans indicated that increasing L-AmB dosing from the currently recommended 3–4 mg/kg given routinely in HICs may lead to improved outcomes in cryptococcal meningitis, and that very short-course regimens may be as effective as daily therapy (Albert et al.; Hope et al., 2012; Lestner et al.; O'Connor et al., 2013).

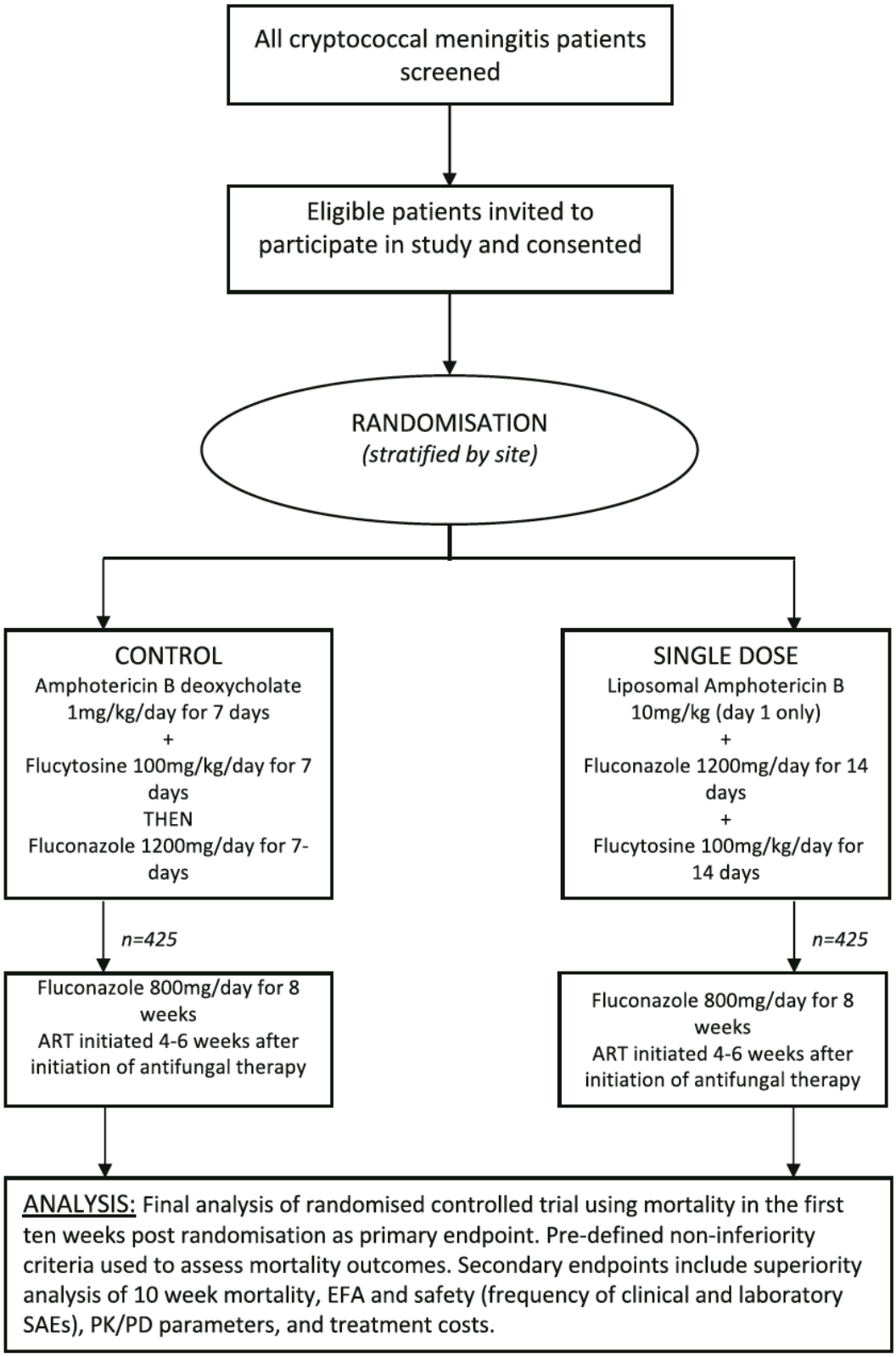
This led to the conceptualisation of the AMBIsome Therapy Induction OptimisatioN (AMBITION-cm) trials. I joined the AMBITION-cm team at the end of their phase-II clinical trial examining the efficacy of three different short-course L-AmB regimens. The team trialed a single 10mg/kg high dose of L-AmB given on day one, two high doses of L-AmB given on days one and three (10mg/kg and 5mg/kg) , and three high doses of L-AmB given on days one, three and seven (10mg/kg, 5mg/kg, and 5mg/kg), and compared all three with a control regimen of 14 daily, standard doses of 3mg/kg (Jarvis et al., 2018). Eighty participants were recruited across Botswana and Tanzania and the results demonstrated that the rate of clearance of *Cryptococcus* from the cerebrospinal fluid around the brain in all three short-course, high-dose arms was non-inferior to the control arm. Maximal effect was achieved

with the single 10mg/kg L-AmB dose with no evidence of additional benefit with further doses. The high-dose L-AmB was also well tolerated compared with prior experience in trials using amphotericin B deoxycholate (Bicanic et al., 2015).

The AMBITION-cm phase III trial was therefore planned, based on the findings of the phase-II trial, and with the need for an objective endpoint of all-cause mortality. AMBITION-cm aimed to establish a definitive treatment regimen for cryptococcal meningitis and therefore combined this single, high-dose of liposomal amphotericin with both flucytosine and fluconazole. This regimen was tested against the WHO recommended standard of care, as defined by the ACTA trial (Figure 4).

In summary, AMBITION-cm planned to recruit 850 participants between 2019 and 2021. Patients consented for themselves if they had decision making capacity however if they were confused or comatose then a surrogate decision maker consented on their behalf. These participants then re-consented for themselves if they regained decision making capacity. Participants were followed up daily during their initial inpatient admission (roughly two-weeks in duration) and then every two weeks as an outpatient until they completed the study at ten-weeks. Throughout the study participants had their medical expenses paid for and they also received transport reimbursements to attend outpatient appointments. The full protocol for the trial is presented elsewhere and is available in Appendix 10 (Lawrence et al., 2018).

Figure 4: AMBITION-cm Phase III trial study schema

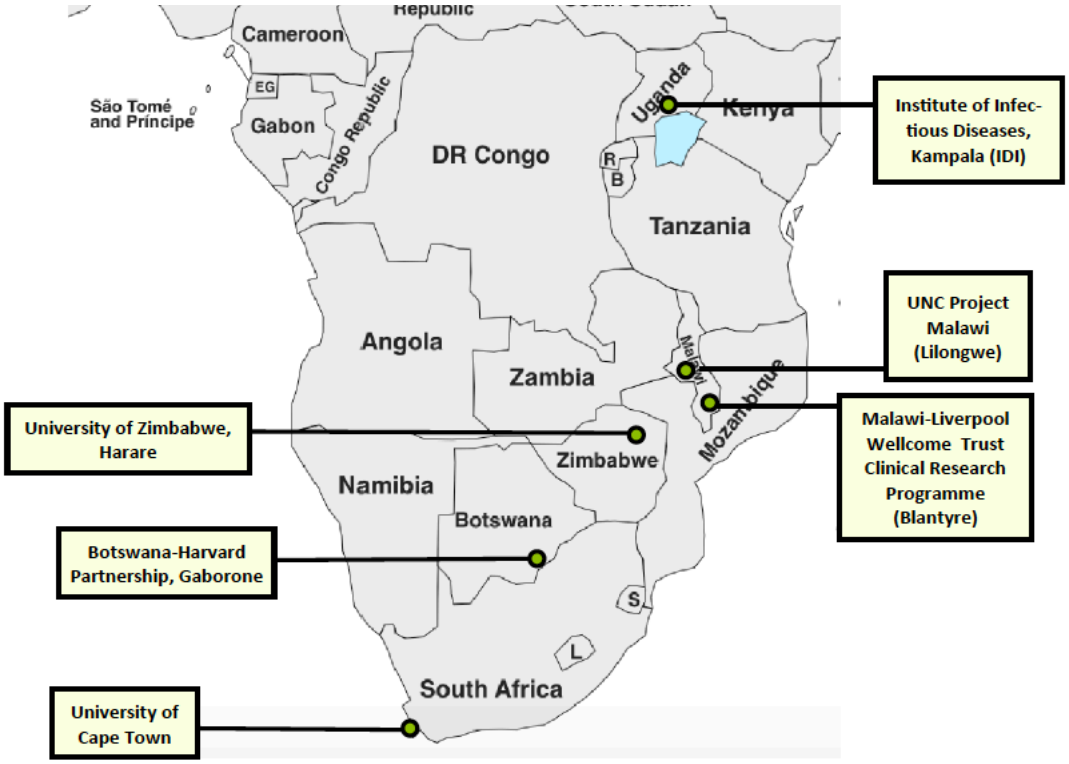


Situating myself within the AMBITION-cm trial

My first visit to Botswana was when I moved there in 2017. I was employed by the London School of Hygiene and Tropical Medicine (LSHTM) and seconded to the Botswana Harvard AIDS Institute Partnership (BHP) where I was based full-time. My role was as International Lead Clinician and under the guidance of the two co-Chief Investigators, Professors Joe Jarvis and Tom Harrison, I was delegated with responsibility for the clinical oversight of the trial. Along with core colleagues, a Trial Manager and a Clinical Adviser, I worked to ensure the trial was conducted in accordance with the protocol, international principles of clinical research and done so consistently across sites.

Within two days of moving to Gaborone we held the First Investigators Meeting where I met collaborators on the trial from both Africa and Europe. The funders were the European and Developing Countries Clinical Trials Partnership (EDCTP), and the trial sponsor was LSHTM. The recruiting sites had been carefully chosen, based on a high incidence of cryptococcal meningitis, proven track record in clinical trials, and strong relationships between senior researchers. The trial was planning to recruit from eight hospitals in six cities across five countries in southern and eastern Africa (Figure 5). In addition, there were European partners from St George's University London, the Liverpool School of Tropical Medicine, University of Liverpool and Institut Pasteur.

Figure 5: A map showing the locations of the research institutions recruiting AMBITION-cm trial participants



Within my first week I went on what became the first of many trips to each of the African sites, meeting with the teams, learning about the research institutions, and visiting the hospitals where AMBITION-cm participants would be recruited. As I gradually made my way to each of these sites to start planning the immense logistical challenge of implementing a clinical trial, I started to become familiar with the healthcare setting within which the trial would be operating. This built on previous experience visiting Uganda several times a year since 2010 for a combination of tourism, charity work, and placements in different hospitals. During my time in Gaborone, I also quickly began spending time working on the medical wards and in the busy outpatient HIV clinic at Princess Marina Hospital. It was these first few months that helped me to situate myself within the trial but also to situate the trial within the existing healthcare system. Within the next section I will outline those aspects of the trial and its context which led to the development of this thesis.

Framing the research aim and objectives

I will discuss how the development of cryptococcal meningitis represents failure across the HIV care cascade and highlight the lack of in-depth, qualitative methods data to explore the lived experience of this infection. Within this thesis I use the term lived experience to mean learning from an individual's first-hand experience of a particular situation, rather than the specific phenomenological method of enquiry and analysis. Next, I will outline the bioethical complexities of a clinical trial which provides a superior standard of care to that which would routinely be available and consider the therapeutic misconception. I then discuss more broadly my interest in how individuals make decisions around clinical trials when suffering with a life-threatening illness and the potential for structural coercion. I will then discuss the consent process for the trial, how participants experience a trial once enrolled, the acceptability of the intervention, and the value of the researcher perspective.

Cryptococcal meningitis represents a failure of implementation

For an individual to develop cryptococcal meningitis they will have been infected with HIV for a prolonged period of time (multiple years, maybe a decade, or longer), and during this time they have not been consistently taking effective ART. This may be because they are unaware of their diagnosis or because of the numerous challenges in accessing, taking, and tolerating effective ART described above. The tools to prevent HIV infection and the development of AHD exist and throughout this time I believe there will have been very many missed opportunities to intervene and so, in my mind, cryptococcal meningitis represents a failure of implementation; a failure which requires a careful assessment of the wider context of an individual's life. Qualitative research methods provide the tools through which to gain this deeper understanding.

To date there has been very limited research exploring the pathways to care of individuals diagnosed with cryptococcal meningitis, primarily because of the severity of the infection and the poor outcomes. The sole study using qualitative methods to explore cryptococcal meningitis specifically from the perspective of survivors was a mixed-methods study in Uganda which explored patient-related delays in diagnosis and found a lack of education and knowledge among patients and healthcare workers, and in those for whom this led to a delay in receiving care the outcomes were much worse (Link et al., 2022).

Further, more in-depth qualitative methods research can provide valuable insights into the lived experience of individuals diagnosed with cryptococcal meningitis that could be used to improve care and outcomes across the entire HIV care continuum. Exploring and learning from their experience of living with HIV and developing AHD can inform approaches to care that stretch far beyond cryptococcal meningitis.

In addition, in the case of cryptococcal antigenaemia there is a window of opportunity for healthcare systems to intervene and prevent meningitis which may not always be realised. Most southern and eastern African countries now have laboratory based cryptococcal antigen (CrAg) screening programmes that aim to identify antigenaemia prior to the development of meningitis (Greene et al., 2021). These are most commonly 'reflex' in nature in which a CD4 result <100 cell/µL will prompt a CrAg test. If this test is positive the individual should be screened for meningitis and, if negative, given pre-emptive therapy with fluconazole which aims to avert the development of meningitis. These programmes have been hampered by the large reduction in CD4 testing in recent years (Nasuuna et al., 2020). Qualitative methods

research from the perspective of PLWH could help highlight areas for improvement in healthcare delivery and missed opportunities for both CD4 and CrAg testing.

Finally, cryptococcal meningitis typically causes what begins as a mild headache that worsens over days and weeks before leading to more severe symptoms such as confusion, seizures and coma. Mortality rates are more than double in those with severe symptoms at presentation to hospital (Jarvis et al., 2022) and qualitative research can explore whether individuals are aware of cryptococcal meningitis and the need to present to care soon after symptoms develop.

The standard of care and therapeutic misconception

AMBITION-cm aimed to establish a definitive treatment regimen for cryptococcal meningitis and therefore combined a single, high-dose of L-AmB with both flucytosine and fluconazole. This regimen was tested against the WHO recommended standard of care. During the trial the available treatment at the AMBITION-cm trial sites was not the WHO recommended first-line treatment for cryptococcal meningitis in resource-limited settings(WHO, 2018). Access to amphotericin is variable in sub-Saharan Africa and there have been long-standing issues with access to flucytosine which was not available at any of the sites at the start of the trial and only became available in South Africa during the course of the trial (Shroufi et al., 2020). As a result, the standard of care within the trial was superior to the routinely available treatment.

What should constitute the standard of care in global health research has not been universally defined (Benatar & Singer, 2000). There was much controversy in the past surrounding HIV trials which used a placebo-controlled design despite other effective treatments being known

and available (McGrory et al., 2009). This spurred anthropologists, bioethicists and others to argue that control arms in clinical trials ought to provide the best treatment available for that condition (Farmer, 2002). The Declaration of Helsinki states that the standard of care should be the 'best proven intervention' but fails to specify in which context (World Medical Association, 2013), whereas the Council for International Organisations of Medical Sciences guidelines state that the standard does not need to be the best treatment available if the purpose of the study is to identify a pragmatic treatment option for a resource-limited settings (Council for International Organization of Medical Sciences, 2002, 2021).

I have already outlined that, when comparing the same treatments, there is a mortality benefit to participating in a cryptococcal meningitis trial in sub-Saharan Africa (roughly 50% versus 40%). In AMBITION-cm, when the control arm is significantly superior to the routine treatment available in that setting, the benefits of participation increase further (roughly 50% versus 25%). The concept of 'therapeutic misconception' is well documented in clinical research and is the belief that every aspect of the research project to which someone has consented has been designed to benefit them directly (Appelbaum et al., 1987). Clinical trials are primarily designed to answer a research question, the findings of which it is hoped will later be of benefit to a larger population. Some individuals may benefit by participating but it is not designed so that everyone will (Molyneux et al., 2004). Despite this it is not uncommon for research participants to expect a personal therapeutic benefit from the treatment they receive, including in placebo-controlled trials, and this is often one of many motivators behind participation (Houghton et al., 2018; Leach et al., 1999).

The design and implementation of the AMBITION-cm trial was different because it was fair to anticipate that there would be a therapeutic benefit in both arms, compared to routine care. What is not understood is how this knowledge of a real therapeutic benefit impacts both patients and researchers when it comes to motivating to enrol in the trial and this is something that I set out to investigate.

Enrolling in a clinical trial whilst suffering from a life-threatening illness

There has been much research conducted in both HICs and low- and middle-income countries (LMICs) as to the underlying motivation for joining clinical trials. Research exploring this subject and conducted in LMICs has typically utilised interviews and focus group discussions and, in addition to the therapeutic misconception, the motivating factors most commonly identified are material benefits including free healthcare and transport reimbursements (Corneli et al., 2015; Gikonyo et al., 2008; Ssali et al., 2015). Altruism is also a factor but is described as being 'conditional' on receiving these personal benefits (Katz et al., 2019). This is in contrast to research in HICs where altruism is the more prominently presented but certainly not the only motivator (Cox & McDonald, 2013; Smailes et al., 2016). This motivation for material gain may be rooted in poverty and the economic inequality that exists between patient and research institution and which permeate the concept of voluntary participation.

Voluntariness is understood as an autonomous choice without material entanglements and the principle of autonomy is often held above others when it comes to consenting for a clinical trial (Geissler et al., 2008). The design of a trial and the informed consent process make assumptions about choice and autonomy that are at odds with the lives of some individuals living in LMICs (Marsland & Prince, 2012) and neglect to appreciate that decisions are

sometimes made under conditions of extreme poverty. Research participants who lack agency are therefore described as being subject to 'structural coercion' in which their social and economic situation drives them into research participation as a means of navigating their illness and because they may not have any other options to get the care they need or desire (Fisher, 2013). Within the context of structural coercion, potential research participants are not weighing the risks and benefits of a specific study but rather they are considering how the trial fits within their personal situation.

These arguments are polarised in the context of a life-threatening illness such as cryptococcal meningitis. A qualitative methods study of the informed consent process in Kenya identified that the parents of children recruited to a epilepsy study felt that if they had not signed the consent form their child would have not been treated optimally, or at all, and this is why they agreed (Molyneux et al., 2004). These concerns about care in routine care settings have also been voiced in relation to research institutions in which those who enrol feel that although they may come to harm from the research process, they have no choice but to consent (Fairhead et al., 2006).

The informed consent process

By understanding that the AMBITION-cm trial is likely to lead to an improved outcome for the individual and acknowledging that those diagnosed with cryptococcal meningitis are likely to have reduced agency due to both poverty and acute illness, it is essential to examine the consent process which is the gateway to the trial. The process of informed consent has been subject to much scrutiny by clinical trialists and social scientists alike. It is a widely held belief that the move towards informed consent, and the dominance of patient autonomy in

bioethics, reflects the increased centrality awarded to individualism as a consequence of Western liberalism (Corrigan, 2003). Current approaches to consent frame patients as active, decision-makers and may exaggerate their agency. Paul Farmer (2002) has written that focusing on the process of informed consent leads to an overemphasis on the consent form as the key to rendering research in LMICs as ethical. `Doing consent' is seen as an easily auditable process which protects researchers rather than participants (Gikonyo et al., 2008) and limits the concerns around the ethics of informed consent to those surrounding information provision and the readability of forms (Kingori, 2013).

In the context of a life-threatening illnesses there are questions about when to obtain consent and who to obtain it from. Regarding the former, one option is to commence trial procedures and defer consent until the patient is stable. This approach has been found to be broadly acceptable in multiple qualitative methods studies in the UK, including with consenting adults, where participants felt that being approached to consent during an acute illness made it too difficult to absorb the information (Behrendt et al., 2011; Corrigan, 2003; Kenyon et al., 2006). Few quantitative data on this subject have been published in situations in which adults consent for themselves however in a UK-based emergency paediatric study this was demonstrated to be acceptable to 70% of consenting parents who felt that the informed consent process was too much to handle in such a stressful situation (Gamble et al., 2012). An alternative is to waiver informed consent completely, as was the approach for some participants in a trial of tranexamic acid to treat post-partum haemorrhage in the UK (Houghton et al., 2018). In this study the perceptions of those who gave consent, had a surrogate, or waived consent were not dissimilar. The Declaration of Helsinki states that it is acceptable to recruit someone without capacity in best interests (World Medical Association,

2013). It has been argued that by delaying treatment whilst waiting for consent both risks losing out on the potential health benefit of that specific emergency treatment but also underappreciating the impact of emergency treatment due to systematically delayed initiation (Roberts et al., 2011).

Regarding whom provides the consent, it is typical for surrogates to consent on behalf of an unwell patient who is confused or comatose. Within the AMBITION-cm study we expected 40% of participants to be lacking decision-making capacity at baseline and to be consented by a surrogate. If they regained capacity, they were asked to consent for themselves. A few studies in HICs have identified that there is generally good concordance between surrogates and patients when it comes to agreeing to consent to both real-life and hypothetical trials but that this is reduced in trials that are deemed high-risk (Coppolino & Ackerson, 2001; Newman et al., 2012). In LMICs it is not uncommon for multiple actors to be involved in the consent process with partners, parents, older family members and community leaders to be consulted before the form is signed (Kingori, 2013; Leach et al., 1999), particularly in the case of severe illness or high-risk (Gikonyo et al., 2008). This extends the process of gaining consent and can delay recruitment and treatment. This is particularly relevant to trials for life-threatening illnesses because it is often early or immediate treatment which is being trialled and delays in the obtaining consent may result in individuals having already received an intervention which leaves them ineligible for the trial.

Comprehension of the informed consent process, although not universally defined, has been well studied. One systematic review of 21 studies in Africa found that 47% of participants understood trial procedures such as randomisation and placebo and that only 30% were

aware they may not experience a therapeutic benefit of participation (Afolabi et al., 2014). Another review found that understanding is significantly diminished amongst those who are critically ill (Tam et al., 2015). Approaches to enhance comprehension include the use of video/audio, pictures and simplifying the participant information sheet and informed consent form (Gikonyo et al., 2008; Negussie et al., 2016; Vallely et al., 2010) which is often felt to be too long and technical (Vischer et al., 2016; Vischer et al., 2017). It is also argued that consent should not be perceived as a one-off event but a continuous process because it involves a multiplicity of interactions between the key actors involved rather than a single moment in time (Ssali et al., 2015). When comparing different methods for eliciting understanding of the consent process it has been found that quantitative methods often yield falsely high levels of comprehension whereas qualitative methods, particularly narratives and vignettes, can better elicit whether an in-depth understanding has been achieved (Lindegger et al., 2006; Molyneux et al., 2007).

To date there have been no in-depth qualitative methods studies in LMICs exploring the process of consent from the perspective of an acutely unwell adult, including those who have regained capacity and been given the chance to simultaneously reflect on having consent delegated to a surrogate. Similarly, research conducted in LMICs has focused on the parents of children enrolling in clinical trials, rather than adults, and these were predominantly around vaccine studies which differ considerably from trials for an unfolding life-threatening illness (Fairhead et al., 2006; Gikonyo et al., 2008; Tindana et al., 2012). In a context where both capacity and agency may be reduced and the therapeutic benefits of participation are clear it is important to hear from both participants and researchers about how they navigate this complex process, the importance they place upon it, and how it could be improved.

The consent process is the gateway to the trial but, as discussed, its importance may be over emphasised by researchers and the ethical considerations of the trial extend far beyond this single event. In this next section, I will consider what I have broadly termed the 'participant experience' in the trial. That is, their impression of the sequence of scheduled events, including those that occur after consent, and which create the structure for their ongoing engagement and follow-up with a research study. By gaining an insight into their perspective we can begin to understand the ways in which trials for life-threatening illnesses can be improved.

The participant experience and acceptability of the interventions

I use the broad term of participant experience to encompass the way that an individual navigates through the scheduled events of a clinical trial as detailed in the protocol. These events include the screening and consent process, administration of study drugs, diagnostic and therapeutic procedures, adverse events and complications, discharge from hospital, outpatient appointments and discharge from the study. Time is a prominent factor throughout this process. An illness occurs at a specific time in someone's life and the entire trial experience is time-bound and shaped by the protocolised schedule of events. I am interested in knowing how participants experience these key events within the structured timeline of the trial, how they perceive them to be related to one another (or not) and how they relate to the context of their pre-existing health problems, the specific trial within which they are enrolled and the research institution and field with which they are now affiliated.

A large portion of the ethnographic work exploring participant experience of research in LMICs has elicited data concerning rumours, most commonly blood stealing, which are often

dismissed by some researchers as expressions of ignorance but are interpreted by social scientists as forms of popular resistance (Fairhead et al., 2006; Geissler, 2005; Geissler & Pool, 2006). Rumours often contain local interpretations of medical research ethics, especially related to the problems of resource transfers and flows of value. Geissler has argued that rather than ignoring rumours, engaging with them could enrich medical research ethics debates and improve relations between medical researchers and study communities (Geissler & Pool, 2006). Most ethnographic exploration of rumours has been situated in trials of healthy individuals in vaccine or mass drug administration trials and less commonly in acute, life-threatening illness. Lumbar puncture, the procedure used to diagnose and treat cryptococcal meningitis is known to be associated with rumours of causing death (Thakur et al., 2015). This has not been extensively studied using ethnographic methods but among clinicians is perceived to be due to the often-close timing between someone having a lumbar puncture and then dying due to the illness. These rumours are likely less a form of social resistance and more a reflection of events which do not lend themselves to the first interpretation of clinicians (Molyneux et al., 2004). The reality however is that lumbar puncture refusal can be fatal. In the context of AMBITION-cm, it often took time to address these rumours before recruiting participants into the study and after the diagnostic lumbar puncture, further lumbar punctures in accordance with the protocol or for therapeutic reasons were frequently refused.

Rumours are entangled with the concept of trust and may be interpreted as being driven by a lack of trust. Trust is defined here as 'assured reliance in the character, ability, strength, or truth of someone or something' (Merriam-Webster Dictionary, 2002). Trust may exist (or not) between potential participants and researchers, institutions, and/or processes and previous

literature exploring decision making in clinical trials for life-threatening illnesses has found that where a comprehensive understanding of information could not be achieved this has resulted in trust being a predominant factor (Agård et al., 2001). Trust is therefore particularly important when considering the AMBITION-cm trial. Trust and vulnerability are inter-related, in where trust is interpreted by some as a way of controlling for the uncertainties that the future holds and that the need to trust follows from the fact that the future contains many possibilities (Luhmann et al., 1979). The vulnerability of an individual, be that emotional, physical, or financial, grants discretionary power to researchers and institutions to operate to achieve something that the patient desires, including life itself (Goold, 2002). Given the uncertainty posed by a diagnosis of cryptococcal meningitis and that many of the possible outcomes are negative, including death and disability, the extremes of these possibilities increase the significance of trust when it is placed (or not) in the hands of another.

In the United States there has been an increasing call to assess clinical trial participant 'patient satisfaction' through the use of surveys or interviews which aim to hear the participant's voice and respond by making local improvement to the trial (Pflugeisen et al., 2016). This work centres on the participant as a client, in the business of clinical trials, and the need to improve satisfaction in a competitive market (Smailes et al., 2016). In LMICs this approach is less common but the concept of 'good participatory practice' has been developed by the WHO over the years, particularly in reaction to outrage surrounding HIV prevention trials using placebo-controlled designs (McGrory et al., 2009). Good participatory practice guidelines have six core components which are relevant to local stakeholder engagement: stakeholder advisory mechanisms, stakeholder engagement plans, education plans, communication plans, issues management plan, and trial closure and results dissemination. Issues

management relates to the participant experience and is described as 'how research teams intend to manage issues of concern or any unexpected developments that may emerge before, during, or after the trial, including those that could limit the support for, or success of, the specific trial or future trials' (Mack et al., 2013). No ethnographic work has explored these 'issues' in the context of acute illness research in sub-Saharan Africa. Research within healthy volunteer studies has found that where poor outcomes such as severe disability or death occur, this has led to the apportioning of blame or the generation of rumours about research studies and institutions (Fairhead et al., 2006; Geissler, 2011). An exploration within AMBITION-cm, where poor outcomes are not uncommon, could provide an opportunity to inform and potentially improve the conduct of this trial and others in the future. Finally, given that the AMBITION-cm regimen has been designed to be easier to administer than the standard of care regimen, there is a need to consider the acceptability of this novel regimen from both participant and researcher perspective.

Above I have outlined the severe nature of cryptococcal meningitis and the complex bioethical issues surrounding participation in the AMBITION-cm trial, underlining the need to learn from participants and understand how the trial can be improved for their benefit, as well as the acceptability of the intervention. In order to do this, it is important to also consider the perspective of those who work in the field of global health research.

The researcher experience

'Researcher and subject are living in different worlds' (Farmer, 2002) and it is commonly perceived that there is a mismatch between researcher and participant understanding of the research process (Fairhead et al., 2006). To date there has been little investigation of the

researcher in clinical trials in LMICs, those professionals tasked with performing bioethics (Crane, 2013; Kingori & Gerrets, 2016). Large, randomised controlled trials frequently employ a large number of individuals from different countries, working together to answer a research question, who can share their experience and insight (Molyneux & Geissler, 2008). AMBITION-cm, in keeping with the ethos of the funding body, the EDCTP, is no different in this regard.

Doctors and nurses who interact with trial participants daily: assessing capacity, obtaining consent, performing procedures, following up participants and meeting with them and their next-of-kin 'on the ground' can provide insights into these processes (Kingori, 2013; Kingori & Gerrets, 2016; Monroe et al., 2017; Ssali et al., 2015). By understanding their perspective and how they experience the series of events that form the trial structure, we can identify aspects which could be improved that may not be immediately apparent to participants. In a similar vein, understanding how the trial impacts researchers themselves and identifying areas to optimise their working experience may enable us to have an indirect, positive effect on the trial participant.

Individuals working at research institutions where trial participants are being recruited are well placed to comment on the research process. Their experience caring for trial participants can be combined with an intimate understanding of the processes of obtaining regulatory approvals and implementing a trial to provide a practical insight and suggestions for improvement (Vischer et al., 2017). As partners in the research process they can reflect on how clinical trials are conceptualised and designed in addition to the benefits and

shortcomings of trans-national partnerships and how we can optimise these relationships for the benefit of participants (Franzen et al., 2013).

Researchers who work internationally are often skilled individuals who may have a broad range of prior experience working in clinical trials. Although they may not be based in a country different from their home nation permanently, they often have been in the past and can reflect on the evolution of clinical trials over time. As representatives of institutions which are partners (and often the lead) on grant applications, they can help to steer the clinical trial agenda in the region and are well placed to comment on how trials can be improved. Therefore, their reflections are included in this thesis.

Within this background I have summarised the epidemiology of AHD and cryptococcal meningitis in sub-Saharan Africa and the rationale for the AMBITION-cm trial. I have outlined how the trial provides a rich setting for an anthropological study exploring the ethical issues around clinical trials for life-threatening illnesses in LMICs and how this can build on the existing literature and address gaps in the research. In the next section I will present the overarching research aim and five research objectives.

RESEARCH AIM AND OBJECTIVES

Aim

To document the AMBITION-cm participant experience in order to build an understanding of how to improve trial delivery for participants in this and future trials.

Objectives

Through the review of published research:

1. To perform a meta-analysis exploring how representative and inclusive clinical trials for cryptococcal meningitis are, from both the participant and the researcher perspective.
2. To conduct a critical interpretive synthesis of qualitative data relating to participation in a clinical trial when an individual was suffering specifically from a life-threatening illness.

Through ethnographic research:

3. To explore pathways to care with cryptococcal meningitis and identify recommendations to avert mortality.
4. To begin to understand decision-making around the AMBITION-cm trial and how the study design and broader social context impacted that process.
5. To identify how the AMBITION-cm trial could be improved and the acceptability of the AMBITION-cm regimen from both the participant and the researcher perspective.

CHAPTER TWO: METHODS

METHODS PART ONE - SYSTEMATIC REVIEWS

Within this section I will outline the rationale behind two different systematic reviews: the first using quantitative data and the second using qualitative data. The aim of the reviews was to begin to understand more about the 'who' in cryptococcal meningitis and the 'why' in trials for life-threatening illnesses. I had initially hoped to conduct a qualitative systematic review of literature exploring experiences of living with cryptococcal meningitis, but after a thorough search I found there were no papers looking at this specifically. One paper has been published in the intervening years (Link et al., 2022).

OBJECTIVE ONE: CRYPTOCOCCAL MENINGITIS TRIALS META-ANALYSIS

Background

This lack of any publications of substantial qualitative data led me to consider which descriptive data about people with cryptococcal meningitis exist and how best one could synthesise and analyse such data. The more granular quantitative data available has primarily been derived from clinical trials. There have also been many observational studies, both cross-sectional and longitudinal, but clinical trial data is typically more detailed and comprehensive. Whilst considering this question I was invited by a colleague to contribute to a systematic review looking at outcomes from different HIV-related central nervous system pathologies. It was in this review that we compared outcomes in clinical trials and observational studies and observed that mortality was lower in clinical trial settings (Tenforde et al., 2020). This was not the primary objective of the review, we were trying to compile disparate data to present mortality risks, but it was an objective description of something that we were all aware of and

explained why as researchers we were so eager to recruit each individual into AMBITION-cm and give them the best chance of survival.

Having demonstrated this difference in mortality and wanting to know more about individuals with cryptococcal meningitis I then considered taking a step back and instead considered the characteristics of those recruited into clinical trials, how these may have changed over time, and how they might compare to our best available composite observational data. I doubted whether they were significantly different enough at baseline to explain the difference in outcomes, expecting the differences to be due to the enhanced care provided in clinical trials, but was eager to know if there were any specific groups who were under-represented in clinical trials.

At the same time, I had been reading and engaging with the rapidly increasing body of literature around inclusion and representation in global health research – both in terms of research participants and researchers. There was a growing body of literature discussing epistemology and epistemic injustice (Bhakuni & Abimbola, 2021; Bhargava, 2013). During this time global health practitioners were increasingly reflecting on the ethos and equity of research (Abimbola, 2019; Blehar et al., 2013; Mbaye et al., 2019) and concerns had been raised that clinical trials were disproportionately conducted in a limited number of countries (Ahmad et al., 2011; Siegfried et al., 2005; Sumathipala et al., 2004; Zani et al., 2011).

Building from this work I was therefore keen to also add another component to this review of cryptococcal meningitis trials and opted to include representation and inclusion in trials from the researcher (or author) perspective. In addition to ensuring that research participants

are representative of the general population suffering from a disease, it is equally important to ensure that the researchers and institutions involved are representative of where the disease burden lies. At present, the majority of HIV funding comes from HICs (UNAIDS., 2016) and therefore the resources (both economic and human) flow from HICs to LMICs. Individuals and institutions from HICs lead the research and researchers from LMICs are often found in the middle of author lists or excluded altogether from publications arising from African health research (Hedt-Gauthier et al., 2019). Inclusive research teams are essential to shape priorities and develop studies based on an in-depth understanding of the local context and inclusive representation will promote fairness, strengthen capacity, and ensure the future sustainability of research.

Aim

The aim of this review was therefore to describe the location of cryptococcal meningitis trials and the characteristics of those enrolled to perform a comparison with the current epidemiology. We also aimed to describe the gender, location and nationality of researchers involved in cryptococcal meningitis trials.

Research Group

This project was conceived by me with support from Professor Joseph Jarvis. The protocol was subsequently developed by me and Dr Tshepo Leeme, a colleague in Botswana who was the lead doctor for the AMBITION-cm site in Gaborone. Collaborators were Prof Joseph Jarvis, Prof Tom Harrison, Prof Janet Seeley, and Prof Mosepele Mosepele. I performed the search and along with TL we independently reviewed titles and abstracts from the primary search to identify potential articles for inclusion using predefined criteria. We both then independently

extracted data from included studies and conducted the analysis. JNJ and MM were consulted for review and consensus. TL and I then analysed the data. I created the visuals and wrote-up the first draft of the manuscript which was reviewed by all members of the team.

Methods

We included any trial in which individuals with HIV-associated cryptococcal meningitis were randomly assigned to one of at least two intervention arms. The intervention could be any treatment for their condition and there was no restriction on the nature of the comparator arm. Our focus was on the characteristics of individuals who were recruited into the trials and the researchers conducting the studies, and not on trial outcomes.

Search method and data collection: We searched for studies published up to 4th March 2020 using Medline, EMBASE, Cochrane Library, Africa-Wide, CINAHL Plus and Web of Science. We also searched ClinicalTrials.gov for completed and published trials. Our search strategy combined terms related to HIV-associated cryptococcal meningitis and clinical trials (Table 1). No restrictions were placed on language. We excluded studies related to cryptococcal meningitis that was not associated with HIV or where data from people living with HIV could not be extracted, observational studies, healthy volunteer studies recruiting participants with previously treated CM, studies without comparator arms, manuscripts where data were presented elsewhere in a primary manuscript, and non-original research articles such as editorials. The search strategy and protocol were developed by the authors prior to commencing the search and were registered with PROSPERO (CRD42020171845).

All papers were entered into Covidence (Covidence systematic review software). Duplicates were removed and then titles, and abstracts were independently screened against the eligibility criteria by DSL and TL. Non-eligible studies were removed, and the full texts of potentially eligible titles were assessed for inclusion. JNJ and MM adjudicated in the case of any conflict regarding study inclusion. The reference lists of included studies were searched to identify any additional eligible studies.

Data extraction: We extracted the relevant variables from each included paper in five key domains (Table 1): Study location and design, screening, participants, researchers, and funders. If necessary, the authors of an article were contacted for information that may not have been presented in the final publication. Researcher data were augmented by online searches of institutional webpages and profiles on sites such as LinkedIn and Research Gate. If gender data could not be confidently elicited, then the gender of authors was determined using a website called Genderize.io that predicts the gender of a person given their name. Either DSL or TL performed the data extraction and then the other verified the data. Any discrepancies were discussed and resolved.

Table 1: Systematic review and meta-analysis. A) Search strategy B) Summary of the variables extracted from included papers.

A) Search Strategy		
#1	Search (Meningitis, Cryptococcal[Mesh] OR cryptococcal meningitis)	
#2	Search (trial[mesh] OR Clinical Trial OR Clinical Trial, Phase I OR Clinical Trial, Phase II OR Clinical Trial, Phase III OR Clinical Trial, Phase IV OR Randomized Controlled Trial)	
#3	Search (Prospective Studies[Mesh] or prospective)	
	Searching #1 and #2 and #3 up to and including 04 March 2020	
B) Variables extracted from included papers		
Study	• Year of publication • Period of study • Location of study • Type of healthcare facility • Study design • Intervention(s)	• Control • Inclusion criteria • Exclusion criteria • Primary outcome • Secondary outcome(s)
Screening and Randomisation	• Number screened • Number screen failures • Reasons for each	• Withdrawals • Loss to follow-up
Participants	• Number of participants • Gender • Antiretroviral status	• Baseline Glasgow Coma Scale • First episode or relapse
Researchers	• Number of authors • Gender • Country of origin	• Country of residence during research period
Funders	• Name of funders • Category of funder	• Location of funder • Funding amount

Note: This table is repeated in Research Paper One.

Data synthesis and analysis: Data were summarised using descriptive statistical analysis. To describe the geography of where participants were recruited the location of trial sites were analysed individually and also grouped into World Bank Regions. To demonstrate trends over time, comparison was made over 3 different periods: pre-2000, 2000-2009, post-2010 to broadly demonstrate the pre-widespread ART era, early ART era and established ART era respectively. The end date of recruitment was used to determine within which of these time periods the study would be categorised. In papers where the specific months of recruitment were not stated the year of publication was used. Where data could not be extracted for individual sites within multi-country trials these numbers were averaged. We compared the characteristics of trial participants (gender, relapse rate, ART status and baseline Glasgow Coma Scale (GCS)) to a composite reference of recently published observational and surveillance data from routine care settings (Adeyemi & Ross, 2014a, b; Meiring et al., 2016; Patel et al., 2018; Tenforde et al., 2017). ART experienced was defined as being on ART at the time of randomisation, including individuals who were on zidovudine monotherapy prior to the availability of combination ART. Chi squared testing for trend was performed to describe trends in the demographics of trial participants and researchers over time. With regards to the gender, countries where researchers were born and where they resided during the trial, each study was categorised as either taking place in HICs or LMICs and Chi-squared calculations allowed comparison between these two groups. Statistical analysis was conducted in Stata/SE 15.0.

OBJECTIVE TWO: CRITICAL INTERPRETIVE SYNTHESIS

Background

One of the key aspects of the AMBITION-cm trial that makes it such an important setting for an in-depth qualitative methods study is the life-threatening nature of the illness. This second systematic review centres on the collation, synthesis and interpretation of qualitative data obtained from individuals who have decided to enrol themselves or someone else into a trial whilst suffering from a life-threatening illness and their experience of being in the trial.

I had become increasingly familiar with the literature during the early stage of this thesis and prior to this there were no other qualitative reviews on this specific topic. The initial challenge was in deciding which type of qualitative systematic review methodology would be best suited to the research question. There are several methodologies, some of which overlap considerably, and a decision required several discussions with my supervisor, Prof Janet Seeley, and my collaborator, Dr Agnes Ssali, a social scientist who also supervised the data collection for the ethnographic study in Uganda.

My initial familiarity with the literature led me to anticipate that the appropriate methodology would need to be capable of encompassing a broad range of research papers, spanning several disciplines and theoretical approaches, but also different research contexts and questions. This was particularly true because the phenomenon of interest, 'participant experience' was a broad term that could encompass multiple areas of focus such as motivations to enrol, the decision-making process, informed consent, and subsequent trial procedures. In addition, some qualitative methods studies had been conducted alongside

clinical trials for life-threatening illnesses, but the life-threatening nature had not been centred within the methodological approach or data interpretation. My aim was therefore to synthesise these disparate data and reinterpret them to develop a theoretical approach to the participant experience in clinical trials for life-threatening illnesses.

Dixon-Woods and colleagues (2006), in their seminal research, developed the critical interpretive synthesis as a methodology that could be better suited to this kind of diverse body of literature. They argued that conventional and well-established systematic review methodologies such as meta-ethnography (Noblit & Hare, 1988) were more suited for synthesising or aggregating data and not as useful for interpreting them. These aggregative reviews are more focused on summarising data and tend to have well defined population groups or outcomes of interest. Interpretive reviews, on the other hand, are more interested in the development of theoretical concepts and are therefore more iterative and inductive in their approach, with fewer pre-specified concepts defined in advanced of the synthesis. The critical interpretive synthesis first presented by Dixon-Woods and colleagues still adopted some of the core methods of meta-ethnography including reciprocal translational analysis; refutational synthesis and lines-of-argument synthesis, but adapted them and took them further to include higher-order constructs that involved more critical interpretation and ultimately resulted in the development of a 'synthetic construct' which they describe as a 'result of a transformation of the underlying evidence into a new conceptual form' (Dixon-Woods et al., 2006, Page 5).

Given the broad area of interest, disparate data, and what could otherwise potentially be viewed as an 'ill-defined' question, this approach provided an ideal framework for this review.

However, whilst Dixon-Woods and colleagues developed the critical interpretive synthesis, after trying to perform a meta-ethnography and finding that the methods weren't quite working for them, I became aware that their methods, particularly in terms of how to perform the analysis, were not clear or explicit. In an attempt to gain clarity, I referred to additional analyses. There have been many critical interpretive syntheses published since 2006 and they are often based on broad, disparate data sets and aim to develop new theoretical concepts. However, after reviewing several, with a focus on health, and global health in particular, although it was clear how data should be synthesised the methods around critical interpretation were not always transparent and there was clear variation between studies (Lin & Melendez-Torres, 2017; Plamondon et al., 2021; Ray et al., 2021; Schaaf et al., 2020). This has been described as flexibility embedded within the methods however a systematic review found that the reporting of methods in critical interpretive syntheses was suboptimal and that this flexibility could hamper its implementation and raise concerns around trustworthiness (Depraetere et al., 2021). With this in mind, we agreed on each step of the analysis as a group and in the following methods section I will describe in detail those steps and, where applicable, if and how they deviate or are in addition to those described by Dixon-Woods and colleagues. The following methods are therefore more detailed than those presented in the submitted research paper.

Aim

To conduct a critical interpretive synthesis with the aim of collating and interpreting data which relates to the experience of participants and their caregivers who have been enrolled into a clinical trial whilst suffering from a life-threatening illness.

Research Group

I conceptualised the project. The methodology was developed and refined by the team which included me, Dr Agnes Ssali, Prof Janet Seeley, and Prof Joseph Jarvis. I performed the searches and then AS and I reviewed the abstracts; selected the included papers; extracted the data; analysed the data and drafted the initial manuscript. We were supervised and advised by JS and JNJ. All authors refined and approved the final manuscript.

Methods

We conducted a critical interpretive synthesis broadly in line with the methodology outlined by Dixon-Woods et al (2006). As discussed, we acknowledged that there was significant heterogeneity in the methodology of published critical interpretive syntheses and that this approach has evolved over time (Depraetere et al., 2021). We therefore adopted an approach to the methodology that was flexible and evolved to enable us to best try and meet our aim.

Defining the population: We defined our population of interest as any individual (or their caregiver), regardless of age, diagnosed with a life-threatening illness and recruited into a clinical study. A life-threatening illness was defined as any medical condition that required emergency inpatient admission to a healthcare facility and for which the potential sequelae included death. Clinical study was defined as any prospective observational or interventional study that required the individual or a surrogate to provide consent. We wanted to begin to understand the entire experience from beginning to end so included studies exploring all aspects of the clinical study including being approached, screened, consented, randomised, managed, and followed up as a participant. We did however exclude clinical studies with a waiver of consent as despite not wanting to focus entirely on the consent process itself we

were interested in experiences in which individuals had been involved in a decision-making process. Systematic reviews of research without prior consent in both adult (Fitzpatrick et al., 2022) and paediatric (Furyk et al., 2018) studies have been published elsewhere. We were solely interested in in-depth qualitative research conducted in English that related to the trial experience rather than that which focused specifically on the acceptability of the intervention under investigation.

Scoping review: An initial scoping review was conducted to identify published work that was relevant to the research question. Following Eakin and Mykhalosvsky (2003), we reviewed and discussed a selection of relevant papers and then used this broad review as a basis to refine our comprehensive search strategy. We approached the concept of life-threatening illnesses by searching for broad terms such as 'emergency', 'mortality' and 'life-threatening' as well as a select number of pathologies that are deemed to be life-threatening such as 'meningitis' and 'stroke'. During this process we acknowledged that a broad range of pathologies and scenarios could technically be life-threatening and therefore accepted that any comprehensive search strategy was likely to produce a large number of results. From this initial scoping review, we were then able to define a comprehensive search strategy. The inclusion and exclusion criteria for the critical interpretive synthesis are presented in Table 2.

Table 2: Inclusion and exclusion criteria for the critical interpretive synthesis.

Inclusion	Exclusion
Enrolled in a prospective (observational or interventional) clinical study that required the provision of consent	Involved in a retrospective study or did not need to provide consent
Clinical study focuses on a life-threatening condition	Not a life-threatening condition
Data from study participant or their caregiver/relative/surrogate/parent/guardian	Data from anyone else
Qualitative or mixed-methods study	Exclusively quantitative analysis
Semi-structured or in-depth interview, focus group, ethnography, observation, diaries	Self-administered, short answer or structured questionnaire, multiple-choice answer survey
Data relating to the trial experience	Data focusing on the intervention, data for secondary outcomes e.g. acceptability
Full-length, original research paper	Abstracts, poster, conference proceeding, viewpoint, commentary
English	Not in English

Note: This table is repeated in Research Paper Two.

Comprehensive search*:* We developed a comprehensive search strategy (Appendix 1) and searched the following information sources: Medline, Embase, Web of Science, Global Health, JSTOR, Academic Search Complete, Scopus, African Journals Online, PsychINFO and PsychEXTRA. There was no restriction on publication date. Reference lists of included studies were also searched to identify any additional potentially eligible studies. All papers were then entered into Covidence and duplicates were removed. The titles and abstracts of all potentially eligible studies were screened by both DSL and AS to determine which were suitable for full-text review. DSL and JNJ are clinicians with specialist training in internal medicine and were able to provide professional opinion on the life-threatening nature of the illness under study. In the case of disagreement, the two reviewers discussed and, if

necessary, JS and JNJ were also available for arbitration. DSL and AS then reviewed the full-text of those studies and the same arbitration approach was adopted to determine which would be included in the full review. When planning this stage there was uncertainty around the number of papers that would be identified by the search and how many would be eligible for inclusion in the review. If faced with an unmanageable workload we therefore considered drawing on purposive sampling and employing theoretical sampling and theoretical saturation to decide on a collection of papers that would be appropriate, however, as we shall discuss in the results, this was not necessary.

Data extraction and analysis: We developed a data extraction form (Appendix 2) with domains related to the focus of the clinical study; the methodology of the qualitative study; the results including any themes and their description; theoretical frameworks; all primary data presented and a quality assessment. We extracted both primary data such as direct quotes as well as interpretive data including themes, frameworks, and conclusions. Where data were collected from a range of informants, we focused on the perspective from study participants and surrogate decision makers, rather than researchers or those who declined to participate. We did not include those who declined as we were interested in the entire continuum of a clinical trial and that can only be elicited from those who have participated; however, this could be a focus for a future review. DSL and AS extracted data from half of the included papers each, with the other then reviewing the data extraction form and amending after discussion, as necessary.

Critical interpretive synthesis*:* Throughout the searching and extraction process DSL and AS met regularly to develop the following analytical approach. We broadly followed a thematic

analysis approach (Braun & Clarke, 2006) and combined this with major strategies of meta-ethnography (Noblit & Hare, 1988) to develop a synthetic construct. During the review process we became increasingly familiar with the papers and the extracted data to develop a codebook which was refined over multiple iterations. DSL coded the extracted data in NVivo 12 and AS did so manually. Together we then met regularly and began to identify possible themes and a preliminary foundation for an overarching synthetic construct. As these were refined, we also adopted three major strategies of meta-ethnography, utilising an interpretive approach: Reciprocal translational analysis to identify the key themes or concepts in each paper as reported; Refutational synthesis to identify any contradictions between study reports and attempt where possible to explain them; and lines of argument synthesis to build on interpretations that were found in the papers. This process then enabled us to refine our synthetic construct which was a higher order construct which aimed to broadly encompass the entirety of the critical interpretive synthesis. This synthetic construct was edited on multiple occasions in line with the emerging discussions and ongoing analysis before being finalised.

Ethics: As this was a review using published data there was no requirement for ethical approval. The review was prospectively registered on PROSPERO (CRD42020207296).

RESEARCH PAPER ONE: EQUITY IN CLINICAL TRIALS FOR HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS: A SYSTEMATIC REVIEW OF GLOBAL REPRESENTATION AND INCLUSION OF PATIENTS AND RESEARCHERS

Summary of findings

Our search yielded 1040 studies. Sixty-five were included in the full-text review and a final 39 were included in the analysis. No additional studies were identified after reviewing the reference lists of included studies.

We identified a geographical shift with trials moving from the USA to both Africa and Asia over time. We found that recent trials were conducted in areas heavily affected by cryptococcal meningitis but we did identify geographical areas that have been under-represented for example high-burden countries such as Nigeria, Kenya, Mozambique and India have not been recruitment sites for clinical trials.

When comparing trial participants with a composite reference of observational data we observed that there were some patient groups that were under-represented in clinical trials. Individuals with a relapse of cryptococcal meningitis likely make up around 10% of admissions and the most recent trials had excluded 8-9% of those screened because of this. As a result, we only identified 28 individuals with a relapse who had been recruited into a trial since 2010. Those with severe disease, defined as a GCS <15 at baseline, were under-recruited compared to observational data but the proportion had increased statistically over time. This reduction is likely explained by the severity of the illness and that for some individuals it may not have been possible to obtain surrogate consent and/or they had died before this was possible. Female participants were fewer - 38% of all trial participants since 2010 - but this was

consistent with the epidemiology. It was not possible to determine if any pregnant or lactating women had been enrolled into clinical trials however they were typically excluded because the oral antifungals are highly teratogenic and only 12 had been excluded from all trials conducted to date, which is consistent with the relatively low rates of conception among women with advanced HIV disease (Blair et al., 2004).

We also found inequality within authorship that was skewed towards male researchers from HICs. Broadly, over time, as clinical trials were increasingly conducted outside of HICs the proportion of first and last authors who were not born in the country where the clinical trial took place increased significantly. When considering all authors, we found that trials which recruited in LMICs had more female authors.

Importance of findings

These findings outline areas for our discipline to focus on, both in terms of recruitment strategies and the composition of research teams. We can also use this study as a benchmark from which to monitor our progress over time and to compare with future trials which are published, including AMBITION-cm. In addition, this is a broad methodology that could be adopted and adapted by other research groups.

Dissemination and Impact

This paper was published in PLOS NTDs in May 2021 (Lawrence et al., 2021a). It was also of great use in responding to reviewers' comments on the AMBITION-cm clinical trial manuscript as we were asked to comment on how well the trial participants reflected those recruited into previous trials and observational data.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1800328	**Title**	Dr
First Name(s)	David		
Surname/Family Name	Lawrence		
Thesis Title	The Lived Experience of Participants in an African Randomised Trial (LEOPARD)		
Primary Supervisor	Prof Joseph Jarvis		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLOS Neglected Tropical Diseases		
When was the work published?	27/05/2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This project was conceived by myself with support from Professor Joseph Jarvis. The protocol was developed by myself and Dr Tshepo Leeme, a colleague in Botswana who was the lead doctor for the AMBITION-cm site in Gaborone. Collaborators were Prof Joseph Jarvis, Prof Tom Harrison, Prof Janet Seeley and Prof Mosepele Mosepele. I performed the search and along with TL we independently reviewed titles and abstracts from the primary search to identify potential articles for inclusion using predefined criteria. We both then independently extracted data from included studies and conduct the analysis. JJ and MM were consulted for review and consensus. Myself and TL then analysed the data. I created the visuals and wrote-up the first draft of the manuscript which was reviewed by all members of the team.

SECTION E

Student Signature	[redacted]
Date	01/09/2022

Supervisor Signature	[redacted]
Date	01/09/2022

PLOS NEGLECTED TROPICAL DISEASES

REVIEW

Equity in clinical trials for HIV-associated cryptococcal meningitis: A systematic review of global representation and inclusion of patients and researchers

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

It is essential that clinical trial participants are representative of the population under investigation. Using HIV-associated cryptococcal meningitis (CM) as a case study, we conducted a systematic review of clinical trials to determine how inclusive and representative they were both in terms of the affected population and the involvement of local investigators.

Methods

We searched Medline, EMBASE, Cochrane, Africa-Wide, CINAHL Plus, and Web of Science. Data were extracted for 5 domains: study location and design, screening, participants, researchers, and funders. Data were summarised and compared over 3 time periods: pre-antiretroviral therapy (ART) (pre-2000), early ART (2000 to 2009), and established ART (post-2010) using chi-squared and chi-squared for trend. Comparisons were made with global disease burden estimates and a composite reference derived from observational studies.

Results

Thirty-nine trials published between 1990 and 2019 were included. Earlier studies were predominantly conducted in high-income countries (HICs) and recent studies in low- and middle-income countries (LMICs). Most recent studies occurred in high CM incidence countries, but some highly affected countries have not hosted trials. The sex and ART status of participants matched those of the general CM population. Patients with reduced consciousness and those suffering a CM relapse were underrepresented. Authorship had poor representation of women (29% of all authors), particularly as first and final authors. Compared to trials conducted in HICs, trials conducted in LMICs were more likely to include female authors

(32% versus 20% $p = 0.014$) but less likely to have authors resident in (75% versus 100%, $p < 0.001$) or nationals (61% versus 93%, $p < 0.001$) of the trial location.

Conclusions

There has been a marked shift in CM trials over the course of the HIV epidemic. Trials are primarily performed in locations and populations that reflect the burden of disease, but severe and relapse cases are underrepresented. Most CM trials now take place in LMICs, but the research is primarily funded and led by individuals and institutions from HICs.

Author summary

It is essential that clinical trial participants are representative of the population under investigation. Similarly, research must meaningfully include researchers who are from and/or based in the location where the study is being conducted, both to ensure that the research matches the local need but also to promote equity in research. Using clinical trials in HIV-associated cryptococcal meningitis as a case study, we conducted a systematic review to determine how inclusive and representative trials have been across the course of the HIV epidemic. We identified 39 studies. There was a geographical shift with trials moving from the USA to Africa and Asia over time. We found that recent trials were conducted in areas heavily affected by cryptococcal meningitis, but we did identify geographical areas and patient groups that have been underrepresented. We also found inequality within authorship that was skewed towards male researchers from high-income countries. These findings outline areas for our discipline to focus on. We can also use this study as a benchmark from which to monitor our progress over time. This is a broad methodology that could be adopted and adapted by other research groups.

Introduction

Global health research is a rapidly expanding and evolving field, and global health practitioners are increasingly reflecting on the ethos and equity of research [1–3]. Concerns have been raised that clinical trials are disproportionately conducted in a limited number of countries [4–7] and that individual researchers and institutions from high-income countries (HICs) disproportionately benefit from global health research [8], leading to calls to examine and potentially reform how global health research is conceptualised and conducted.

The emergence of the HIV epidemic was a catalyst for huge investment in global health, both in terms of research and service provision [9]. This expansion in investment led to the creation of a large number of transnational research partnerships (TRPs), whereby institutions in HICs partnered with those in low- and middle-income countries (LMICs) to collaborate on research studies [10]. As a consequence, an increasing number of research publications in the field of HIV are published each year, and the number of countries contributing to HIV research continues to grow [11]. This research has contributed to dramatic reductions in the number of new infections and deaths due to HIV over the last 30 years. Despite this, an estimated 1,700,000 people were newly infected with HIV, and 690,000 AIDS-related deaths occurred in 2019 [12], with sub-Saharan Africa at the centre of the epidemic. There remains a clear need for further research in prevention, treatment, and implementation. Ongoing research needs to be appropriate to the research setting, address high-priority research

questions [13], and include representative patient populations in order to generate applicable and generalisable findings [14].

In addition to ensuring that research participants are representative of the general population suffering from a disease, it is equally important to ensure that the researchers and institutions involved are representative of where the disease burden lies. At present, the majority of HIV funding comes from HICs [9], and therefore, the resources (both economic and human) flow from HICs to LMICs. Individuals and institutions from HICs lead the research, and researchers from LMICs are often found in the middle of author lists or excluded altogether from publications arising from African health research [15]. Inclusive research teams are essential to shape priorities and develop studies based on an in-depth understanding of the local context and inclusive representation will promote fairness, strengthen capacity, and ensure the future sustainability of research.

Cryptococcal meningitis (CM) remains a significant contributor to AIDS-related mortality in LMICs despite expanding rollout of effective antiretroviral therapy (ART) [16,17]. Annual global deaths from CM are estimated at 181,000, and CM is responsible for 15% of all AIDS-related deaths [18]. Over the past 30 years, clinical trials have defined treatment strategies that have led to a dramatic reduction in 10-week mortality rates from almost 100% to approximately 30% to 40% [19–21], but further clinical trials remain essential to further improve mortality outcomes and develop treatments appropriate for LMICs. Using CM as a case study, we performed a systematic review to examine how representative and inclusive CM clinical trials have been over the course of the HIV epidemic. Our aim was to describe the location of CM trials and the characteristics of those enrolled in order to perform a comparison with the current epidemiology. We also aimed to describe the gender, location, and nationality of researchers involved in CM trials.

Methods

We included any trial in which individuals with HIV-associated CM were randomly assigned to 1 of at least 2 intervention arms. The intervention could be any treatment for their condition, and there was no restriction on the nature of the comparator arm. Our focus was on the characteristics of individuals who were recruited into the trials and the researchers conducting the studies, and not on trial outcomes.

Search method and data collection

We searched for studies published up to 4 March 2020 using Medline, EMBASE, Cochrane Library, Africa-Wide, CINAHL Plus, and Web of Science. We also searched ClinicalTrials.gov for completed and published trials. Our search strategy combined terms related to HIV-associated CM and clinical trials (see Table 1A). No restrictions were placed on language. We excluded studies related to CM that was not associated with HIV or where data from HIV-infected individuals could not be extracted, observational studies, healthy volunteer studies recruiting participants with previously treated CM, studies without comparator arms, manuscripts where data were presented elsewhere in a primary manuscript, and nonoriginal research articles such as editorials. The search strategy and protocol were developed by the authors prior to commencing the search and were registered with PROSPERO (CRD42020171845).

All papers were entered into Covidence [22]. Duplicates were removed and then titles and abstracts were independently screened against the eligibility criteria by DSL and TL. Noneligible studies were removed, and the full texts of potentially eligible titles were assessed for

Table 1. (A) The search strategy. (B) A summary of the variables extracted from included papers.

A) Search strategy		
#1	Search (Meningitis, Cryptococcal[Mesh] OR cryptococcal meningitis)	
#2	Search (trial[mesh] OR Clinical Trial OR Clinical Trial, Phase I OR Clinical Trial, Phase II OR Clinical Trial, Phase III OR Clinical Trial, Phase IV OR Randomized Controlled Trial)	
#3	Search (Prospective Studies[Mesh] or prospective)	
	Searching #1 and #2 and #3 up to and including 04 March 2020	
B) Variables extracted from included papers		
Study	• Year of publication • Period of study • Location of study • Type of healthcare facility • Study design • Intervention(s)	• Control • Inclusion criteria • Exclusion criteria • Primary outcome • Secondary outcome(s)
Screening and Randomisation	• Number screened • Number screen failures • Reasons for each	• Withdrawals • Loss to follow-up
Participants	• Number of participants • Gender • Antiretroviral status	• Baseline Glasgow Coma Scale • First episode or relapse
Researchers	• Number of authors • Gender • Country of origin	• Country of residence during research period
Funders	• Name of funders • Category of funder	• Location of funder • Funding amount

https://doi.org/10.1371/journal.pntd.0009376.t001

inclusion. JNJ and MM adjudicated in the case of any conflict regarding study inclusion. The reference lists of included studies were searched to identify any additional eligible studies.

Data extraction

We extracted the relevant variables from each included paper (Table 1B) in 5 key domains: Study location and design, screening, participants, researchers, and funders. If necessary, the authors of an article were contacted for information that may not have been presented in the final publication. Researcher data were augmented by online searches of institutional web-pages and profiles on sites such as LinkedIn and Research Gate. If gender data could not be confidently elicited, then the gender of authors was determined using a website called Gender-ize.io that predicts the gender of a person given their name. Either DSL or TL performed the data extraction and then the other verified the data. Any discrepancies were discussed and resolved.

Data synthesis and analysis

Data were summarised using descriptive statistical analysis. To describe the geography of where participants were recruited, the locations of trial sites were analysed individually and also grouped into World Bank Regions. To demonstrate trends over time, comparison was made over 3 different periods: pre-2000, 2000 to 2009, and post-2010 to broadly demonstrate the pre-widespread ART era, early ART era, and established ART era, respectively. The end date of recruitment was used to determine within which of these time periods the study would be categorised. In papers where the specific months of recruitment were not stated, the year of publication was used. Where data could not be extracted for individual sites within multicountry trials, these numbers were averaged. We compared the characteristics of trial participants (gender, relapse rate, ART status, and baseline Glasgow Coma Scale (GCS)) to a composite

reference of recently published observational and surveillance data from routine care settings [16,23–26]. ART experienced was defined as being on ART at the time of randomisation, including individuals who were on zidovudine monotherapy prior to the availability of combination ART. Chi-squared testing for trend was performed to describe trends in the demographics of trial participants and researchers over time. With regard to the gender, countries where researchers were born and where they resided during the trial, each study was categorised as either taking place in HICs or LMICs, and chi-squared calculations allowed comparison between these 2 groups. Statistical analysis was conducted in Stata/SE 15.0.

Results

The initial database search yielded 1,040 studies (Fig 1), of which 291 were duplicates. A total of 749 titles and abstracts were reviewed, with 65 selected for full-text review. Of these, 26 were excluded. No additional studies were identified after reviewing the reference lists of included studies. A total of 39 studies were included in the final data analysis (Table 2).

Study design and location

We identified 39 trials that recruited a total of 5,056 participants between 1985 and 2017 and were published between 1990 and 2019 (Table 3). Fig 2 highlights the location and number

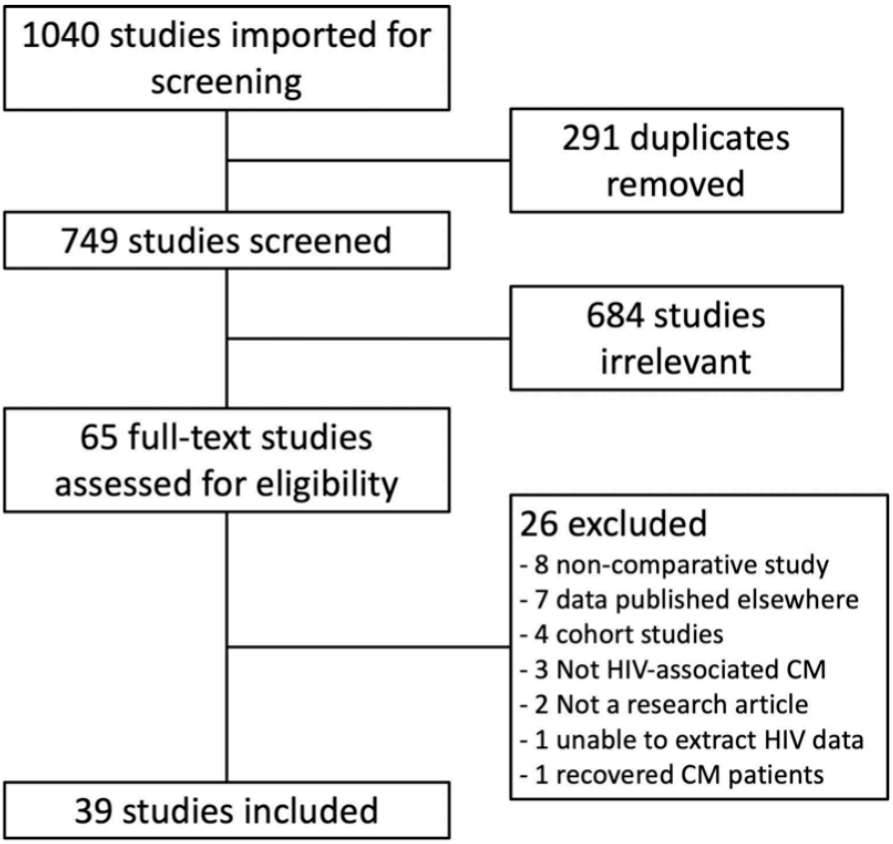

Fig 1. PRISMA diagram.

https://doi.org/10.1371/journal.pntd.0009376.g001

Table 2. A summary of the 39 included studies.

Study	Title
Larsen 1990 [27]	Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. A randomized trial.
Bozzette 1991 [28]	A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome.
deGans 1992 [29]	Itraconazole compared with amphotericin B plus flucytosine in AIDS patients with cryptococcal meningitis.
Saag 1992 [30]	Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis.
Powderly 1992 [31]	A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome.
Sharkey 1996 [32]	Amphotericin B lipid complex compared with amphotericin B in the treatment of cryptococcal meningitis in patients with AIDS.
Joly 1996 [33]	Randomized comparison of amphotericin B deoxycholate dissolved in dextrose or Intralipid for the treatment of AIDS-associated cryptococcal meningitis.
Leenders 1997 [34]	Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis.
Chotmongkol 1997 [35]	Comparison of amphotericin B, flucytosine and itraconazole with amphotericin B and flucytosine in the treatment of cryptococcal meningitis in AIDS.
Van der Horst 1997 [36]	Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome.
Mayanja-Kizza 1998 [37]	Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS.
Saag 1999 [38]	A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis.
Newton 2002 [39]	A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis.
Vibhagool 2003 [40]	Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study.
Mootsikapun 2003 [41]	The efficacy of fluconazole 600 mg/day versus itraconazole 600 mg/day as consolidation therapy of cryptococcal meningitis in AIDS patients.
Pappas 2004 [42]	Recombinant interferon- gamma 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis.
Brouwer 2004 [43]	Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial.
Chotmongkol 2005 [44]	Initial treatment of cryptococcal meningitis in AIDS.
Tansuphaswadikul 2006 [45]	Comparison of one week with two week regimens of amphotericin B both followed by fluconazole in the treatment of cryptococcal meningitis among AIDS patients.
Techapornroong 2007 [46]	Alternate-day versus once-daily administration of amphotericin B in the treatment of cryptococcal meningitis: a randomized controlled trial.
Milefchik 2008 [47]	Fluconazole alone or combined with flucytosine for the treatment of AIDS-associated cryptococcal meningitis.
Bicanic 2008 [48]	High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial.
Pappas 2009 [49]	A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis.
Nussbaum 2010 [50]	Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi.
Makadzange 2010 [51]	Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa.
Jadhav 2010 [52]	Liposomal amphotericin B (FungisomeTM) for the treatment of cryptococcal meningitis in HIV/AIDS patients in India: A multicentric, randomized controlled trial

(*Continued*)

Table 2. (Continued)

Study	Title
Hamill 2010 [53]	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.
Loyse 2012 [54]	Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis.
Jarvis 2012 [55]	Adjunctive interferon-gamma immunotherapy for the treatment of HIV-associated cryptococcal meningitis: a randomized controlled trial.
Jackson 2012 [56]	A phase II randomized controlled trial adding oral flucytosine to high-dose fluconazole, with short-course amphotericin B, for cryptococcal meningitis.
Day 2013 [57]	Combination antifungal therapy for cryptococcal meningitis.
Bisson 2013 [58]	Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis.
Boulware 2014 [59]	Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis.
Vaidhya 2015 [60]	Combination versus monotherapy for the treatment of HIV associated cryptococcal meningitis
Beardsley 2016 [21]	Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis.
Villanueva-Lozano 2018 [61]	Clinical evaluation of the antifungal effect of sertraline in the treatment of cryptococcal meningitis in HIV patients: a single Mexican centre experience.
Molloy 2018 [19]	Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa.
Rhein 2019 [62]	Adjunctive sertraline for HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial
Jarvis 2019 [63]	Short-course High-dose Liposomal Amphotericin B for Human Immunodeficiency Virus-associated Cryptococcal Meningitis: A Phase 2 Randomized Controlled Trial

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of participants that were recruited into clinical trials during the different time periods and presents this in comparison with data from the comprehensive 2014 global burden of disease estimates highlighting the 12 countries with the largest annual number of incident cases [18]. During the 30 years covered by this review, trials have moved from predominantly being conducted in the United States of America to sub-Saharan Africa where 75% of all CM trial participants were recruited since 2010. Only 43 patients from Europe and Central Asia have been recruited into a CM trial. The majority of trials (n = 29 (74%)) focused on induction therapy for CM. Primary outcomes were initially centred around clinical and microbiological markers, but in recent years, there has been an increasing trend towards mortality being the primary outcome. The majority (n = 38 (97%)) of trials only included HIV–infected patients and, where data were available, 20/24 (83%) trials only permitted the inclusion of patients suffering from a first episode of CM and 9/20 (45%) permitted only ART-naïve patients to be included. No studies specifically stated that pregnant or lactating women could be included but 30 (77%) and 23 (59%) studies, respectively, explicitly excluded these populations.

Screening and randomisation

Screening data were not available for all studies but were reported more thoroughly in recently published papers. Out of 18 papers where data were available, a total of 5,011 potential participants were screened, and 2,763 (55%) were randomised. Seven percent of individuals that were approached declined consent, and this was consistent across time periods. There were 12 documented instances of a patient not being included due to pregnancy and 5 due to lactation. The majority of studies (n = 38 (97%)) reported data on those who were withdrawn due to

Table 3. Characteristics of HIV-associated cryptococcal meningitis trials within different time periods and overall. Where data were not available, the number of trials with available data is presented as a denominator.

		PRE-2000	2000–2009	2010 ONWARDS	OVERALL N(%)	
TRIAL DESIGN						
Number of trials		14	14	11	39	
Focus of trial	**Induction**	10 (71%)	10 (71%)	9 (82%)	29 (74%)	
	Maintenance	3 (21%)	2 (14%)	0	5 (13%)	
	ART timing	0	1 (7%)	2 (18%)	3 (8%)	
	Other	1 (7%)	1 (7%)	0	2 (5%)	
Primary outcome	**Mortality**	0	1 (7%)	6 (55%)	7 (18%)	
	Microbiological	4 (29%)	7 (50%)	5 (45%)	16 (41%)	
	Clinical	3 (21%)	6 (43%)	0	9 (23%)	
	Combined	7 (50%)	0	0	7 (18%)	
Inclusion	**HIV infected only**	14 (100%)	13 (93%)	11 (100%)	38 (97%)	
	First episode only	4/7 (57%)	9/10 (90%)	7/7 (100%)	20/24 (83%)	
	ART naïve only	0/5	5/6 (83%)	4/9 (44%)	9/20 (45%)	
SCREENING AND RANDOMISATION						
Number of studies with data		1	7	10	18	
Number screened		42	965	4,004	5,011	
Number screened out		16	589	1,643	2,248	
% screen failures		38%	61%	41%	45%	
Screen failures	**Declined**	6 (14%)	66 (7%)	292 (7%)	364 (7%)	
	Pregnant	0	2 (0.2%)	10 (0.2%)	12 (0.2%)	
	Lactating	0	0	5 (0.1%)	5 (0.1%)	
Number randomised		1,814	797	2,455	5,066	
Withdrawal	**Number of studies with data**	13	14	11	38	
	Number randomised	1,759	797	2,455	5,011	
	Late exclusion	132 (8%)	26 (3%)	50 (2%)	208 (4%)	
	Withdrawal of consent	24 (1%)	3 (0.4%)	8 (0.3%)	35 (1%)	
	Loss to follow-up	58 (3%)	48 (6%)	16 (0.7%)	122 (2%)	
PARTICIPANTS						***P* value**
Gender	**Number of studies with data**	13	14	11	38	
	Number male	1,454	480	1,494	3,427	
	Number female	183	285	901	1,369	
	% female	11%	37%	38%	29%	$p < 0.0001^*$
ART status	**Number of studies with data**	7	9	9	25	
	Number ART naïve	906	594	1,196	2,696	
	Number ART experienced	288	11	889	1,188	
	% ART experienced	24%	2%	43%	31%	$p < 0.0001^*$
Episode	**Number of studies with data**	6	9	7	22	
	Number first episode	997	557	1,822	3,376	
	Number relapse	28	0	0	28	
	% relapse	3%	0%	0%	1%	$p < 0.0001^*$
Baseline GCS	**Number of studies with data**	8	9	9	26	
	Number GCS 15	765	410	1,654	2,829	
	Number GCS <15	131	58	697	886	
	% number GCS <15	15%	12%	30%	24%	$p < 0.0001^*$

ART, antiretroviral therapy; GCS, Glasgow Coma Scale.

*Statistically significant.

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Fig 2. Number of participants recruited into HIV-associated cryptococcal meningitis cryptococcal trials by country and broken down into time periods: (A) pre-2000, (B) 2000–2009, (C) 2010 onwards, and D) data from the global disease burden estimates identifying the 12 countries globally with the largest number of annual cases in 2014 [18]. Created using a base map available at www.displayr.com/create-a-geographic-map/.

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meeting an early withdrawal criteria (n = 208/5,011 (4%)), withdrew their consent (n = 35/5,011 (1%)), or were lost to follow-up (n = 122/5,011 (2%)).

Participants

Data from 38/39 included studies demonstrated that 1,369/4,796 (29%) of participants in CM trials were female (Fig 3). There was a significant increase over time in the proportion of female participants ($p < 0.0001$). There was no report of any pregnant or lactating women being included in any clinical trial. A total of 1,188/3,884 (31%) participants were ART experienced upon enrolment into the trial. The proportion of ART experienced participants fluctuated from 24% prior to 2000 to 2% between 2000 and 2009 and 43% after 2010 demonstrating a general increase ($p < 0.0001$). A total of 28/3,404 (0.8%) participants were presenting with a relapse of CM, and these were all recruited prior to 2000. Twenty-four percent (886/3,715) of participants were recruited with a GCS <15, indicating impaired decision-making capacity, and there was a trend for the proportion with reduced GCS to increase over time ($p < 0.0001$).

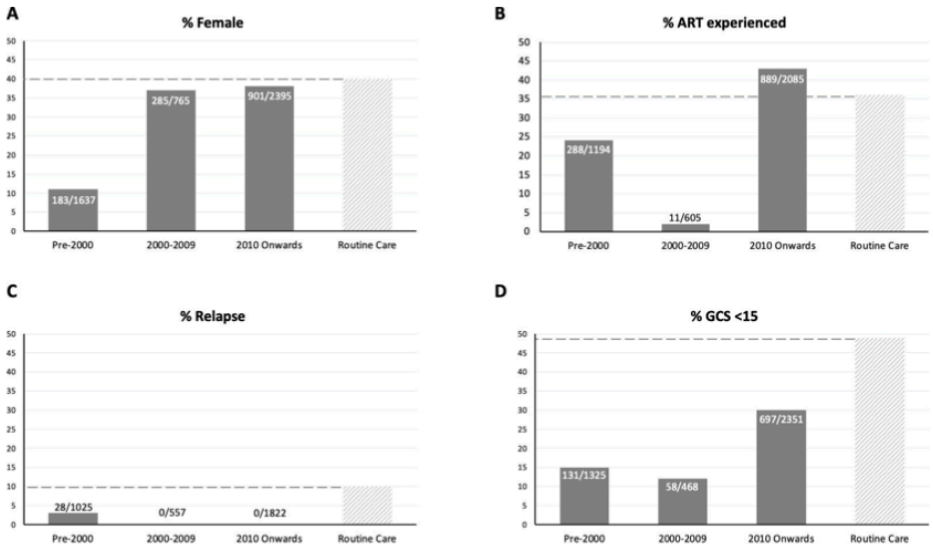

Fig 3. The characteristics of HIV-associated cryptococcal meningitis trial participants across 3 different time periods (pre-2000, 2000–2009, and 2010 onwards) broken down by (A) Sex, (B) ART experience, (C) Relapse, and (D) Baseline Glasgow Coma Scale (15) score, all compared with a composite reference from recently published observational data.

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Table 4. Researcher data summarising the number, gender, country of residence, and nationality of named authors on the primary manuscript of HIV-associated cryptococcal meningitis clinical trials.

		PRE-2000	2000–2009	2010 ONWARDS	OVERALL	
Number of papers		14	14	11	39	
Median number of authors (range)		12 (3–17)	8 (2–14)	17 (4–37)	11 (2–37)	
POSITION IN LIST OF AUTHORS						***P* value**
First author	number female (%)	3 (21%)	6 (43%)	1 (9%)	10 (26%)	$p = 0.5712$
	Number resident of research location (%)	13 (93%)	14 (100%)	10 (91%)	37 (95%)	$p = 0.0885$
	Number national of research location (%)	12 (86%)	9 (64%)	2 (18%)	23 (59%)	$p = 0.0008$*
Second author	number female (%)	2 (14%)	5/13 (38%)	4 (36%)	11/38 (29%)	$p = 0.2037$
	Number resident of research location (%)	12 (86%)	12/13 (92%)	10 (91%)	34/38 (89%)	$p = 0.6541$
	Number national of research location (%)	12 (86%)	12/13 (92%)	8 (73%)	32/38 (84%)	$p = 0.4167$
Final author	number female (%)	2 (14%)	3 (21%)	0	5 (13%)	$p = 0.3316$
	Number resident of research location (%)	12 (86%)	10 (71%)	7 (64%)	29 (74%)	$p = 0.2026$
	Number national of research location (%)	12 (86%)	9 (64%)	5 (45%)	26 (67%)	$p = 0.0331$*
OF ALL NAMED AUTHORS						
Number of named authors		147	116	193	456	
Gender balance	number female (%)	31 (21%)	44 (38%)	58 (30%)	133 (29%)	$p = 0.1027$
Residence	Number resident of research location (%)	132 (90%)	99 (85%)	141 (73%)	372 (82%)	$p < 0.0001$*
Nationality	Number national of research location (%)	124 (84%)	88 (76%)	105 (54%)	317 (70%)	$p < 0.0001$*

OF ALL NAMED AUTHORISED CATEGORISED BY INCOME STATUS OF RESEARCH LOCATION					
		HIC	**LMIC**	**OVERALL**	***P* value**
Number of papers		11	28	39	
Number of named authors		122	334	456	
Gender balance	number female (%)	25 (20%)	108 (32%)	133 (29%)	$p = 0.014$*
Residence	Number resident of research location (%)	122 (100%)	250 (75%)	372 (82%)	$p < 0.0001$*
Nationality	Number national of research location (%)	114 (93%)	203 (61%)	317 (70%)	$p < 0.0001$*

HICs, high-income countries; LMICs, low- to middle-income countries.

*Statistically significant.

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Researchers

The median number of researchers named as authors on the primary manuscript was 11 (range 2 to 37), and 7 papers also had additional contributors listed within an appendix (Table 4). Of all named researchers, 29% were women. Overall, female researchers were underrepresented as first (26%), second (29%), third (19%), and final author (13%). No significant change was observed over time. Regarding whether named authors were resident in one of the research locations during the period of the study, this was case for the majority of first (95%), second (89%), and final (74%) authors. A total of 82% of all named authors were resident in one of the research locations, and there was a trend for this proportion to reduce over time ($p < 0.0001$). Finally, in terms of whether authors were nationals of countries where participants were being recruited, this was the case for a smaller majority of first (59%), second (84%), and final (67%) of authors. A total of 70% of named authors were nationals of research sites, and there was a strong downward trend observed over time ($p < 0.0001$). When comparing these same 3 domains by comparing studies that were conducted in HICs and LMICs, there were significantly more female authors on studies conducted in LMICs ($p = 0.014$). There were also significantly fewer named authors who were resident or nationals of research sites within trials conducted in LMICs ($p = < 0.0001$ and $p = < 0.0001$, respectively).

Funding

There were significant missing data related to the funding of trials, particularly the funding amount. Of the 33 trials where data were available, 19 (58%) were funded by a single funder, and 14 (42%) had multiple funders. Thirty-six percent of trials had funding from industry, 67% from government bodies, and 42% from nongovernmental bodies. Twenty-nine (88%) trials were entirely funded by institutions based in HICs, and 4 (12%) were entirely funded by institutions based in LMICs.

Discussion

Our systematic review findings show that HIV-associated CM trials are generally conducted in locations reflecting the global burden of disease. There has been a marked shift from the USA to sub-Saharan Africa over the last 2 decades. CM trials are broadly representative of the patient population, but there is an underrepresentation of very sick patients with a low baseline GCS and those suffering with a relapse of CM. With the change in location from HICs to LMICs, there has been a significant trend for authors to be nonnationals of the country where research is performed, particularly in first and senior author positions. Female authors are generally underrepresented and, again, this is most marked in first and particularly senior author positions.

CM remains a major public health problem, and it is reassuring that the number of trials being performed has remained steady throughout the HIV epidemic. The bulk of CM disease has likely always been in sub-Saharan Africa, and roughly 75% of all CM deaths currently occur in sub-Saharan Africa. As the number of cases of CM reduced in North America and Western Europe, there was a shift in focus to LMICs with a clear desire to identify simpler, less toxic, and more effective treatment regimens for CM. It is therefore appropriate that sub-Saharan Africa is now the epicentre of CM trials, recruiting 76% of all trial participants in the last decade. This is followed by the Asia and Pacific region where 22% of all CM deaths occur and 21% of participants were recruited. This demonstrates that the regional distribution of CM trials is now well matched to the epidemiology and likely mirrors a general increase in funding for global health [64], including HIV research in LMICs [65]. The bulk of research has taken place in a small number of countries (particularly Malawi, South Africa, and Uganda). By studying Fig 2, which compares the number of participants recruited in different countries with data from the global disease burden estimates identifying the 12 countries globally with the largest number of annual cases in 2014, one can see areas with a high burden of disease that have not been involved in clinical trials such as Nigeria, Kenya, and Mozambique. Other countries, such as India for example, have a lot of CM cases but have only recruited a small number of participants into clinical trials. This uneven geographical spread is not unique to CM trials and is reflected in the global distribution of clinical trials more broadly. There are multiple, overlapping reasons for this which include the levels of internal and external funding made available to research and development in a specific country [66]; access to partnerships with other research institutions; experience with clinical research (including having hosted previous CM trials); and the efficiency of the regulatory approval process in country [67].

When considering the participants in CM trials, the proportion who are female, ART experienced, and suffering with severe disease has increased over time. The majority of earlier trials were conducted in HICs where the epidemic particularly affected men who have sex with men, and over time as trials were increasingly conducted in sub-Saharan Africa and the Asia and Pacific region, there has been an increase in the proportion of female participants: 38% of all trial participants recruited since 2010 were female. Men are more likely to be diagnosed with advanced HIV disease, either due to delayed testing or nonadherence to ART and therefore

more likely to develop CM. In routine care conditions, the proportion of CM patients who are female is roughly 40% [16,23,24,68], so although there is no gender parity, the most recent CM trials mirror the general patient population.

CM almost entirely occurs in individuals with very advanced HIV disease (CD4 <100 cells/mm^3), and conception is quite rare in this population [69]. Pregnant and breastfeeding women are however most often excluded from CM trials due to a number of reasons. Often there is reluctance from ethics committees to include pregnant women in research studies, and sponsoring institutions may not be willing to take on the risk of litigation in the event of a poor outcome [70]. In addition, there are scientific concerns about antifungal toxicity, particularly with regard to fluconazole as there is weak evidence to suggest it is teratogenic at the high doses given for CM [71,72]. One caveat to this is whereby trials include lactating women who voluntarily stop breastfeeding to participate in the trial and are supplied with formula milk by the research team. In routine care settings, pregnant and lactating women with CM often receive treatment with fluconazole, particularly where this is the only treatment available. The inclusion of pregnant and lactating women in clinical trials is a broad and urgent issue [2,73,74], and there is reassuring evidence to suggest that this deficit is slowly being addressed in HIV-related clinical trials at least. Our research has identified that, out of 5,011 patients who were screened, only 12 were excluded due to pregnancy and 5 due to lactation, so this is not a large population that is being excluded. That does however not negate the need to build an evidence base to guide the management of pregnant and lactating women suffering from this potentially fatal infection. The most comprehensive collection of clinical data on CM in pregnancy is a case series from Uganda [75]. Teams across the globe should strongly consider collecting and combining observational data sets to build a deeper understanding of the safety profile of different treatment regimens and to collate maternal and neonatal outcomes. In addition, pregnant and lactating women should be considered for inclusion in future trials.

Despite allowing treatment-experienced patients (those predominantly on zidovudine monotherapy) to be recruited in the earlier trials in the USA, concerns about ART status and the potential for that to be a confounding factor led to most trials in the 2000s only including ART-naïve patients. These concerns proved to be unfounded, and there has been no difference in outcome observed between these groups [19]. Over the last decade, the number of CM patients who were ART experienced has steadily increased to the current levels seen today of roughly 36% [23,24,26], and clinical trial participation has matched this.

Importantly, almost all trials have excluded patients suffering from a relapse of CM. Only 28 individuals in total were recruited into trials, and these were all before 2000. The rationale for this is that patients may have acquired antifungal resistance and that the induction regimens may not be effective. The 2 largest CM trials conducted in recent years excluded 8% to 9% of all patients screened due to relapse [19,62], and recent published data from routine care settings have shown relapse to occur in roughly 10% of cases [16,23,25,26]. Relapse is therefore relatively common and drug resistance testing is not widely available so this population should be considered for future clinical trials, either among those suffering a first episode or within independent studies.

The methodology adopted in this study can also assist with the planning of future clinical trials and the assumptions that can be made about participant attrition when calculating a sample size. We have learned that it is rare for participants to withdraw their consent (1%) or be lost to follow-up (2%). This likely reflects the fact that CM is a life-threatening condition and clinical trials often provide promising therapies or, particularly in LMICs, a standard of care that is superior to the routine care available. There is extensive literature to demonstrate that individuals with CM who enrol in a clinical trial have a better outcome, regardless of treatment arm [23,76]. The reasons for this include having a dedicated clinical research team who

have more time to care for patients, better monitoring and correction of drug-induced toxicities, and aggressive management of raised intracranial pressure, a common and potentially fatal complication of CM. These quantitative data do not however determine the impact of structural coercion into these trials, nor does it draw on any lived experience of trial participants. This is the focus of our research team who have embedded an ethnographic study into the ongoing AMBIsome Therapy Induction OptimisatioN (AMBITION) study [77].

It is essential to include researchers who are from and/or based in the location where the study is being conducted in a meaningful way. We found that, over time, there was a significant trend of named authors being decreasingly a resident or national of a research site. This finding mirrors the increase in research conducted in LMICs through TRPs and is supported by the significant difference in these 2 domains when comparing trials conducted in HICs and LMICs. This is consistent with broader reviews of global health research in Africa in general which has found that indigenous researchers are frequently "stuck in the middle" [3,15]. For example, Hedt-Gauthier and colleagues found that among general health-related studies published between 2014 and 2016, just 54% of authors were from the country of the paper's focus and this was 52.9% among the first author. Overall, in this study, we found this to be 70% and 59%, respectively, which is marginally better. There is no doubt that our discipline needs to work much harder to address this inequality, and we acknowledge the authorship of this paper itself lacks the diversity we aspire to. An in-depth discussion is beyond the scope of this article, and we encourage readers to access and actively engage with the growing body of literature on this topic, including discussions on the role of researchers from HICs when it comes to decolonising global health [78–81].

Authorship of CM trial manuscripts was found to have poor representation of female authors. Of all named authors, 29% were female, but a lower proportion were first (26%) and final (13%) author. Although there was no significant change over time, women were better (but still under) represented as authors of trials conducted in LMICs, and as the majority of trials are currently conducted in LMICs, there may be an increase over time. There were however no female authors from LMICs who were listed as the first or final author in the last decade. This finding is consistent with numerous other studies that have found female researchers to be underrepresented in clinical trials and more likely to occupy the middle section of the authorship list [82,83]. This may be partially due to the fact that, in Africa for example, 72% of all physicians are male [84], and in patriarchal societies, female physicians may have competing demands with regard to childcare and family responsibilities [67]. There is an urgent need to ensure female researchers are given the opportunity to gain research experience, be appointed to and supported within senior research roles, and ultimately become eligible for more of the prestigious authorship positions. The Global Health 50/50 initiative provides extensive guidance for individuals and institutions to address gender inequality in the workplace [85].

This is the first systematic review that has described the characteristics of participants in CM interventional trials over time and made a comparison with the general population who develop the disease. There are several limitations to this study. We only included clinical trials in this review, and we acknowledge that clinical trials are not the only useful source of data. There has been a large body of observational work conducted that has informed CM policy which was not included in this review. Observational study participants are more likely to resemble the overall population affected, and, given less stringent requirements in terms of conduct and monitoring, the authors and funders are likely more representative of study locations. There is an urgent need and opportunity with electronic systems to streamline and simplify data collection and monitoring for randomised studies, so that smaller institutions (especially at primary and secondary level) and local investigators are not, in effect, excluded from participation. In addition, there were rare instances where, despite additional efforts, it was not possible to extract data for

all variables from published papers. In particular, the earlier studies did not consistently present full screening information. This resulted in some studies being excluded from specific aspects of the analysis which may have led to an inaccurate overall picture.

This work was motivated by the pursuit of equity in global health research. Although broad reviews and commentaries have highlighted concerns regarding representation and inclusion, it is important to acknowledge that each individual disease tends to have its own tight-knit research community and that there may be considerable heterogeneity between groups. We have presented a comprehensive but simple methodology to describe trends in the representation and inclusion of patients and researchers over time. This methodology can be used to help focus our future efforts as we strive for equity. In addition, we now have the foundation of what can be an ongoing monitoring exercise to map our progress over the coming years. We believe that this methodology could be simply adopted and adapted by other research groups.

Conclusions

HIV-associated CM trials are generally conducted in locations which are heavily affected by the disease. Women and ART-experienced individuals are well represented as participants in clinical trials, but there is an underrepresentation of those with severe CM and those suffering from a relapse. Recent trials have been predominantly conducted in LMICs, and when compared to earlier trials in HICs, there is a tendency for first and senior authors to be nonnational and/or nonresident of the research location. Female researchers are underrepresented in general but particularly as first and senior authors. This paper highlights areas for the CM research community to focus on as we strive for equity.

Key Learning Points

- HIV-associated cryptococcal meningitis remains a significant contributor to AIDS-related mortality, and ongoing clinical trials are needed to improve outcomes.
- Trials for cryptococcal meningitis occurred in high-incidence countries, but some highly affected countries have not hosted trials.
- The sex and antiretroviral therapy status of trial participants matched the general population with cryptococcal meningitis, but individuals with reduced consciousness and those suffering a relapse were underrepresented.
- Women were underrepresented as authors, particularly as first and final authors.
- Compared to trials conducted in high-income countries, trials conducted in low- and medium-income countries were less likely to have authors resident in or nationals of the trial location.

Top Five Papers

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. Lancet Infect Dis. 2017;17(8):873–8

2. Azzo C, Tsholo K, Tlhako N, Patel RKK, Leeme T, Jarvis JN, et al. High Mortality in HIV-Associated Cryptococcal Meningitis Patients Treated With Amphotericin B–Based Therapy Under Routine Care Conditions in Africa. Open Forum Infect Dis. 2018;5(11).

3. Heyrana K, Byers HM, Stratton P. Increasing the Participation of Pregnant Women in Clinical Trials. JAMA. 2018;320(20):2077–8.

4. Hedt-Gauthier BL, Jeufack HM, Neufeld NH, Alem A, Sauer S, Odhiambo J, et al. Stuck in the middle: a systematic review of authorship in collaborative health research in Africa, 2014–2016. BMJ Glob Health. 2019;4(5):e001853

5. Global Health 50/50. Power, privilege and priorities: the Global Health 50/50 2020 report. 2020.

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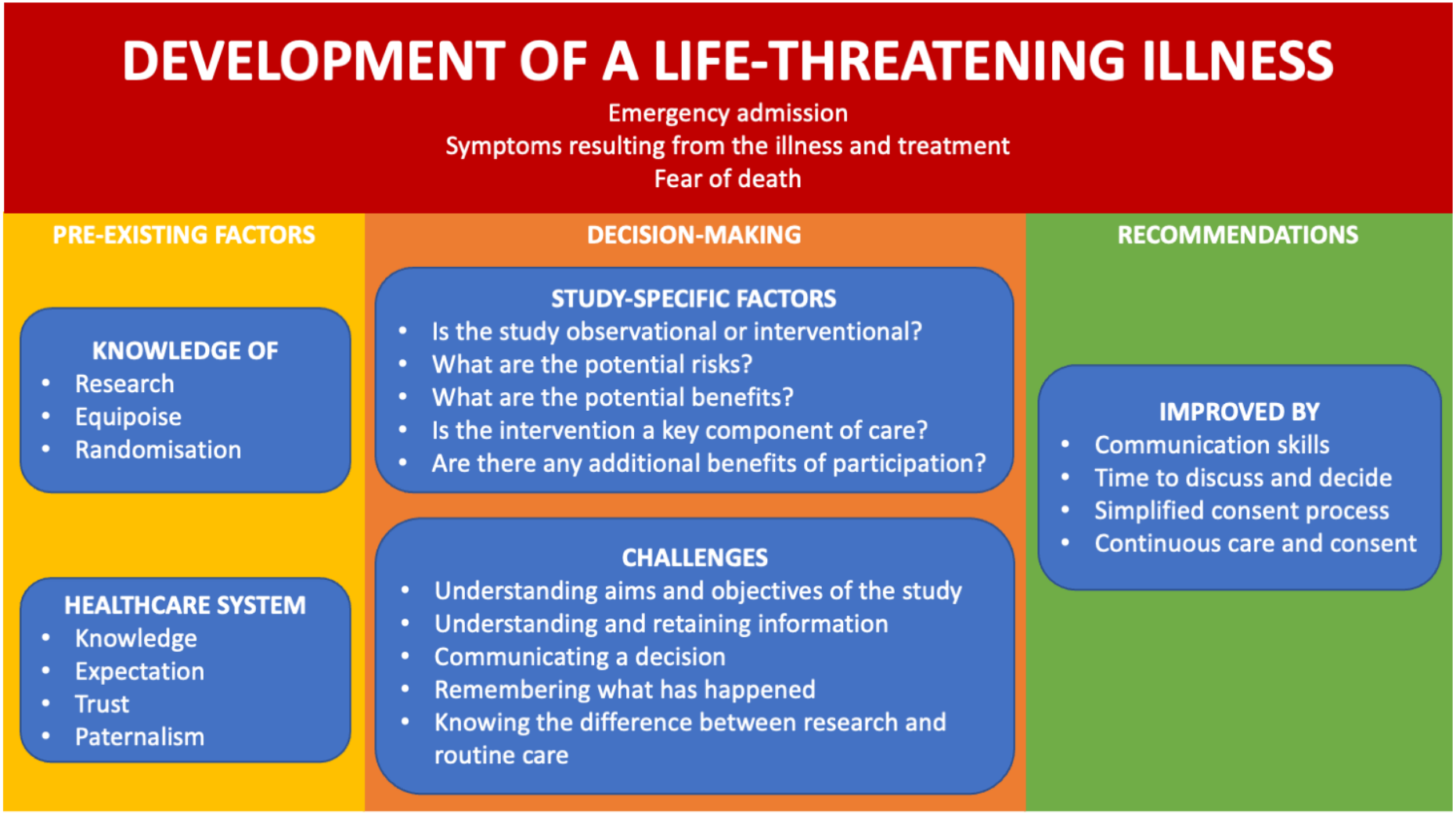
RESEARCH PAPER TWO: CLINICAL RESEARCH FOR LIFE-THREATENING ILLNESSES: A CRITICAL INTERPRETIVE SYNTHESIS OF QUALITATIVE DATA RELATED TO THE EXPERIENCE OF PARTICIPANTS AND THEIR CAREGIVERS

Summary of Findings

The comprehensive search strategy yielded 16,418 studies, of which 5,477 were duplicates and 10,941 were screened. Sixty-two full-text studies were assessed for eligibility and 22 studies with a total of 668 participants were included in the final analysis. Nineteen of the studies were conducted in HICs and three in LMICs (Ghana, Kenya, and Uganda). The studies were embedded within 18 randomised controlled trials and one observational study. Of the 22 qualitative studies, 14 were embedded within clinical studies that recruited adults and eight in clinical studies which recruited children and/or neonates.

The synthetic construct, a higher order construct which aimed to broadly encompass the entirety of the critical interpretive synthesis is presented in Figure 6. The life-threatening illness was identified as an overarching context that permeated the analysis and the experience of the clinical study. Life-threatening illnesses were often associated with severe symptoms and fear brought about by an emergency hospital admission with death as a possible outcome. In addition, the treatment of the underlying illness could itself be painful or disorientating, particularly if strong analgesia and/or invasive procedures were required. All this process takes place within an accelerated period of time in which diagnosis and initiation of treatment need to take place rapidly in order to improve the chance of survival, which itself is not certain.

Figure 6: Critical Interpretive Synthesis - Synthetic Construct



Note: This figure is repeated in Research Paper Two.

We then considered this life-threatening context across four broad domains. The first was pre-existing knowledge of research and expectations of healthcare. Most individuals had no previous knowledge or experience with clinical research and a lack of understanding of core principles such as equipoise and randomisation, which meant there was often a limited foundation to build on when being introduced to clinical studies. The difficulty in understanding these concepts was further exacerbated by the life-threatening illness. In addition, previous experience with and expectations of healthcare systems and professionals impacted on the trust placed in both the routine care and the research environment. This was particularly marked in studies conducted in LMICs. Trust was a core concept that permeated throughout the analysis and when faced with a life-threatening illness individuals explained that although it was not always possible to understand and digest the information, they often defaulted to agreeing to participate based on trust in the research team approaching them. In some settings where the healthcare system is more paternalistic there would be a similarly passive approach towards decision making which was based more on acquiescence than coercion.

The second domain was study specific factors. Given the life-threatening nature of the illness, the potential benefits of clinical studies were immense and, in many instances, we found that decision makers expected there to be a direct effect on them or the person they were representing. This was true even in scenarios in which the intervention itself was not necessarily expected to improve survival and where it was naturally expected that those randomised to the standard of care would receive no additional benefit at all, due to a lack of awareness of the concept of randomisation. We found that this led to an underestimation of

risk, an overestimation of benefit and an expectation of being allocated to the intervention arm.

The third domain related to challenges with the decision-making process which were not necessarily specific to the clinical study but were exacerbated by the life-threatening nature of the illness. This included difficulties in understanding the aims and objectives of the study; understanding and retaining information; communicating a decision; recollecting what had happened in the days and weeks following the event; and knowing, or being able to tell, the difference between research and routine care.

Finally, the fourth domain centred on recommendations for researchers. Broadly, these included improved communication skills; being given adequate time to ask questions, consult others, and make a decision; simplified consent processes and ongoing interaction with the research teams, including continuous consent.

Importance of Findings

This was the first systematic review of qualitative methods data exploring this subject of being enrolled in a clinical trial when suffering from a life-threatening illness. By collating and interpreting these disparate data we were able to develop a comprehensive synthetic construct which enabled broad recommendations to be made that could be applied to future clinical trials.

Dissemination and Impact

This paper has been submitted to *Trials*.

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Student ID Number	1800328	**Title**	Dr
First Name(s)	David		
Surname/Family Name	Lawrence		
Thesis Title	The Lived Experience of Participants in an African Randomised Trial (LEOPARD)		
Primary Supervisor	Prof Joseph Jarvis		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	DSL conceptualised the project. All authors developed the methodology. DSL performed the searches. DSL and AS reviewed the abstracts; selected the included papers; extracted the data; analysed the data and drafted the initial manuscript. All authors refined and approved the final manuscript.

SECTION E

Student Signature	[redacted]
Date	15/09/2022

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Clinical research for life-threatening illnesses: A critical interpretive synthesis of qualitative data related to the experience of participants and their caregivers

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ABSTRACT

Background: Research into life-threatening illnesses which require emergency hospitalisation is essential. This group of patients are unique in that they are experiencing an unfolding emergency when they are approached, enrolled, and followed up in a research study. We aimed to synthesise qualitative data from trial participants and surrogate decision makers to deepen our understanding and inform the design and conduct of future clinical trials for life-threatening illnesses.

Methods: We conducted a critical interpretive synthesis of qualitative data from trial participants and surrogate decision makers related to the experience of participating in a clinical research study when suffering from a life-threatening illness. A scoping review informed a systematic review of published data. We searched research databases and reviewed papers for inclusion. Primary data and interpretations of data were extracted from each paper. Data were analysed using reciprocal translational analysis, refutational synthesis, and lines of argument synthesis to develop a synthetic construct.

Results: Twenty-two papers were included. Most individuals had no previous knowledge or experience with clinical research. Individuals making decisions were directly experiencing or witness to an unfolding emergency which came with a myriad of physical and psychological symptoms. It was difficult to differentiate clinical research and routine care and understanding of core concepts around research, particularly randomisation and equipoise were limited. We found that this led to an underestimation of risk, an overestimation of benefit and an expectation of being allocated to the intervention arm. The decision-making

process was heavily influenced by trust in the research team. Individuals suggested that abbreviated information, presented in different ways and continuously throughout the research process, would have increased knowledge and satisfaction with the research process.

Conclusion: Individuals suffering from a life-threatening illness who are being invited to participate in clinical research need to be managed in a way that adapts to the severity of their illness and there is a need to tailor research processes, including informed consent, accordingly. We provide suggestions for further research and implementation work around research participation for individuals suffering from a life-threatening illness.

Registration: PROSPERO: CRD42020207296.

Keywords: Informed consent; emergency; clinical trial; clinical research; decision-making; review; qualitative research

BACKGROUND

Clinical trials are essential to determine how to manage illness and improve lives. Randomised controlled trials are recognised as the gold-standard in the generation of medical evidence and are a primary source of data when generating treatment guidelines. Interventional clinical trials would not be possible without the willing participation of individuals who are suffering with the illness under investigation. All prospective participants for a clinical trial must be fully informed of the study and be willing to provide consent, free from coercion. Once enrolled, participants move through a series of processes which may include the provision of personal and medical information, physical examination, investigations such as blood tests or imaging, administration of an intervention such as medication and ongoing follow-up to measure or determine their response. All participants are free to withdraw their consent at any time during the course of the study and can do so without having to provide a reason. These processes are guided by ethical principles laid out by the Declaration of Helsinki (World Medical Association, 2013) and the International Conference on Harmonisation Good Clinical Practice (European Medicines Agency, 2017).

Qualitative methods research is often conducted alongside clinical trials, both to measure the personal, psychological or 'quality-of-life' outcomes of an intervention but also more broadly to explore bioethical aspects of clinical research. This work has focused particularly on the motivation for participating in trials, experience of the informed consent process, and participant satisfaction with the trial experience as a whole.

Motivation: There has been much research conducted as to the underlying motivation for joining clinical trials (Corneli et al., 2015; Cox & McDonald, 2013; Gikonyo et al., 2008; Katz et al., 2019; Smailes et al., 2016; Ssali et al., 2015). Clinical trials are primarily designed to answer a research question, the findings of which it is hoped will later be of benefit to a larger population. The concept of 'therapeutic misconception' is well documented in clinical research and is the belief that every aspect of the research project to which someone has consented has been designed to benefit them directly (Appelbaum et al., 1987). Some individuals may benefit by participating but this research is not designed so that everyone will (Molyneux et al., 2004). Despite this it is not uncommon for research participants to expect a personal therapeutic benefit from the treatment they receive, including in placebo-controlled trials (Houghton et al., 2018; Leach et al., 1999). Altruism is also a factor but may be described as being 'conditional' on receiving these personal benefits (Cox & McDonald, 2013; Katz et al., 2019; Smailes et al., 2016).

Informed Consent: The process of informed consent has been subject to much scrutiny by clinical trialists and social scientists alike. Current approaches to consent frame patients as active decision-makers and can exaggerate their agency (Farmer, 2002). `Doing consent' is seen as an easily auditable process which protects researchers rather than participants (Gikonyo et al., 2008) and as a result discussions around the ethics of informed consent often focus on information provision and the readability of forms (Kingori, 2013). Comprehension of the informed consent process, although not universally defined, has been well studied and found to be generally poor (Afolabi et al., 2014; Tam et al., 2015), particularly where

participant information sheets are considered too long and technical (Gikonyo et al., 2008; Negussie et al., 2016; Vallely et al., 2010; Vischer et al., 2016; Vischer et al., 2017).

Participant Experience: Understanding the participant experience as they navigate through the scheduled events of a clinical trial can provide an opportunity to improve ongoing trials and develop better trials for the future. A broad range of qualitative methods have been used to explore participant experience, ranging from interviews focused on 'participant satisfaction' (Pflugeisen et al., 2016) or 'good participatory practice' (Mack et al., 2013) to in-depth ethnographic studies adopting a range of theoretical perspectives (Geissler, 2005, 2011).

This review of qualitative methods research aims to explore participation in a clinical trial when an individual was suffering specifically from a life-threatening illness. We aim to synthesise the experience of participants and their loved ones who are recruited whilst suffering from a condition that has led them to be admitted to hospital and for which there is a risk of death. We believe that the severity of their underlying condition and the urgency with which treatment (and therefore enrolment) must be initiated create a complex sociological context. This context could have a unique impact on their motivation to participate, the informed consent process, and their perspective on the clinical trial experience as a whole. Given the high stakes of such a scenario there is value in collating and synthesising qualitative data to understand how individuals navigate this process, make decisions, and reflect on the experience from beginning to end. This stands to deepen our

understanding and inform the design and conduct of future clinical trials for life-threatening illnesses.

We therefore conducted a critical interpretive synthesis with the aim of collating data from the perspective of participants and their caregivers related to the experience of being in a clinical trial for a life-threatening illness.

METHODS

We conducted a critical interpretive synthesis broadly in line with the methodology outlined by Dixon-Woods et al (Dixon-Woods et al., 2006). We acknowledged that there was significant heterogeneity in the methodology of published critical interpretive syntheses and that this approach has evolved over time (Depraetere et al., 2021). We therefore adopted an approach to the methodology that was flexible and evolved to enable us to best try and meet our aim.

Defining the population: We defined our population of interest as any individual (or their caregiver), regardless of age, diagnosed with a life-threatening illness and recruited into a clinical study. A life-threatening illness was defined as any medical condition that required emergency inpatient admission to a healthcare facility and for which the potential sequelae included death. Clinical study was defined as any prospective observational or interventional study that required the individual or a surrogate to provide consent. We wanted to begin to understand the entire experience from beginning to end so included studies exploring all aspects of the clinical study including being approached, screened, consented, randomised,

managed and followed up as a participant. We did however exclude clinical studies with a waiver of consent as despite not wanting to focus entirely on the consent process itself we were interested in experiences in which individuals had been involved in a decision-making process. A systematic review of research without prior consent in paediatric trials has been published elsewhere (Furyk et al., 2018). We were solely interested in in-depth qualitative research published in English that related to the trial experience rather than that focused specifically on the acceptability of the intervention under investigation.

Scoping review: An initial scoping review was conducted to identify published work that was relevant to the research question. Following Eakin and Mykhalosvsky (Eakin & Mykhalovskiy, 2003), we reviewed and discussed a selection of relevant papers and then used this broad review as a basis to refine our comprehensive search strategy. We approached the concept of life-threatening illnesses by searching for broad terms such as 'emergency', 'mortality' and 'life-threatening' as well as a select number of pathologies that are deemed to be life-threatening such as 'meningitis' and 'stroke'. During this process we acknowledged that a broad range of pathologies and scenarios could technically be life-threatening and therefore accepted that any comprehensive search strategy was likely to produce a large number of results. From this initial scoping review, we were then able to define a comprehensive search strategy. The inclusion and exclusion criteria for the critical interpretive synthesis are presented in Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion	**Exclusion**
Enrolled in a prospective (observational or interventional) clinical study that required the provision of consent	Involved in a retrospective study or did not need to provide consent
Clinical study focuses on a life-threatening condition	Not a life-threatening condition
Data from study participant or their caregiver/relative/surrogate/parent/guardian	Data from anyone else
Qualitative or mixed-methods study	Exclusively quantitative analysis
Semi-structured or in-depth interview, focus group, ethnography, observation, diaries	Self-administered, short answer or structured questionnaire, multiple-choice answer survey
Data relating to the trial experience	Data focusing on the intervention, data for secondary outcomes e.g. acceptability
Full-length, original research paper	Abstracts, poster, conference proceeding, viewpoint, commentary
English	Not in English

Comprehensive search: We developed a search strategy (Appendix 1) and searched the following information sources: Medline, Embase, Web of Science, Global Health, JSTOR, Academic Search Complete, Scopus, African Journals Online, PsychINFO and PsychEXTRA. There was no restriction on publication date. Reference lists of included studies were also searched to identify any additional potentially eligible studies. All papers were then entered into Covidence and duplicates were removed. The titles and abstracts of all potentially eligible studies were screened by both DSL and AS to determine which were suitable for full-text review. DSL and JNJ are clinicians with specialist training in internal medicine and were able to provide professional opinion on the life-threatening nature of the illness under study. In the case of disagreement, the two reviewers discussed and, if necessary, JS and JNJ were also available for arbitration. DSL and AS then reviewed the full-text of those studies and the same

arbitration approach was adopted to determine which would be included in the full review. When planning this stage there was uncertainty around the number of papers that would be identified by the search and how many would be eligible for inclusion in the review. If faced with an unmanageable workload we therefore considered drawing on purposive sampling and employing theoretical sampling and theoretical saturation to decide on a collection of papers that would be appropriate, however this was not necessary.

Data extraction and analysis: We developed a data extraction form (Appendix 2) with domains related to the focus of the clinical study; the methodology of the qualitative study; the results including any themes and their description; theoretical frameworks; all primary data presented and a quality assessment. We extracted both primary data such as direct quotes as well as interpretive data including themes, frameworks, and conclusions. Where data were collected from a range of informants, we focused on the perspective from study participants and surrogate decision makers, rather than researchers or those who declined to participate. We did not include those who declined as we were interested in the entire continuum of a clinical trial and that can only be elicited from those who have participated. DSL and AS extracted data from half of the included papers each, with the other then reviewing the data extraction form and amending after discussion, as necessary.

Critical interpretive synthesis: Throughout the searching and extraction process DSL and AS became increasingly familiar with the papers and the extracted data to develop a codebook. DSL coded the extracted data in NVivo 12 and AS did so manually. Together they then met regularly and adopted three major strategies of meta-ethnography to support the

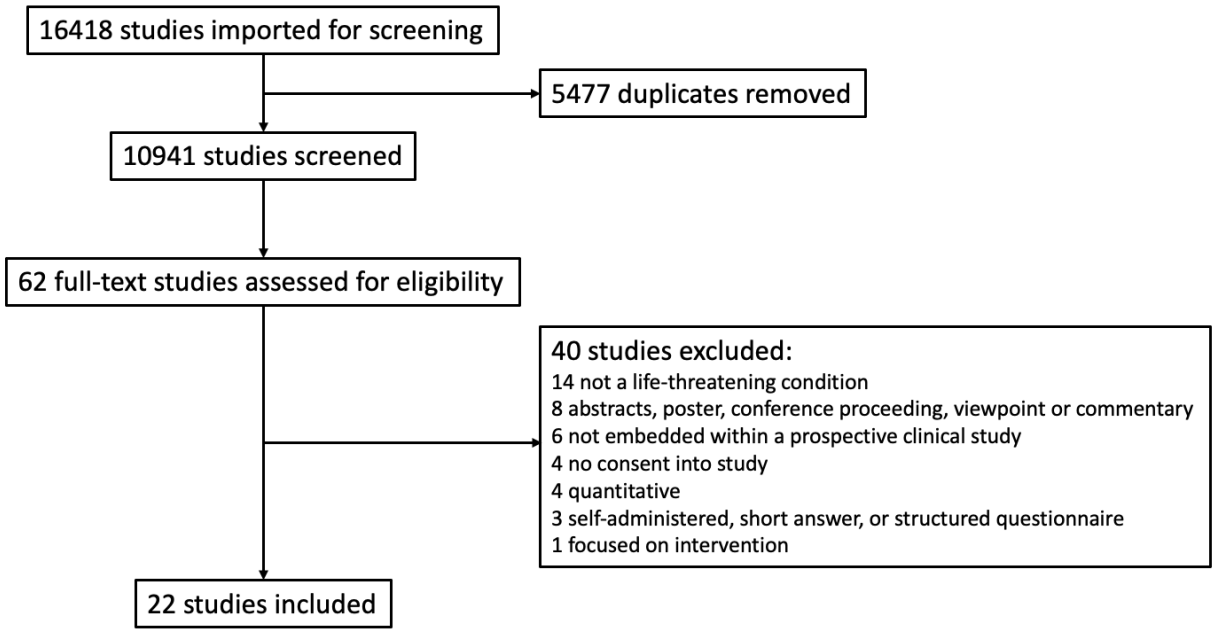
interpretive synthesis. Reciprocal translational analysis to identify the key themes or concepts in each paper as reported; Refutational synthesis to identify any contradictions between study reports and attempt where possible to explain them; and lines of argument synthesis to build on interpretations that were found in the papers. This process then facilitated the development of a synthetic construct which aimed to broadly encompass the entirety of the critical interpretive synthesis.

As this was a review using published data there was no requirement for ethical approval. The review was prospectively registered on PROSPERO (CRD42020207296).

RESULTS

The comprehensive search strategy took place on 12th and 13th November 2020 and the results of the process are presented in the PRISMA diagram (Figure 1). 16,418 studies were imported for screening and after removing duplicates 10,941 underwent title and abstract review. A total of 62 papers underwent full-text review and 22 were included. No additional papers were included after reviewing bibliographies.

Figure 1: PRISMA Diagram



Summary of the papers: We identified 22 papers published between 1997 and 2019 (Table 2) (Agård et al., 2001; K. Burns et al., 2017; K. Burns et al., 2015; Chatio et al., 2016; Dickert et al., 2015; Dotolo et al., 2017; Gammelgaard et al., 2004; Houghton et al., 2018; Lawton et al., 2017; Lawton et al., 2016; Mangset et al., 2008; Molyneux et al., 2013; Scicluna et al., 2019; Snowdon et al., 2014; Snowdon et al., 2006; Snowdon et al., 1997; Thomas & Menon, 2013; Tindana et al., 2012; Tutton et al., 2018; van den Berg et al., 2017; Véron et al., 2018; Ward, 2009). Nineteen were conducted in high-income countries (eight in the UK (Houghton et al., 2018; Lawton et al., 2017; Lawton et al., 2016; Snowdon et al., 2014; Snowdon et al., 2006; Snowdon et al., 1997; Tutton et al., 2018; van den Berg et al., 2017), four in the USA (Dickert et al., 2015; Dotolo et al., 2017; Scicluna et al., 2019; Ward, 2009), three in Canada (K. Burns et al., 2017; K. Burns et al., 2015; Thomas & Menon, 2013), and one in each of Denmark (Gammelgaard et al., 2004), Norway (Mangset et al., 2008), Sweden (Agård et al., 2001) and Switzerland (Véron et al., 2018)) and three in lower and middle-income countries (two in

Ghana (Chatio et al., 2016; Tindana et al., 2012) and one multi-site in Kenya and Uganda (Molyneux et al., 2013)). The qualitative methods studies were embedded within 18 RCTs (Agård et al., 2001; K. Burns et al., 2015; Chatio et al., 2016; Dickert et al., 2015; Dotolo et al., 2017; Gammelgaard et al., 2004; Houghton et al., 2018; Lawton et al., 2017; Lawton et al., 2016; Mangset et al., 2008; Molyneux et al., 2013; Scicluna et al., 2019; Snowdon et al., 2014; Snowdon et al., 2006; Snowdon et al., 1997; Tutton et al., 2018; van den Berg et al., 2017; Véron et al., 2018) and one within an observational study (Tindana et al., 2012), with three embedded within intensive care units hosting a variety of different interventional and observational studies but not within a specific named study (K. Burns et al., 2017; Thomas & Menon, 2013; Ward, 2009). The populations of the parent study were adults in 14 studies (Agård et al., 2001; K. Burns et al., 2017; K. Burns et al., 2015; Dickert et al., 2015; Dotolo et al., 2017; Gammelgaard et al., 2004; Houghton et al., 2018; Lawton et al., 2017; Lawton et al., 2016; Mangset et al., 2008; Scicluna et al., 2019; Tutton et al., 2018; van den Berg et al., 2017; Véron et al., 2018) and children and/or neonates in eight studies (Chatio et al., 2016; Molyneux et al., 2013; Snowdon et al., 2014; Snowdon et al., 2006; Snowdon et al., 1997; Thomas & Menon, 2013; Tindana et al., 2012; Ward, 2009). The diseases studied included myocardial infarction and acute coronary syndrome (Agård et al., 2001; Dickert et al., 2015; Gammelgaard et al., 2004; Scicluna et al., 2019; van den Berg et al., 2017), stroke (Mangset et al., 2008; Scicluna et al., 2019), chronic obstructive pulmonary disease (Véron et al., 2018), malaria (Chatio et al., 2016; Tindana et al., 2012), severe febrile illness (Molyneux et al., 2013), post-partum haemorrhage (Houghton et al., 2018), retained placenta (Lawton et al., 2017; Lawton et al., 2016) and open fractures (Tutton et al., 2018). In studies where there was no focus on a specific pathology the participants were all individuals admitted to intensive care units and were therefore undoubtedly suffering with a life-threatening illness (K. Burns et al.,

2017; K. Burns et al., 2015; Dotolo et al., 2017; Snowdon et al., 2014; Snowdon et al., 2006; Snowdon et al., 1997; Thomas & Menon, 2013; Ward, 2009).

Qualitative data were collected from a total of 668 participants. The informants within the qualitative methods studies were adult participants in 11 studies (Agård et al., 2001; Dickert et al., 2015; Gammelgaard et al., 2004; Houghton et al., 2018; Lawton et al., 2017; Lawton et al., 2016; Mangset et al., 2008; Scicluna et al., 2019; Tutton et al., 2018; van den Berg et al., 2017; Véron et al., 2018) and surrogate decision makers – mainly parents - in 10 studies (K. Burns et al., 2017; K. Burns et al., 2015; Chatio et al., 2016; Molyneux et al., 2013; Snowdon et al., 2014; Snowdon et al., 2006; Snowdon et al., 1997; Thomas & Menon, 2013; Tindana et al., 2012; Ward, 2009), with one study interviewing both (Dotolo et al., 2017). Where stated the data collection for the qualitative methods studies took place from within a few days up to 18 months from enrolment into the parent study. Most papers used interviews for data collection which were subject to either thematic or content analysis. There were no major methodological weaknesses identified which precluded any of the papers from being included in this synthesis.

The synthetic construct: Our synthetic construct is presented in Figure 2, and we will explain this in a relatively chronological format throughout the time course of a research study.

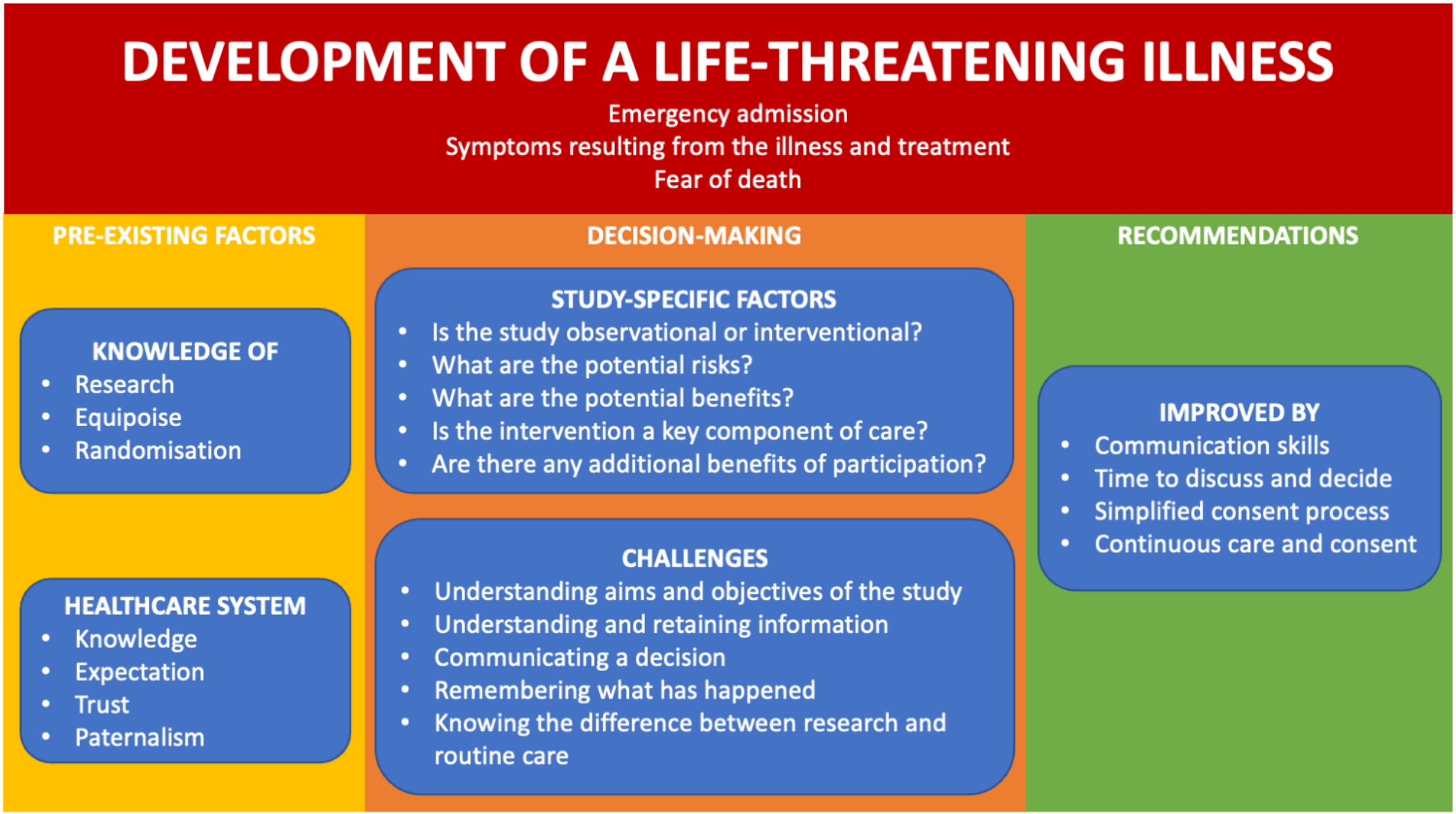
Table 2: Critical Interpretive Synthesis – Summary of included papers

Study	Location	Embedded within	Clinical study population	Disease/s	Qualitative population
Agard et al. (2001)	Sweden	RCT	Adults	Myocardial infarction	Participants
Burns et al. (2015)	Canada	RCT	Adults	Not specified but in ICU	SDMs
Burns et al. (2017)	Canada	Various	Adults	Not specified but in ICU	SDMs and decliners
Chatio et al. (2016)	Ghana	RCT	Children	Acute malaria	SDMs
Dickert et al. (2015)	USA	RCT	Adults	Myocardial infarction	Participants
Dotolo et al. (2017)	USA	RCT	Adults	Not specified but in ICU	Participants, SDMs and decliners
Gammelgaard et al. (2004)	Denmark	RCT	Adults	Myocardial infarction	Participants and decliners
Houghton et al. (2018)	UK	RCT	Adults	Post-partum haemorrhage	Participants
Lawton et al. (2016)	UK	RCT	Adults	Retained Placenta	Participants, research staff
Lawton et al. (2017)	UK	RCT	Adults	Retained placenta	Participants
Mangset et al. (2008)	Norway	RCT	Adults	Stroke	Participants
Molyneux et al. (2013)	Kenya and Uganda	RCT	Children	Severe febrile illness and shock	SDMs
Scicluna et al. (2019)	USA	RCT	Adults	Myocardial infarction or stroke	Participants
Snowdon et al. (1997)	UK	RCT	Neonates	Extracorporeal membrane oxygenation	SDMs
Snowdon et al. (2006)	UK	RCT	Neonates	Neonatal related conditions	SDMs
Snowdon et al. (2014)	UK	RCT	Neonates and Children	Multiple but all life-threatening	Bereaved SDMs, clinicians, trial team members

Thomas et al. (2013)	Canada	Various	Children	Not specified but in ICU	SDMs
Tindana et al. (2012)	Ghana	GWAS	Children	Malaria	SDM and researchers
Tutton et al. (2018)	UK	RCT	Adults	Open fracture lower limb	Participants and one decliner
Van den Berg et al. (2017)	UK	RCT	Adults	Acute coronary syndrome	Participants
Veron et al. (2018)	Switzerland	RCT	Adults	Chronic obstructive pulmonary disease	Participants
Ward et al. (2009)	USA	Not stated	Neonates	Not specified but in ICU	SDMs

ICU: Intensive care unit, RCT: randomised controlled trial, SDM: surrogate decision makers.

Figure 2: Synthetic Construct



Within this analysis we will focus on five key domains. The first is the experience of suffering with a life-threatening illness which is overarching and permeates the subsequent four; pre-existing knowledge of research and expectations of healthcare; study-specific factors; challenges in the decision-making process; and recommendations for improvement.

The experience of suffering with a life-threatening illness: Conducting clinical research within an emergency situation is the focus of this critical interpretive synthesis. Our aim was to try and understand the experience of participants and caregivers living through those moments and then apply this as a lens through which we could try and understand its impact on all aspects of research participation. As described, study participants were suffering from severe illnesses that could, and in some cases did, lead to death. In some situations this would be an exacerbation of a previously diagnosed condition but in many it was an acute event which was completely unexpected and diagnosed for the first time or which occurred as complication of a normal process such as childbirth. Participants shared their experience of often being rushed to a healthcare facility and thrown into a completely unfamiliar environment whilst suffering with acute symptoms of their illness. This may have been acute pain from a myocardial infarction (Agård et al., 2001; Dickert et al., 2015; Gammelgaard et al., 2004; van den Berg et al., 2017) or a road traffic accident (Tutton et al., 2018), breathlessness from a respiratory illness (Véron et al., 2018), septic shock from an overwhelming infection or severe bleeding due to a post-partum haemorrhage (Houghton et al., 2018) or retained placenta (Lawton et al., 2017; Lawton et al., 2016). These are symptoms which are uncomfortable and distressing and which can cause difficulty in understanding and retaining information as well as impairing communication such as asking questions and

communicating decisions. This impairment may be due to distraction caused by fear (Dickert et al., 2015; Snowdon et al., 2006; van den Berg et al., 2017; Ward, 2009) or abnormal mental function as a result of the underlying pathology. In addition, individuals rapidly undergo invasive procedures such as the insertion of intravenous lines and are initiated on emergency treatments which aim to alleviate their symptoms and manage their diagnosis but which can cause discomfort and disorientation such as strong analgesia for severe pain (Gammelgaard et al., 2004; Tutton et al., 2018). All of this process takes place within an accelerated period of time in which diagnosis and initiation of treatment need to take place rapidly in order to improve the chance of survival, which itself is not certain. When considering this from the perspective of a surrogate decision maker, they are witness to these events, and in the case of neonatal research, the decision makers may have also been through a traumatic childbirth experience from which they are still recovering (Snowdon et al., 2014; Snowdon et al., 1997).

Having framed the acuity of the situation and the rapid emergence of a life-threatening diagnosis with its accompanying symptoms and potential treatment related side-effects we now consider how this can impact on the experience of being in a clinical study.

Pre-existing knowledge of research and expectations of healthcare: Before the development of a life-threatening illness and being approached to enrol in a clinical study, individuals already have their own pre-existing knowledge of research. We view these factors as laying the foundation upon which an individual makes a decision to enrol. We found that there were generally very low levels of awareness and understanding of the principles of clinical research prior to being approached to enrol and the vast majority of individuals did not have any

previous first-hand experience of clinical research. This means that core principles such as equipoise and randomisation as well as broader issues such as how clinical trials are organised and implemented alongside routine care were poorly understood. These factors are independent of the life-threatening nature of the illness as they precede it. Few individuals had previous experience of research however we found prior research experience to be more common in resource-limited settings where parents had often enrolled multiple children in several research studies. Those who did have previous experience framed this as a positive reason to contribute (Dotolo et al., 2017; Thomas & Menon, 2013; Tindana et al., 2012).

Individuals also present to healthcare facilities with their own pre-existing experience of and relationship with healthcare. Some may present with exacerbations of chronic conditions that are already managed within primary care, sometimes with previous episodes of hospitalisation, whereas others may suffer from an initial presentation of a life-threatening illness which is being diagnosed for the first time. Expectations of different healthcare facilities and professionals may come directly from first-hand experience as a patient or a caregiver or indirectly via second-hand information from friends and family, or more broadly through exposure to external sources such as the government or the media. These expectations are crucial when it comes to determining how much trust to place in both the routine care and the research environment. For example, where an individual has low expectations of the routine care provided and is aware that research groups have access to greater resources then this may lead them towards agreeing to participate in a research study. This was observed particularly in research studies conducted in resource-limited setting (Chatio et al., 2016; Molyneux et al., 2013). However, in all settings it is often difficult

to disentangle routine care from research and therefore it becomes more difficult to understand the potential added benefits of being part of a research study, if they exist. Conversely, suspicions about research as a form of experimentation by using people as a 'guinea pig' (Agård et al., 2001) or as a means to obtain blood samples for illicit testing reduced trust (Chatio et al., 2016).

The expectation of healthcare professionals specifically, whether based on prior experience or not, was found to be crucial in both the decision-making process and the broader experience of the research. Trust was a core concept that permeated throughout. When faced with a life-threatening illness individuals explained that although it was not always possible to understand and digest the information, they often defaulted to agreeing to participate based on trust in the research team approaching them (Agård et al., 2001). Where there was awareness of broader research infrastructure there were also expressions of trust in research ethics committees and research institutions which were felt to provide safeguards through their regulatory procedures (Mangset et al., 2008; Thomas & Menon, 2013). Some individuals explained that they thought the researchers were the experts and knew best and that it seemed pointless to be asked their opinion with regards to enrolment as they knew so little about the subject themselves (Mangset et al., 2008; Molyneux et al., 2013). We therefore found that in an emergency scenario, trust in healthcare workers was of paramount importance and influence. In contrast, we observed that in some settings where the healthcare system is more paternalistic there would be a similarly passive approach towards decision making which we found to be based more on acquiescence than coercion.

Study-specific factors: Despite the above, we found that the decision-making process was highly impacted by several factors related to the research study specifically. The first is whether the study was observational or interventional. Within observational studies there were fewer concerns about the risks of participation simply because these only involved collection of data and/or specimens. We found that in the context of a life-threatening illness this was both seen as a positive because of the reduced risks and as a negative because of the potential inconvenience or discomfort of participating when an individual expects no personal, health-related gain through participation. It was when considering these observational studies that we were able to understand more how individuals felt about providing blood samples as these were often the primary focus of the research. Here we found that it was important to explain the purpose of taking blood samples, what they would be tested for and why there may not be any immediate results available (Tindana et al., 2012). In terms of avoiding unnecessary discomfort, additional blood samples taken when venepuncture was being conducted for another reason were deemed more acceptable than taking a specific blood sample just for research purposes (Thomas & Menon, 2013).

When considering interventional studies, we found that discussions around risk and benefits were more prevalent given the potential for the study to impact directly on the life-threatening illness. Given that the worst possible outcome of the illness was death it was important to understand how the treatment being offered could improve chances of survival. The potential benefits of the study were often felt to be immense and in many instances we found that decision makers expected there to be a direct effect on them or the person they were representing (K. Burns et al., 2017) and the decision to enrol was made without

hesitation (Snowdon et al., 2006). This was true even in scenarios in which the intervention itself was not necessarily expected to improve survival (Dotolo et al., 2017). It was also true in trials of an intervention versus a standard of care where it was naturally expected that half of all participants would receive no additional benefit at all due to a lack of awareness of the concept of randomisation (Snowdon et al., 1997). When considering risk we found that the overriding trust in the research team and the wider research infrastructure meant that there was little consideration given to the possibility that the intervention could actually cause harm, rather that it might make no difference at all (Snowdon et al., 2014; Ward, 2009). As a result, we conclude that the focus was more towards the potential benefits than the risks.

When considering risks and whether to participate we found that the nature of the intervention being studied was also of great importance. Where the intervention was perceived to be clearly related to the underlying pathology and was directly addressing the main problem, such as a blocked coronary artery, then the potential benefits were amplified (Dickert et al., 2015). This was still the case but to a lesser extent when considering if the intervention could avert something felt to be important but was not life-saving, such as avoiding having surgery, or reducing the length of a hospital admission (Lawton et al., 2016; van den Berg et al., 2017). However, when the intervention was perceived to be of less importance to the bigger picture, such as the type of dressing applied after a major operation to repair an open fracture, then the potential benefits and risks were deemed to be smaller and the gravity of the decision was reduced (Tutton et al., 2018; Ward, 2009). When risks were perceived, rightly or wrongly, to be low or absent then it was articulated as there being nothing to lose and potentially something to gain if the intervention proved to be efficacious.

In addition to the impact of the intervention on health, there was also consideration given to any additional benefits of participation. These may be health-related such as optimised management concomitant diagnoses or financial in terms of transport reimbursement and financial incentives (Tutton et al., 2018). We found these to be more prevalent in research conducted in resource-limited settings but they were not interpreted as being prevailing factors in the decision-making process which was driven much more by a desire to survive (Chatio et al., 2016).

Given the above, in the context of a life-threatening illness we found that in general individuals expressed a strong desire to participate for a personal health benefit rather than from any more altruistic motive such as generating important scientific information or benefiting future patients because of the urgent, personal situation they faced. Where the risks and benefits were felt to be minimal the decision was sometimes articulated as being made more in ambivalence or due to altruistic motives (van den Berg et al., 2017; Véron et al., 2018).

Challenges in the decision-making process: As well as considering the study-specific factors there were additional aspects of the decision-making process that were exacerbated by having a life-threatening illness. The first of these was that it was harder to understand the aims, objectives and procedures of the research. This was articulated directly in some cases but also interpreted to be the case in others. In the most extreme scenarios participants reflected that they did not consider themselves competent to understand the information or to be able to make an autonomous decision in that particular situation saying that they

'signed without understanding anything' (Agård et al., 2001) and/or that they had forgotten about the study entirely (Dickert et al., 2015; Gammelgaard et al., 2004; Houghton et al., 2018). In others participants had not understood that enrolment was voluntary (Mangset et al., 2008).

As discussed earlier, there was limited pre-existing knowledge about how clinical research works and therefore limited foundations from which to build when inviting individuals to participate. However, the severity of the unfolding situation made it harder for individuals to receive, retain, and weigh up information in the limited time they had to do so. This was particularly important when considering two factors: equipoise and randomisation. All interventional trials must have equipoise, an element of uncertainty, to be considered worth conducting and this means that the results cannot be predicted or assumed until the analysis is complete. We found a lack of appreciation for equipoise which resulted in an assumption that the intervention would lead to overall benefit (Mangset et al., 2008; Molyneux et al., 2013). This resulted in what we interpreted to be an overestimation of benefit and an underestimation of risk. Alongside, there was a limited understanding of the concept of randomisation, that there is an equal probability of receiving one of two or more interventions, including a placebo or the best available routine care (Snowdon et al., 1997). As a result, participants were found to be making decisions based on the assumption that they would be receiving the intervention rather than the control arm (Dickert et al., 2015; Scicluna et al., 2019). In some situations participants thought that they were being invited to choose one of several different treatment options (Gammelgaard et al., 2004). In others, where there was understanding of randomisation but they were randomised to the control

arm some felt 'let down' (Scicluna et al., 2019) whilst others thought this meant that they had not been 'chosen for the trial' (Snowdon et al., 1997). We did not identify any discussions about the blinding process and only two trials used placebos which were not discussed in the qualitative papers (Lawton et al., 2016; Snowdon et al., 2006). When considering all of the above, in the context of a life-threatening illness there is a possibility for individuals to make decisions based on an underestimation of risk, and an overestimation of benefit, which is centred on an expectation that the intervention will work and that they will receive it.

Another way the severity of the situation was interpreted to exacerbate the experience of those involved in research studies was a difficulty in differentiating research from routine care (Houghton et al., 2018). As these individuals were being managed in a hospital setting, they explained that in the emergency situation they are in an unusual environment and meet a lot of new people (Snowdon et al., 2014). It was therefore not always possible to disentangle what was being provided as part of routine care and what was part of research, as well as who was providing it. This lack of differentiation made it hard to then pull apart the research from routine care when providing testimonies about being in the research study.

Recommendations for improvement: The studies included were primarily focused on decision-making and the experience of being in a clinical study rather than specifically aiming to identify areas for improvement. It was however possible to extract data which focused on this, and we identified two core areas for development. The first relates to the formal aspects of the consent process, particularly with regards to how and when this takes place and using which documents. It was felt that consent took place at the most intense time when all of the

impairments caused by the life-threatening illness were heightened and, as discussed, the ability to fully understand, retain and communicate information was as its lowest (Snowdon et al., 1997). It was regularly cited that the information conveyed during this process was too extensive and detailed, particularly in terms of what was written on consent forms and that a simplified or abbreviated form of consent would be preferred (Gammelgaard et al., 2004; Lawton et al., 2017; Scicluna et al., 2019). Another reason for this was that the consent process was seen to delay the treatment which was in many cases potentially lifesaving (Molyneux et al., 2013). Several studies concluded that a shorter summary of the study should be provided in which more time could be spent conveying the most important information (Lawton et al., 2017). Consent was viewed as a single, one-off event and some participants felt that it would have been beneficial to have the opportunity to review that decision and discuss further with members of the research team as additional questions or concerns often arose in the following days. In studies where this was offered by the research team it was appreciated (Lawton et al., 2016). Some individuals expressed feeling deserted by research teams who recruited and treated them on day one at the height of their illness and from their recollection were never seen or heard from again (Ward, 2009). In these contexts, the consent process was felt to be more of a legal procedure designed to protect the researchers rather than the participants (Agård et al., 2001).

The second area for development was regards to the communication skills of researchers. Effective, professional and dignified communication was felt to be critical (Scicluna et al., 2019). This follows on from the above regarding the consent process which could have been improved by researchers taking time to explain the key information in a clear way and then

being available for ongoing discussions around the study (Thomas & Menon, 2013). In addition, our interpretation of the data was that at times the research teams tended to indirectly convey an assumption that the intervention would be of benefit to the individual which would further exacerbate the lack of understanding of both equipoise and randomisation. This occurred both during the consenting process but also later on when considering the individual participant outcome outside of the context of the final results. For example, attributing an improvement in symptoms or a better outcome to the intervention (Houghton et al., 2018).

DISCUSSION

Within this review we have been able to critically interpret and synthesise data from a broad range of settings related to the experience of being enrolled in clinical research when suffering from a life-threatening illness. We have shown that the severity of the illness has a significant impact on all aspects of this experience, particularly the decision-making process. Individuals making decisions are either themselves directly experiencing or witness to an unfolding emergency which comes with a myriad of physical and psychological symptoms. When combined with limited previous knowledge or experience of clinical research this can result in difficulty comprehending core concepts and the pertinent details of a specific study which can in turn lead to an underestimation of risk, an overestimation of benefit and an expectation of being allocated to the intervention arm. This is also exacerbated by a difficulty in differentiating clinical research and routine care.

A core theme that emerged related to trust in research teams, institutions, and governance. When faced with a life-threatening emergency, and with limited previous knowledge or experience of clinical research, we found that a great deal of trust was placed in clinical researchers, and this was sometimes an acceptable alternative to understanding. These findings emphasise the huge responsibility that researchers have and the need to provide unbiased information that does not unduly influence or pressure individuals into participation. Research concepts are complicated, and the nuances of a study can be particularly so, however we found a clear preference among decision-makers to be continuously engaged by researchers throughout the duration of a study and to regularly provide information in manageable, bite-size portions. This could be in the form of an abbreviated summary of a study when it is first introduced, outlining the pertinent information, and then providing aftercare: regular, ongoing interaction between participants and researchers throughout the trial process where the information is relayed again and participants are provided with continuous opportunities to seek clarification, re-confirm consent, and opt to withdraw from the study.

The conventional, one size fits all approach of providing all the information in a single, written form upon enrolment was clearly inadequate. The use of a variety of tools, including summaries and visual information can help to increase understanding. A systematic review of audio-visual consent practices in high-income countries was limited by poor reporting of data but identified trends with regard to improvements in knowledge obtained and satisfaction with the process (Synnot et al., 2014). A core component of any further research into informed consent is the need for well-defined outcomes for evaluating interventions, for

example those which have been proposed by researchers as part of the ELICIT study (Gillies et al., 2021).

Further research around the best way to optimise both understanding of and satisfaction with the consent process is needed. A number of randomised controlled trials of different approaches to informed consent have been conducted or are underway (Pal et al., 2021) however these have not been in the context of individuals hospitalised in an emergency and this critical interpretive synthesis has clearly highlighted the nuances of this situation. One area where research is increasing however is with individuals who lack the capacity to consent, most often due to cognitive impairment or intellectual disabilities (Shepherd, 2020). There also remains a significant gap in the literature in which most of the research around this subject and the interventions developed as a result have been based in high-income settings. This was exemplified in this critical interpretive synthesis where only three of the included studies were conducted in lower and middle-income countries. Finally, although we reviewed data from decision-makers for paediatric patients there were no data from those who took part, and this may be possible where participants are older and able to communicate or potentially further down the line as they become more mature.

There were some limitations to this review. We adapted the methodology first described by Dixon-Woods which has itself been subject to variation by other researchers and therefore our methods may not be entirely comparable with other critical interpretive syntheses, however this adaptation was justified throughout the process and any changes were made to fit within our research question and the evolving analysis. Second, life-threatening illnesses

and experience vary significantly. We tried to group them together because we felt individuals were facing a similar sociological context but some of the heterogeneity within this group may have been lost. In addition, we did not compare studies of life-threatening illnesses with those which were not life-threatening. Third, as previously discussed, there was a lack of data from lower and middle-income countries so our interpretation may be less generalisable for these settings however we did attempt to emphasise the differences within our analysis. Finally, one of our key findings was that individuals struggled to differentiate research from routine care when providing testimonies about being in the research study. It is therefore possible that some of the observations and interpretations provided by informants were actually related to routine care rather than research.

CONCLUSION

Within this critical interpretive synthesis, we have developed a synthetic construct which aims to outline the experience of enrolling into a clinical research study whilst suffering from a life-threatening illness. We found most individuals had no previous knowledge or experience with clinical research. The decision-making process was hugely impacted by the physical and psychological impact of the life-threatening illness. It was difficult to differentiate clinical research and routine care and understanding of core concepts around research were limited. This led to an underestimation of risk, an overestimation of benefit and an expectation of being allocated to the intervention arm. We found that the decision-making process was heavily influenced by trust in the research team. Finally, we provide some suggestions for further research and implementation work around informed consent for individuals suffering from a life-threatening illness.

DECLARATIONS

Ethical approval and consent to participate: N/A

Consent for publication: N/A

Availability of data and materials: The data extraction forms for each included study are available from the corresponding author on reasonable request.

Competing interests: None declared.

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Authors contributions: DSL conceptualised the project. All authors developed the methodology. DSL performed the searches. DSL and AS reviewed the abstracts; selected the included papers; extracted the data; analysed the data and drafted the initial manuscript. All authors refined and approved the final manuscript.

Acknowledgements: None

References: The references for this paper are incorporated into the main bibliography of the thesis.

METHODS PART TWO - ETHNOGRAPHIC STUDY

Background

I have previously outlined how the AMBITION-cm trial provided a rich setting for an ethnographic study exploring the experience of individuals who develop AHD and cryptococcal meningitis; ethical issues and decision-making around clinical trials for life-threatening illnesses in LMICs; and the acceptability of the AMBITION-cm regimen.

The two review papers provide a further rationale for an in-depth, qualitative methods study. In the first review, I described in detail the demographics of participants in cryptococcal meningitis trials, how these have changed over time and how they compare with those treated in routine care settings. Although this quantitative data can broadly describe this population, there is a dearth of qualitative, in-depth data. Given the ongoing burden of advanced HIV disease and cryptococcal meningitis, and the sociological complexity of the illness, it is vital to understand more about this group of individuals who develop this severe infection. By understanding how they come to develop cryptococcal meningitis and how they navigate pathways to care we can make recommendations to avert meningitis and, knowing that those who present with more severe disease have worse outcomes, also encourage prompt presentation to care.

The second review paper enabled the life-threatening context of disparate qualitative data to be centred as a core, overwhelming factor which impacts on all aspects of a trial experience, including the decision-making process. In addition, the review highlighted the lack of in-depth, qualitative methods research conducted in LMICs where disparities in standards of care and the concepts of a therapeutic misconception and structural coercion may be

amplified. I therefore conceptualised an ethnographic study entitled The Lived Experience of Participants in an African Randomised Trial (LEOPARD) which was embedded within the AMBITION-cm trial sites in Gaborone and Kampala. Within this thesis I use the term lived experience to mean learning from an individual's first-hand experience of a particular situation, rather than the specific phenomenological method of enquiry and analysis.

Aim

The aims of this ethnographic study were therefore in line with objectives three to five of the overall thesis:

1. To explore pathways to care with cryptococcal meningitis and identify recommendations to avert mortality.
2. To begin to understand decision-making around the AMBITION-cm trial and how the study design and broader social context impacted that process.
3. To identify how the AMBITION-cm trial could be improved and the acceptability of the AMBITION-cm regimen from both the participant and the researcher perspective.

Research Group

I conceptualised the study, but it was refined and implemented by a large group of individuals. The concept matured after initial discussions with Prof Janet Seeley and Prof Joseph Jarvis. In Gaborone, Prof Jarvis introduced me to Ms Neo Moshashane, a social science research assistant working at the BHP within Prof Chelsea Morroni's group, and I later employed Mrs Lebogang Maphane to help with administrative tasks. In Kampala, we had support and input from Prof David Meya, the Principal Investigator of the AMBITION-cm site there. Prof Seeley introduced me to Dr Agnes Ssali, a post-doctoral social scientist who was based at the

MRC/UVRI and LSHTM Uganda Research Entebbe Unit, in the Social Aspects of Health Across the Life Course Programme and whose PhD focused on informed consent in clinical trials. Dr Ssali kindly agreed to be involved and introduced me to her colleague, Mrs Georgina Nabaggala, a highly experienced social science research assistant. We also had additional input from Prof Thomas Harrison, co-Chief Investigator on the AMBITION-cm trial, and an Advisor to this PhD.

Initially I had hoped to collect data in all five AMBITION-cm country settings. I therefore made contact with Dr Deborah Nyirenda at the Malawi-Liverpool-Wellcome Clinical Research Programme in Blantyre, Malawi; Dr Agatha Bula at the UNC-Project in Lilongwe, Malawi; Dr Graeme Hoddinott at Stellenbosch University in Stellenbosch, South Africa and Dr Zivai Mupambireyi at the Centre for Sexual Health and HIV/AIDS Research (CeSHHAR) in Harare, Zimbabwe. Initial meetings with each of these individuals helped to develop the methodology and a group call led to extremely fruitful and valuable discussions, for which I am hugely appreciative. Sadly, despite multiple funding applications it was not possible to conduct this study in all five countries, however they were all named authors on the protocol manuscript and have been acknowledged in the resultant papers. Finally, it would not be possible to embark on such a project without engaging communities of people living with HIV. I was fortunate to receive input from friends and advocates in Botswana, Malawi, and Uganda as well as members of the BHP Community Advisory Board, who helped to focus this work.

Conceptual Framework

I am interested in how the concept of time shapes the trial experience from the perspective of the participant, next-of kin and researcher and the qualitative concept of time, that being

the representation of time and its movement, particularly in the context of ethnography. Time is an 'inescapable dimension' of all aspects of social experience and Nancy Munn describes the notion of 'temporalization' to be a view of time as a symbolic process that is continually being produced in everyday practice (Munn, 1992). The AMBITION-cm trial is a rich setting to explore how time is perceived by different actors through this lens of temporalization. The severe illness of cryptococcal meningitis occurs at a specific time in someone's life and as cryptococcal meningitis is only seen in AHD, significant time has lapsed since contracting HIV which may have been spent in/out of care and on/off treatment. Upon developing cryptococcal meningitis, participants typically develop symptoms of a headache which may be mild and take days, weeks or even months to reach an intensity severe enough to warrant seeking medical attention. As the illness progresses, they may spend periods of time in different states of confusion and awareness, impacting their understanding of what is happening and their interpretation of events. Upon presentation to a healthcare facility there is a time pressure to intervene and start treatment and time spent awaiting consent can run out and make someone ineligible for the trial. The entire trial experience is time-bound and shaped by a protocolised schedule of events.

Pierre Bourdieu (1990) says our actions are not only unfolding in time, they are also playing strategically with time, and especially with tempo. Practice unfolds with time, and it is this temporal structure that is constitutive of its meaning. This is particularly true in the case of acute illness where time has lapsed up to the moment the patient is admitted with cryptococcal meningitis, at which point the tempo may increase and time may move at a faster rate for patients and their relatives. At this point the research team enter with a sense

of familiarity with the situation and an appreciation of the multiple procedures that are required and the acceptable speed with which each must occur.

In her work exploring how mothers of unwell children navigated healthcare centres in Eastern Uganda, Mogensen (2005) found that the time-space of the health centre was not the time-space of the domestic sphere and the actions taken prior to reaching the health centre were within a time-space other than the one favoured by the healthcare worker. This change in tempo between settings subjects meaning to a 'destructuration' and as different tempos are experienced by different actors this can lead to disconnect (Bourdieu, 1990). In addition, Mogensen found that agency was understood to be a temporally embedded process and that the postponement of time functioned to rework social relations and to negotiate the responsibilities of social actors. When contemplating the need to consent to a trial, or approve a lumbar puncture, the postponement of time may facilitate an increase in knowledge and agency, perhaps by facilitating a collective decision-making process. Alternatively, under conditions of extreme stress, meaning may be flexible and supple and make allowances in extraordinary conditions where time is limited (Abramowitz et al., 2015).

Methods

Study Setting: This study was embedded within the AMBITION-cm trial at the Gaborone and Kampala sites. Funding was received to conduct the study from the UK National Institute for Health Research (NIHR), as part of a Global Health Professorship awarded to Prof Joseph Jarvis (RP-2017-08-ST2-012) and to which I gave the input for this specific piece of work. The two sites were chosen because I was based in Gaborone full-time and because I had previously spent the most time in Uganda, having visited several times a year for many years including

completing my dissertation research there as part of my MSc in Medical Anthropology at Durham University and further researcher as part of an Academic Foundation Programme at Brighton and Sussex Medical School. In addition, the two country settings provided a contrast in terms of HIV epidemics and healthcare systems.

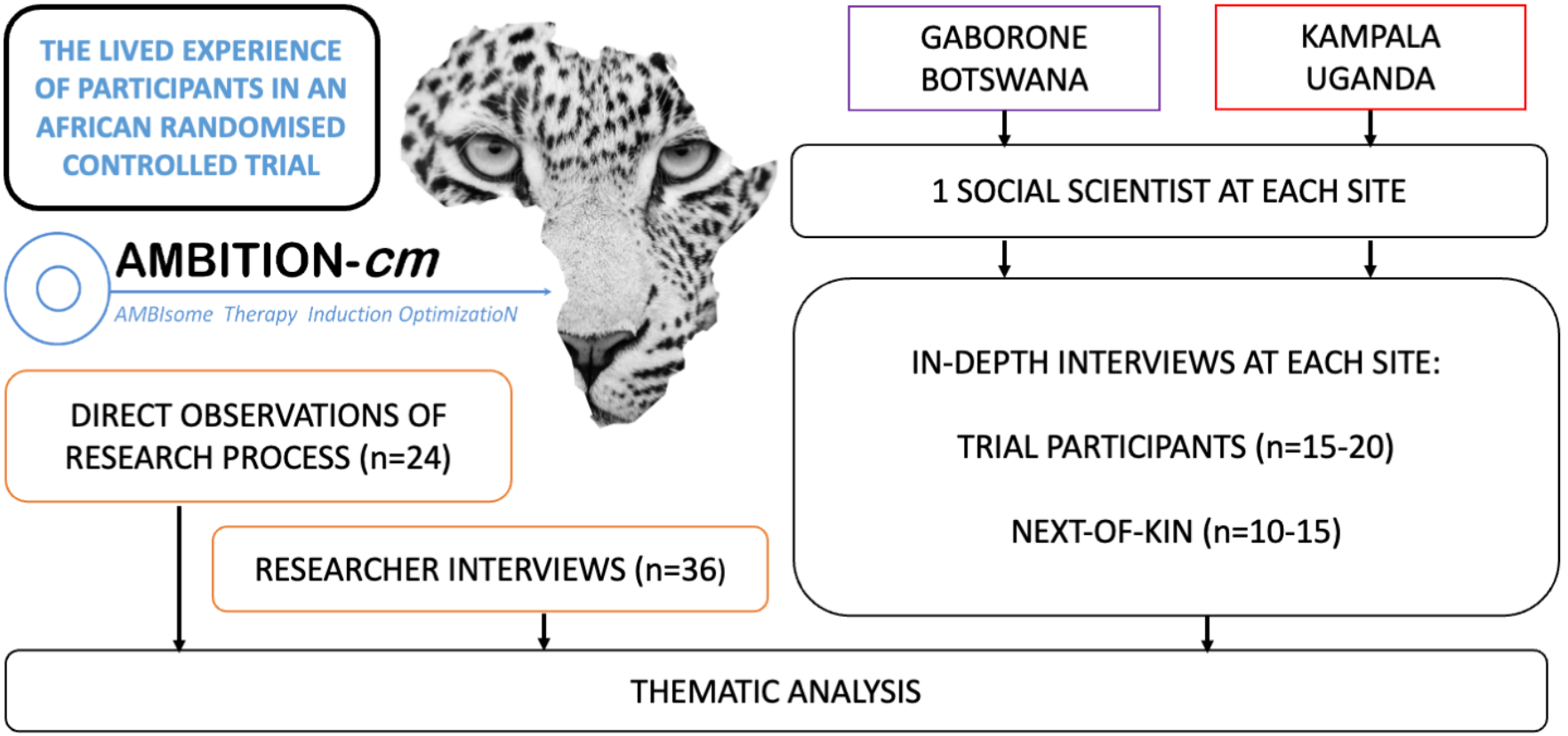
Botswana is an upper-middle income country with a population of 2.35 million and a generalised HIV epidemic, with an adult prevalence of 20.8% (Mine et al., 2022). The country has one of the most mature ART programmes in Africa, being the first on the continent to offer free ART in 2002. Botswana was also an early adopter of dolutegravir as first-line therapy in 2016, prior to the AMBITION-cm trial commencing. It was recently announced that Botswana was the third country in the world to have met the UNAIDS 95-95-95 targets (Mine et al., 2022; Thornton, 2022), and the first in Africa. Despite this, the annual incidence of HIV among adults is 6.03/1000 and the number of AIDS-related deaths has remained fairly constant for the last decade. In addition, healthcare is available to all citizens for free and there are no co-payments required for any outpatient or inpatient care. There is a large migrant community, predominantly Zimbabweans, who do have to pay for healthcare however in 2019 ART was also made freely available to non-citizens (UNAIDS, 2019).

Uganda is a low-income country with a population of 45.74 million and an adult HIV prevalence of 5.2% (UNAIDS, 2021). UNAIDS estimates the country's treatment cascade to be at 89%-82%-78%. Dolutegravir was rolled out from September 2018, mid-way through the AMBITION-cm trial, and the HIV programme has made consistent progress with the adult HIV incidence in 2021 reported as 2.4/1000 and AIDS-related mortality falling consistently for the last two decades. Healthcare is free for citizens however it is not uncommon for co-payments

to be required which can in some cases lead to catastrophic healthcare expenditure, particularly for hospital admissions (Kwesiga et al., 2015).

Of course, all five AMBITION-cm country settings are unique in every respect however these two countries, most familiar to me, were felt to have differences in terms of HIV epidemics and healthcare systems that could be argued to span the full range of the five countries. This study, like most using qualitative methods, was not designed with any expectation of producing findings that were generalisable or definitively applicable to other contexts. In fact, the findings may not have been generalisable to the location where data collection was taking place, however a comparison between Botswana and Uganda may enable relative similarities and differences between contrasting settings to be observed, which could themselves help frame the findings and subsequent recommendations.

Figure 7: LEOPARD Study Schema



Data collection methods (Figure 7)

In-depth interviews with AMBITION-cm trial participants: In-depth interviews (IDIs) were chosen because they provide the opportunity for the conversation to flow, to ask follow-up questions, probe for additional information, and circle back to key questions later. The purpose of the IDIs with AMBITION-cm trial participants was to collect personal accounts of their experience of both cryptococcal meningitis and the AMBITION-cm trial, including the decision-making process and the acceptability of the intervention.

Individuals who upon entry into the AMBITION-cm trial were deemed to have decision making capacity (i.e., decision-orientated) and those who were not (i.e., decision-disorientated), and therefore underwent surrogate consent, were approached to participate in two IDIs. These terms, 'decision-orientated' and 'decision-disorientated' moved through various iterations throughout the research process, including 'oriented' and 'confused' as well as 'self-consent' and 'proxy-consent', and were challenging to operationalise as they related specifically to the situation the individual was in when they were approached to enrol into the AMBITION-cm trial however discussions around confusion and understanding formed a significant component of the broader analysis. When used throughout these two terms relate specifically to whether someone consented for themselves or needed a surrogate decision maker to enrol into the AMBITION-cm trial.

All participants in the LEOPARD study needed to have regained decision-making capacity to contribute to the IDI, meaning that those who lacked decision making capacity at baseline will have clinically improved and regained that capacity. I aimed to recruit a maximum of 20 participants from each of the two sites, 40 in total, with a proposed gender balance of 50-

60% male and 40-50% female, in line with the epidemiology of cryptococcal meningitis at the sites (Table 3). I also aimed to recruit an even number of individuals who were decision-orientated and decision-disorientated upon enrolment into AMBITION-cm. I anticipated 30% of all AMBITION-cm trial participants would be decision-disorientated at baseline however wanted over-representation of this group in this qualitative methods study as this was an aspect of the decision-making process that was of particular interest. Finally, I aimed to recruit similar number of individuals randomised to each arm of the trial. These figures were broad targets, and I acknowledged the need for flexibility which was also reflected in the sampling approach. Consecutively eligible individuals were approached to participate in the two IDIs, in line with the above. Consecutive sampling was adopted as it was anticipated that there may be delays in obtaining approvals for this separate protocol conducted within the ongoing AMBITION-cm trial and also because the complexity of the illness meant that we anticipated a high mortality rate in the trial, that some participants may not regain decision-making capacity, and that the need to prioritise recovery from the illness and/or relocation away from the recruitment site might result in a reduced number of eligible participants.

Table 3: Trial participant in-depth interview sampling matrix

Site	Decision-orientated		Decision-disorientated		Total
	Male	Female	Male	Female	
Gaborone	4-5	4-5	4-5	4-5	16-20
Kampala	4-5	4-5	4-5	4-5	16-20
Total	8-10	8-10	8-10	8-10	32-40

Participants were invited to contribute to two IDIs. One took place at least six weeks into the ten-week AMBITION-cm trial and the other at least four weeks after the trial. The reason for

this was to allow reflection on the trial when one is both within and outside of it. Interviews followed a broad interview schedule, and the participant was invited to draw a timeline of the events before, during and after the trial (Appendix 3). If individuals could only contribute to one IDI, for example due to worsening health or unavailability, then the data from the first IDI was retained and analysed.

In-depth interviews with the next-of-kin of AMBITION-cm trial participants: The purpose of the IDIs with the next-of-kin of AMBITION-cm trial participants was to collect personal accounts from individuals who had cared for and made important decisions about someone with a life-threatening illness. We used the term next-of-kin as a broad umbrella term to include any individual who may be the legal representative, a caregiver, or a surrogate of the participant. This individual must have provided consent for the participant to enrol into the AMBITION-cm trial, even if they may not have been the legally defined next-of-kin. In essence, they were surrogate decision makers, but this term was not used throughout the study as it was not a commonly used phrase. We aimed to recruit a maximum of 15 individuals from each site, 30 in total, with no specification for gender. Consecutively eligible individuals were approached to participate in a single IDI which took place at least six weeks into the AMBITION-cm trial. At the time of the IDI, it was not necessary for the trial participant to have regained decision-making capacity and these IDIs did not need to be linked to those with participants, although it was anticipated that some, or most, would be. Interviews followed a broad interview schedule, and the participant was also invited to draw a timeline of the events (Appendix 4).

In-depth interviews with AMBITION-cm researchers: The purpose of the IDIs with AMBITION-cm researchers was to understand their perspectives on the AMBITION-cm trial in terms of the design and day-to-day implementation, including the acceptability of the intervention. I also explored more broadly their views on how research is implemented in sub-Saharan Africa. Interviews took place with researchers from the Gaborone and Kampala sites. I approached a range of individuals with different roles including senior and junior researchers, research doctors and nurses, laboratory scientists, pharmacists, and study coordinators. In addition, IDIs were conducted with members of the wider AMBITION-cm consortium who were based at European partner institutions. I aimed for a maximum of 12 individuals from each of the two participating African sites and 12 in total from across the five European sites. The maximum number of researcher interviews was therefore 36. Individuals were purposively sampled and interviewed on a single occasion, following a broad interview schedule (Appendix 5).

Direct observations of AMBITION-cm researchers: I also conducted ethnographic fieldwork at the African sites. The objective of this work was to contextualise the data from IDIs within the broader research environment. As the primary focus was on improving the trial for participants, observations were largely based in the clinical environment, with emphasis placed on observing clinical staff and key procedures such as consent and the administration of study drugs. This also allowed me to apportion off specific time with consenting researchers to observe them and create a defined separation between my two roles as Lead Clinician and ethnographer. A total of four researchers from each of the two African sites were to be invited to participate in direct observations on up to three occasions. It was made clear that this was not a method designed to monitor an individual, but an opportunity to

spend a defined period of time observing events that take place within the research process. Observations were coupled with brief questions to those in close proximity to the activity under observation.

Principles of recruitment: Eligible individuals were identified by me and then approached to enrol in the study by a social science research assistant: Neo Moshashane in Gaborone and Georgina Nabaggala in Kampala. Both social science research assistants were separate from the trial and would have been new faces to the prospective participants, and they made this clear. In the case of AMBITION-cm trial participants and their next-of-kin, they were approached in the local language: Setswana or English in Gaborone and Luganda in Kampala. In the case of AMBITION-cm researchers I approached potential participants and invited them to participate. All researcher participants were assured that they were free to decline participation and were not being interviewed or observed for the purposes of any appraisal or formal evaluation of their role within the team. The purpose of the researcher interviews and observations was to understand the research process and not to criticise individuals.

Eligible individuals were provided with a Participant Information Sheet and given the opportunity to ask questions. If they agreed to participate, they signed an Informed Consent Form and were given the opportunity to withdraw their consent at any time, without giving a reason. Those who were not literate signed with a thumbprint and the consent form was signed by a witness independent from both the LEOPARD and AMBITION-cm studies. Interviews took place in a mutually acceptable location: usually a private office nearby to where they came for their outpatient follow-up visits. Interviews were recorded with a digital voice recorder and notes were taken during the interview. These notes along with the

transcriptions were then used as points of discussion between the research assistants and me, allowing us to iteratively adapt the data collection methods, consider preliminary findings, and highlight points to focus on during second interviews with trial participants. Observations were not recorded, and field notes were made after the period of observation has finished.

It was anticipated that this study may identify aspects of the AMBITION-cm trial that need to be improved. To ensure this a formal reporting process was established. Each of the individual social science research assistants would report back to me. Any urgent issues that related to trial conduct and Good Clinical Practice would be communicated through direct communication and reflective summaries written on the day of data collection. In addition, at least weekly meetings took place between the social scientists and me to discuss less urgent issues. These findings would be communicated either urgently to the Trial Management Group or at their weekly meetings, whichever was deemed appropriate. Additional advice could be sought from Prof Janet Seeley who was wholly independent of the AMBITION-cm trial. Following this process, the team would then determine a course of action which may result, for example, in additional training of trial staff or modification of study procedures. This process was of vital importance to ensure that the findings of this study could improve the conduct of the ongoing AMBITION-cm trial. The confidentiality of the participant would be maintained throughout this process so as not to undermine trust in either study.

Confidentiality: All study documents were kept on the person of the researcher or in a secure, locked location at all times. All digital documents were on password protected, encrypted

computers, backed up regularly and only shared with the study team via a General Data Protection Regulation compliant data repository held at LSHTM. Data were not transferred via email. Names of interviewees were not used at any stage of the data collection process. Pre-determined identification numbers were used on any data collection forms. Audio recordings did not start until the interviewee had given consent. Pseudonyms or the pre-determined identification numbers were used throughout. Demographic details of researcher participants were anonymised because the small number of eligible participants meant that stating their location could make it possible to identify them. Instead, only the location was stated when presenting data.

Data analysis: Audio recordings were transcribed verbatim into MS Word, translated into English in a separate second step, if necessary, then exported to NVivo 12 for coding and analysis. After the interviews and observations fieldnotes were written on paper, dictated into a digital voice recorder, and/or typed directly into MS Word then transferred to NVivo 12. The first two IDIs from each group of participants were analysed and discussed to enable iterative refinement of the data collection approach. Similarly, the regular meetings described above allowed an iterative approach to be adopted. Although I was not overly concerned about reaching data saturation or had that as a target in mind, towards the end of the study we did consider whether data saturation had been met and this resulted in the next-of-kin interviews stopping after 20 had been conducted.

Thematic analysis: These data were predominantly analysed using thematic analysis (Braun & Clarke, 2006) and I will therefore give a broad overview of how I did this before summarising the nuances of my approach to the three resultant research papers. I acknowledged that my

previous research in the social sciences had predominantly used content-analysis to summarise broad categories of findings (Lawrence, 2015; Lawrence et al., 2014; Payne et al., 2017) and was mindful of criticisms of research labelled as thematic analysis which was actually using content analysis (Braun & Clarke, 2021). The interpretive approach of thematic analysis leads to the development of higher-order concepts, rather than just summaries of responses to different questions on an interview guide, as is more common in content-analysis (Stemler, 2000), and it was these higher-order concepts that I aimed to generate.

Thematic analysis is composed of six steps and the process was not always linear, particularly when being used to address multiple research questions:

1. **Familiarisation** – this was an ongoing process throughout the data collection period as I became increasingly familiar with the data, the participants, and their stories. I would meet regularly with Neo Moshashane and Georgina Nabaggala to discuss how each interview had gone, combining our discussions with the reflective summaries they had sent to me. I then went through each transcription to note any typos, raise queries, leave comments or questions about the data, and suggest topics of discussion for follow-up interviews. These were then discussed further before the final transcription was approved. This would have resulted in each transcription being read on average three or four times before then being finalised and entered into NVivo for analysis. For data I had collected myself, I went through the transcriptions several times to check for accuracy and consider how I could refine my approach, enabling me to become increasingly familiar with the transcripts before imported the final versions into NVivo. Then, when it came to the subsequent stages of each individual analysis, I revisited the transcripts to re-

familiarise myself and to try and gain more of an overarching oversight of the *data corpus*. This was made easier by how rich and fascinating the data were.

2. **Initial code generation**: I adopted an inductive approach to develop codes as I became increasingly familiar with the data and moved closer towards the formal analysis. The codes were generated in a relatively logical and chronological process, particularly as the initial interviews typically moved through different topics of conversation in a relatively consistent order. Codes were broadly grouped under different categories, or 'buckets', with flexibility to move between these, and flexibility for codes to be removed or edited. Some codes were descriptive (e.g., '*experience with research*' and '*forgotten the trial*') and others more interpretive (e.g., '*gender* and '*unique to Botswana*'). New interpretive codes were added to the codebook, particularly when revisiting the data in the latter stages of the analysis when new ideas were generated. Codes were then applied to the transcriptions and fieldnotes line-by-line.

3. **Searching for themes:** Throughout the first two stages, and generally within broader discussions that took place during the data collection process, significant characteristics of the data became apparent. Some of the codes were grouped together into descriptive themes, some groupings were more interpretive, and some of the interpretive codes were themselves early theme generation. At this stage individual codes often featured under multiple themes and there was frequent movement. It was also here that the analyses of the resultant papers began to diverge in a more meaningful way to become distinct.

4. **Reviewing themes:** Early themes were reconsidered by revisiting the data and performing a refutational analysis to determine if the data were supportive (or not). During this process some themes were merged into a higher-order theme, others were split into pieces because they were too broad and seemed ill-defined, and others were disregarded. I also used this time to consider the differences between the two sites, considering how generalisable the budding themes may be and if there were specific nuances to one site which were regularly encountered.

5. **Defining themes:** It was at this point that discussions with Prof Seeley, in which we talked at length, helped to define themes. In addition, ongoing meetings with Neo Moshashane and Georgina Nabaggala, and the additional input of Dr Agnes Ssali, allowed me to consider whether my interpretation made sense based on their perspectives and knowledge of the data. At this stage the themes were rather well defined, it was more about how they related to one another, and this involved drawing various schematics on large pieces of paper to try and understand how they fit together (or not). This process was used in an attempt to develop a higher, over-arching concept that truly encapsulated the themes and the overall essence of the analysis.

6. **Presenting final conclusions:** I drafted each of the manuscripts. Prof Seeley gave feedback on the earliest versions followed by Prof Jarvis before then sharing with the wider authorship for comments and feedback.

Consideration of alternate forms of analysis: I had initially considered using narrative analysis as a methodology within this study. Illness narratives have been demonstrated to be an

effective method of distinguishing how individuals experience health and illness (Bury, 2001). Narrative analysis has frequently been adopted in the context of chronic illnesses (Kleinman, 1988), most commonly using a contingent narrative approach which focuses on beliefs about the origin of disease, the causes of an illness episode, and the immediate effects of that illness on everyday life. It has also been used before when considering enrolment into clinical trials in HICs (Cox & McDonald, 2013) however has less frequently been used for acute illnesses which tend to have a faster onset, more clear aetiology, and shorter duration in symptoms, but given that cryptococcal meningitis develops a long time after HIV infection this may have been a suitable context. In addition, narrative analysis would have been well suited to an inquiry with a focus on the concept of time. However, on further reflection, I did not proceed. When considering that the participant and next-of-kin interviews had been conducted in a language I was not fluent in, too much meaning would have been lost in the translation and this would have resulted in results lacking validity (van Nes et al., 2010). I therefore used thematic analysis, as described above, and still focused on time within this analysis.

Having described the process of thematic analysis and the justification for this choice, I will now provide more contextual information about the analysis used in each of the three specific papers.

Research Paper Four - Pathways to care: This analysis drew predominantly on the data from trial participants and their next-of-kin. The direct observations occurred after they had reached hospital so were used to contextualise the severity of the illness but could not contribute significantly to an analysis of pathways to care. In addition, I extracted data from the participant IDIs and summarised their pathways to care with a focus on their HIV and ART

history, how long they had been symptomatic with cryptococcal meningitis, and the various interactions they had with healthcare services whilst symptomatic and prior to their admission to the AMBITION-cm trial hospital.

Research Paper Five – Decision-making: This analysis used all the data sources available which were analysed using thematic analysis. This analysis took place over many months and fruitful discussions with Prof Seeley as I circled over and around what would become the central thesis of the paper.

Research Paper Six – Acceptability: Acceptability was defined broadly in line with the theoretical framework developed by Sekhon et al (2017) which states that acceptability is 'a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experiential cognitive and emotional responses to the intervention' (Sekhon et al., 2017, Page 4). This analysis focused specifically on data from trial participants and their next-of-kins and those specific researchers who were providing direct care to trial participants as they had hands-on experience of providing the two different treatment regimens. This was a less interpretive analysis, without the development of higher-order constructs, as the objective was more to present the practical reality of receiving and administering the two different treatment regimens.

Ethical Approvals: In the UK the study was approved by the London School of Hygiene and Tropical Medicine (REF: 17957). In Botswana the study was approved by the Human Resource Development Council, Gaborone (HPDME:13/18/1). In Uganda the study was approved by the

Infectious Diseases Institute Scientific Review Committee (027/2019); Makerere School of Health Sciences Institutional Review Board (REF: 2019-061); Kiruddu National Referral Hospital (KRD/ADM/120/1); and the Uganda National Council for Science and Technology (SS386ES). All approvals were renewed as required throughout the course of the study.

Harare Site: As part of the NIHR funding there was also additional capacity to conduct the same study in Harare, Zimbabwe. This was not formally approved as a component of this PhD and is therefore not included in this thesis however it is mentioned in the protocol manuscript. The study did go ahead, under the supervision of Professor Chiratidzo Ndhlovu, AMBITION-cm site Principal Investigator, with data collected by Dr Zivai Mupambireyi from CeSHHAR. The ethical approvals for this site took more than 18 months due to the COVID-19 pandemic and the AMBITION-cm site was closed early due to low recruitment numbers so all the data were collected after the trial had finished.

COVID-19 Impact: The study began recruitment in February 2020 with IDIs and direct observations taking place in Kampala. When I returned home from Kampala to Gaborone, I had anticipated I would continue with my usual three to four monthly visits to Kampala to conduct the follow-up observations and remaining IDIs, however I did not return until February 2022, long after AMBITION-cm and LEOPARD had concluded. This means that there were only three direct observations which took place in Kampala and more than half of the IDIs with researchers took place virtually. With regards to data collection from trial participants and next-of-kins, this also started in Kampala in February 2020, and it was during the pause to review the first IDIs that the strict lockdowns came into effect. The National Drug Authority then halted all non-essential research activity on 23rd March 2020 which meant that

the AMBITION-cm trial stopped recruitment for several months and just completed ongoing follow-ups. Permission was granted to resume on 25th June, however although the clinical trial was essential and lifesaving and therefore resumed, and clinical research activities were permitted to restart, this qualitative methods study was not. I waited and enacted a COVID-19 Risk Mitigation Plan which was approved internally at the Infectious Diseases Institute in Kampala. Recruitment commenced again in July 2020 with no further pauses. Given that the AMBITION-cm trial was recruiting at a national referral hospital it was not always possible to conduct follow-up interviews in Kampala, particularly when there were travel restrictions in place, as some participants lived a long distance away.

I was based in Gaborone from the start of the pandemic until March 2021 when I moved back to the UK. Although LEOPARD was approved on 5th November 2019 slow recruitment into the AMBITION-cm trial and closure over Christmas had resulted in a lack of eligible participants in early 2020. Recruitment to all research was then halted on 31st March 2020 with only essential follow-up ongoing, so those who had become eligible for LEOPARD having been recruited into AMBITION-cm in the first few months of the year could not be recruited. Recruitment then resumed on 11th May 2020 but was exceptionally slow due to significant restrictions on movement, including across districts, which meant that few patients were able to get access to Princess Marina Hospital. Sadly, during this time the patients with cryptococcal meningitis that came in were usually extremely unwell and the majority died before being approached to enrol into AMBITION-cm. As a result, the first trial participant recruited to the LEOPARD study in Gaborone was in July 2020, eight months after approval was granted. I commenced direct observations in November 2020, in-between lockdowns, and recruited three individuals. However, during most of the pandemic, although I was able

to go into the hospital to work clinically and see AMBITION-cm participants, there was always a significant COVID-19 risk and it would not have been appropriate to conduct direct observations alongside my researcher colleagues during this time. As a result, repeat observations did not take place.

Having outlined the methods of LEOPARD, I will now consider my position in the context of this research and my reflexive practice, and how these may have impacted this ethnographic study.

REFLEXIVITY AND POSITIONALITY

Research is always situated within a particular historical, social, and political context and the process is shaped by the researcher. Positionality situates the researcher within their research in terms of their identity, beliefs, and biases (Holmes, 2020) and reflexivity is a continuous process that enables the researcher to acknowledge how these have shaped the process and put in place mechanisms to recognise, reflect on, and reduce bias (Pillow, 2015). This is an essential component of all research but strikingly so in this study for two main reasons. The first is that considerable power imbalances and cultural differences exist between researcher and participant. The second is my role as the Lead Clinician for the AMBITION-cm trial which was itself being interrogated by this ethnographic study. Fortunately, this is something I consider often, almost to the point of paralysis, and I acknowledge that reflexivity can be uncomfortable (Pillow, 2003). Within this section I will consider my positionality with regards to the subjects under investigation (HIV and clinical trials), the research participants, and the broader research context, and how I adopted reflexive practice throughout.

My background

I am a white, UK-born and UK-trained medical doctor who chose this career path at a young age out of a desire to offer care to people. Throughout my life and medical training I have been drawn to working with socially excluded groups (and pathologies) that are stigmatised and I approach this from a social justice perspective (Jost & Kay, 2010). During medical school I volunteered for and then led several organisations that operated in the field of sexual and reproductive health rights (SRHR), and I also ran a volunteer group that did one-off events renovating neglected community spaces in Liverpool, UK. This work in SRHR allowed me to

travel the world, including to the United Nations, where I met politicians and activists from around the world who campaigned for (and sometimes against) sexual and reproductive rights.

A pivotal experience for me was attending the International AIDS Conference in Vienna in 2010 to deliver a workshop on comprehensive sexuality education. I travelled by bus and spent two weeks meeting AIDS activists from across the globe, learning about the individual and societal challenges of the epidemic, participating in rallies, and joining protests. I believe in the power of community activism which has been manifest so well in the HIV response (Broder, 2010; Epstein, 2000). It was also in Vienna that I met two people who have immeasurably influenced my perspective. The first was a social scientist who has taught me about feminism and intersectionality and the second was a man from Uganda who would become one of my closest friends. I had already planned my first trip to sub-Saharan Africa later that year, volunteering for a library charity in Tanzania, and so I travelled by bus to eastern Uganda to meet him and his family. They ran a small community library which conducted outreach activities around health and education, including community voluntary HIV counselling and testing. We worked together on ideas to expand the charity and have made great progress since.

I did not always have a strong affinity with the reductionist approaches of medicine which often stood in stark contrast with my experience with socially excluded groups for whom the most effective interventions seemed social, political, or economic. This led me to study an MSc in Medical Anthropology at Durham University. I selected all the theoretical modules I could, consumed as many ethnographies as possible, and became a fan of Paul Farmer's. This

experience firmly situated me theoretically as a critical medical anthropologist but the practical, budding clinician in me was drawn to applied anthropology that could use qualitative, ideally participatory, methods to amplify voices and design interventions. My MSc dissertation project used participatory methods with young Ugandans to design, pilot and later implement a comprehensive sexuality education programme that delivered the kind of information and skills that they wanted. This was successfully implemented in several districts in Uganda and was also used to inform the Rwandan National Curriculum. I later returned to Uganda to conduct a study as part of an Academic Foundation Programme at Brighton and Sussex Medical School which used participatory methods to explore young people's preferences for sexual and reproductive health services (Lawrence, 2015). I strongly believed that anthropological methods could help us to understand from lived experiences and these testimonies and their interpretation could improve health.

My motivation

As I have said, I have always been drawn to work with the most excluded or stigmatised groups. This led me to HIV, arguably the most stigmatised infection in history, and sexual health more broadly. I have worked in HIV departments in the UK since 2014 and have cared for many individuals who acquired HIV or died of AIDS through acts of what I would interpret as structural violence (Farmer, 2004). The most tragic outcomes often had the saddest back stories and there are many which linger in my mind. However, HIV medicine in the UK, particularly in Brighton where I was working at the time, is well funded and implemented insomuch that outcomes are generally good. To illustrate, I have only seen a few handfuls of cases of cryptococcal meningitis in the UK. My exposure to the scale of the global HIV pandemic and the inequity in access to treatment and outcomes is what then drew me to

clinical and research work in sub-Saharan Africa and ultimately to Gaborone and the AMBITION-cm trial.

Cryptococcal meningitis is an awful infection, truly one of the worst. Outcomes are terrible and the treatment is long, complicated to administer, and highly toxic. The AMBITION-cm trial offered a potentially safer, well tolerated, and simpler to administer solution to many of these problems. This was to be a definitive trial delivered by a world-leading team. As I became more aware of the trial settings and the reality of hospital care in, for example, Princess Marina Hospital where I had worked, the potential benefits of a less arduous and labour-intensive treatment regimen were apparent and amplified. The trial was ideal. When considering a part-time PhD whilst overseeing the trial I had considered several projects in the fields of epidemiology, diagnostics, or immunology however, I found myself grappling more with questions around those predominantly bioethical issues I have previously outlined.

The standard of care in the trial was not routinely available in the recruiting hospitals and the trial would clearly offer more intensive medical care and better monitoring, leading to improved outcomes. How would this impact the decision to enrol and did people really have a choice? My reading and first-hand experience had led me to concepts of structural coercion and the therapeutic misconception. From a critical perspective, I acknowledged how structural factors related to poverty and inadequate access to good quality routine care could impact enrolment, but my reading had led me to consider how much the participants would notice, or care in AMBITION-cm. This was possibly based on my own assumptions about comprehension, but it would be possible to explore this within LEOPARD. In my opinion, this was fundamentally related to agency. Was the decision to enrol based on free choice or

structural factors? I came to this question with my own stance. My experience working with socially excluded groups and my studies in anthropology had shaped my impression of agency which were manifest in my perspective on aspects of HIV such as linkage to care or adherence to ART, which was that I generally consider individual agency to be exaggerated in these discussions and structural factors to be more influential, limiting both the ability to act but also to make autonomous, self-governing decisions. When considering that one of my primary analyses was with regards to decision-making and free choice it is essential to acknowledge this as my standpoint. I acknowledged that I had previously considered agency to be too binary - you have it, or you don't - and challenged this through further reading (Kabeer, 1999; Mannell et al., 2016; Pells et al., 2016).

Coming back to the therapeutic misconception, I had long considered this to be quite a paternalistic, patronising term. I understood the idea behind the concept, that some individuals expect to benefit from being in a clinical trial when that is not what it is designed to do, and this can arise from a lack of understanding around issues such as equipoise, standard of care and randomisation (Appelbaum et al., 1987). As I have discussed, the AMBITION-cm trial would likely be beneficial for everyone, so this term did not feel appropriate, however I had seen the term being used in similar contexts and it did not seem to fit. Other social scientists had discussed this before (Molyneux et al., 2005). In addition, there may be other benefits to the trial that are not health related. I acknowledge that aspects of this study were designed with the aim of critiquing this concept using primary data and therefore my interpretation may have been subject to confirmation bias. I tried to overcome this by analysing all the data thematically and not overlooking that which could contradict my pre-existing hypothesis through refutational analysis and discussion with my colleagues.

The other bioethical questions that fed into my approach to this study were broader, and less about the AMBITION-cm trial specifically, but more about the mechanisms through which it operated. In earlier proposals for this thesis, I was drawn to explore the neo-colonial aspects of clinical trials in sub-Saharan Africa. I was aware of this issue and the increasing calls to decolonise global health prior to starting my role with AMBITION-cm but neo-colonialism was clearly and abundantly manifest in my day-to-day life, with myself as an actor. After my upgrading I was advised to narrow my focus to cryptococcal meningitis and the trial. My interest in this topic continued, along with a broader interest in the reimagination of how Global Health research could be implemented. In my role as an Associate Editor I co-edited the November 2020 issue of *International Health* with Professor Margaret Gyapong from the University of Allied and Health Science in Ghana, under the title 'Spotlight on Global Health Research' (Lawrence & Gyapong, 2020) (Appendix 12). This experience advanced my theoretical perspective on many issues including the vulnerabilities of research participants (Khirikoekkong et al., 2020), communities of research and community engagement (Henderson et al., 2020; Peay et al., 2020), ancillary care in global health research (Nkosi et al., 2020), and the informed consent process (Ngwenya et al., 2020). Within this special issue, and in collaboration with Dr Lioba Hirsch at LSHTM, I was able to refine a conference talk I had given at the Science Museum in London on the topic of decolonising global health in the context of transnational research partnerships (Lawrence & Hirsch, 2020) (Appendix 13). The special issue was a huge success, and our article was one of the journal's most cited of 2021. Arguments around how best to decolonise global health are however best heard from indigenous scholars and I have followed these closely in recent years to understand how the foreign gaze can lead to epistemic injustice (Abimbola, 2019; Bhakuni & Abimbola, 2021).

Despite not focusing on this subject specifically within the thesis, the neo-colonial aspects of the trial, and my role, cannot be entirely disentangled from this research or my interpretation of the data. This was most obviously manifest in interviews with researchers, particularly as our discussions around the trial and the conflicting standards of care available led to consideration of the responsibilities of the trial, research institutions, and funders, all of whom were operating within these neo-colonial structures. My role and that I was seconded to BHP but clearly employed by and representing LSHTM will have undoubtedly led to some desirability bias, which I discuss in more detail later.

When grappling with being an outsider I must also consider if I have a white saviour complex and whether that is what prompted my early career choices and if it persists today. I am anti-racist and do not think that I am inherently more skilled or capable than people or communities from the countries where I work. I acknowledge that I have been privileged to receive significant specialist medical training and opportunities in HIV medicine that enabled me to make a valuable contribution to the trial and my other clinical responsibilities in Botswana, particularly during the COVID-19 pandemic. Of course, this is extremely unjust given that the HIV prevalence in Botswana is 20.8% and in the UK it is 0.16%. In addition, I am conscious of the history of anthropological enquiry in Africa which has predominantly been conducted by non-indigenous researchers and that a lot of the anthropological literature I have read and referenced is authored by non-indigenous academics. I was however drawn to settings where my growing skillset could be put to the most use, hence the desire to practice HIV medicine outside of the UK. Having since returned to HIV medicine in the UK, I can say that I still feel the same way.

These discussions around decolonising global health and white saviourism fundamentally boil down to one question I keep on asking myself. Should I be here? My answer to this question is both yes and no, and I oscillate on this regularly, often thanks to long discussions with friends and colleagues. I have benefitted a lot, personally and professionally, from my role on AMBITION-cm and through this PhD study, likely more than some of my colleagues, and so I must accept that I may have perpetuated and exacerbated existing inequalities. I have tried to use my skills and experience to help us all benefit by mentoring other clinicians and researchers during my time working on AMBITION-cm, including qualitative methods researchers of which there is a shortage in Botswana, and continue to do so. I acknowledge that this is a common way that global health practitioners justify their actions by classifying themselves as 'experts' (Ojiako, 2022). I know that the results of the AMBITION-cm trial, a huge team effort, have the potential to drastically improve outcomes from cryptococcal meningitis and I hope that these qualitative data will amplify the voices of people living with HIV and have an additive impact on top of the clinical trial, both in terms of cryptococcal meningitis specifically but clinical trials more broadly.

My multi-positionality

Moving on from the broader existential considerations around this research study, I must also consider the practical considerations of my intersecting roles in AMBITION-cm and LEOPARD. LEOPARD is concerned with eliciting the participant experience within the clinical trial and identifying ways that this and future trials can be improved. It was designed by me with this purpose in mind which demonstrates a desire to receive feedback and criticism. In the context of participant and next-of-kin interviews the social scientists who collected data were entirely separate from the core AMBITION-cm team and it was important to emphasise that, although

they were affiliated to the study, they have not been personally involved in the care of trial participants. The social scientist aimed to be seen as an external individual who was primarily interested in improving the experience for participants and their next-of-kin. It was emphasised by the social scientist that prospective participants were under no obligation to participate, and their participation (or not) would have no impact on their relationship with the broader AMBITION-cm study team. Specifically, it was made clear that their contribution would not be fed back directly to the study team without their permission, and that their engagement (or not) would not impact their care within the AMBITION-cm trial.

My multi-positionality and proximity to the trial participants and researchers requires specific reflection on this 'insider ethnography' (Vernooij, 2017). My role as Lead Clinician for AMBITION-cm was to visit the research sites, develop the trial and build relationships with researchers. In the context of researcher interviews this role, as facilitator of the exact clinical trial under scrutiny, warrants discussion. My position made conducting interviews in different settings feasible, and my data collection could be enriched with participant observation. Conversely, my role as a lead figure in the trial, and those other elements of my positionality discussed above will have impacted my ability to both elicit and interpret data and will have led to some desirability bias and a Hawthorne effect. I adopted an open approach with potential researcher participants and offered reassurance, explaining that this was a study borne from my own interest in this complex subject, and identifying a shared goal of improving the experience of participants. The researcher participants were assured that they were not being observed for the purposes of any appraisal or formal evaluation of their role within the team. The purpose of the observations was to understand the research process and not to criticise individuals. A reflective approach to the research process was adopted. I

kept notes and reflected on each interview to consider how this may have been the case, re-phrasing questions and modifying my approach iteratively. An appreciation of how they and others perceived my position, and an analysis of my own subjectivity when interpreting data was essential. Finally, although I tried to separate the direct observations from my day-to-day observations and experience of the trial, carrying them out in distinct periods of time, I accept that there could have been observer bias in which my pre-existing relationship to the person being observed or with the trial may have impacted my interpretation.

When considering the documentation of fieldnotes, I had already developed a tacit understanding of my subject and therefore what I would like to focus on when documenting field notes, purely because I had already been working on AMBITION-cm for nearly three years when data collection commenced, and because it is from that experience that I was drawn to develop the LEOPARD study. My pre-existing participation enabled a focused approach to fieldnotes but also raised concerns that my choice to document (or not) would be biased by conclusions that may already be formed/forming in my subconscious. It was necessary therefore to be reflexive both when writing fieldnotes but also when interpreting them. To mitigate this bias as an existing participant in this field I chose to initially document commonly occurring events that seemed natural or 'normal' to me as well as new, or 'deviant' events (Wolfinger, 2002). This was possible by adopting the approach of comprehensive notetaking, documenting experiences in the order that they occurred, and doing this as soon as possible after the observation, before my memory lapsed too much. Later I reviewed both individual and collective entries to identify similarities and differences and facilitate an iterative and reflexive approach to my documentation of field notes (Emerson et al., 2011).

Reflections on fieldnotes

When reflecting on the experience of conducting observations and the LEOPARD study more broadly, my fieldnotes provide a valuable insight into the reality of my intersecting roles. Within this section I will scatter these fieldnotes among my own reflections. Fieldnotes are verbatim and have only been edited to remove the gender of the researcher being observed.

> *'A man who looked to be around 30 years old. He was lying in bed, on top of a mattress with a sheet covering his legs and his torso exposed. There was a scarf wrapped around his left hand and forearm. His right arm had a cannula, a bandage and a bracelet. His right eye was half closed and his left eye was open. He was writhing around in the bed slightly and looked to be confused. … The doctor then examined the patient, listening to the chest, palpating the abdomen and scanning the skin on his legs. Although this patient had clearly lost lots of weight and muscle mass in recent weeks, he still had a muscular upper body. He must have lost a lot of weight. The doctor and relatives then examined his back which had a small plaster in the centre. The plaster was not removed but the back was examined and there were no visible wounds. So, he was brought back onto his back in the middle of the bed. During this time the patient closed both his eyes and stopped writhing around. The doctor called to him, rubbing his upper chest slightly, but rather than rocking under the pressure of the doctor's hands, he did not respond. The doctor then placed considerably more pressure down onto the chest and said the patient's name a little louder. When, after a few more pushes he was rewarded with a groan, the doctor, medical students and relatives all made eye contact with one another and laughed.'*

Observations on the wards provided me with the opportunity to really describe those individuals who were taking part in the AMBITION-cm trial and to contextualise them within the hospital setting. It is easy to forget about the individual stories when focused on collating large quantities of data and these descriptions remind me just how unwell the participants were. They also provide an opportunity to reflect on my own experiences of caring for exceptionally sick individuals and some of the heart-breaking outcomes we observed regularly within the trial. My awareness of the devastating nature of this infection continues to be a significant motivating factor for me and explains my sense of urgency to develop and implement interventions to prevent and treat cryptococcal meningitis.

> *'Consent obtained from an AMBITION study doctor. A little nervous about being observed by me. Some laughter and discussion about needing to be on their best behaviour!'*

I was highly conscious of my multi-positionality, but that consciousness could not remove it. My role as the Lead Clinician and one of the people who came to monitor the study, combined with a general unfamiliarity with ethnographic methods, would have resulted in observations being interpreted as monitoring visits. That this was not a formal appraisal or assessment was emphasised in the study documents, when approaching potential staff to observe, and during the consent process, but as discussed, there would have been a significant Hawthorne effect. I had the benefit of having worked on hospital wards in Uganda and Botswana before and being familiar with how the different systems worked, both before and during the trial, and the general standards of care and chaos therein, which worked as a basis for my own assessment of how significant this effect may have been. I also knew the people being

observed and had interacted with them on very many occasions by the time the LEOPARD study commenced, enabling me to at least try and identify any significant alterations in their behaviour during the observation. This familiarity also meant that the observations did not feel awkward or uncomfortable.

> *'I then thanked the doctor for their time this morning and we finished the observation. I followed up by asking how the experience was for them. Without specifically prompting, they felt that they had acted the same in my presence as if I was not there. They then asked for some feedback from me on how they were doing their job. I emphasised again that this was not an appraisal of their performance on the study but of course told them that they were doing an excellent job.'*

Code-switching, in which an individual adjusts their style of speech, appearance, behaviour or expressions to optimise the comfort of another, was not overly apparent when I compared my time on the wards undertaking different activities (providing medical care, monitoring patients, observing as part of LEOPARD) but there will no doubt have been subtle changes that I will have missed. My predominant reflection was often that when I came to do a monitoring visit I felt like that would (or should) have happened but it almost always didn't.

> *'The lady was very slight, probably around 40kg, and she had very thin hair. The doctor asked her a few questions to try and understand why she may have suffered a relapse of her condition. The patient who appeared quite tired sat up and began talking about some of the issues she had been facing at home. She was pointing into the distance as she spoke and the doctor told me that she had been struggling at home because her*

neighbour was a witch doctor and was sending snakes and mosquitoes with long tails to come to her house and attack her. The patient then spoke at length about how she had been suffering with vomiting every day, sometimes after taking her tablets. She had tried skipping the tablets but she also ended up vomiting on those days too. She was also feeling some pains in her stomach and up her arm. At this point a medical student joined us. The doctor asked to examine her and when she revealed her abdomen it was wrapped in a blanket which the doctor explained she had done in an attempt to suppress her hunger. The patient removed the blanket and the doctor felt her stomach. She was wincing with pain as they moved their hand across her entire abdomen, applying pressure throughout … The medical student then gave us a summary of how the patient was doing and explained, in English, that actually she was doing quite well over the last few days and had been going out of the hospital to the shops and buying some food down at the local shops because she did not like the maize meal that was offered at the hospital to all patients and caregivers. There was an undertone to this conversation that perhaps the patient was presenting a different picture of herself when being reviewed by the doctor compared to how she had been seen by and interacted with the medical student. There were no specific words used to convey this message.'

This extract demonstrates how it is not just the ethnographic observer who can be witness to different versions of the same person.

'From my own perspective, I found that by not having to focus on monitoring the study, looking for mistakes, or being asked to give input onto the care of the patients, I was

able to really pay attention to the daily activities of the team. I would normally be quite preoccupied with looking through the notes and cross referencing with the electronic data capture system to check the accuracy of the data.'

The reality for me was that the observations provided me with a finite period of time in which I could take off my Lead Clinician hat and just observe what was happening, without feeling like I was conducting some sort of clandestine observation. These short, intensive bursts of time gave me the chance to immerse myself in my ethnographic work and develop detailed fieldnotes that I could later reflect on to help build the core arguments of this thesis. Having obtained consent to do so I felt that this provided me with an ethical opportunity to document the reality of the AMBITION-cm trial.

'It was clear that it will be impossible to be invisible or to be seen as completely separate from the trial as a whole, this was made clear when I was asked for my input on the blood tests.'

The reality however was that in a clinical trial with extremely unwell patients, very few medical staff, and you have the Lead Clinician stood next to you, then there may be a clinical need to temporarily 'pause' the observation to provide input to patient care. Particularly because in my absence I would have been sent a WhatsApp message at the same time with the same question. As time went on, I tried to discourage this during the pre-observation discussion, but I also did not want to inconvenience the teams, slow things down or delay good care when I had already inconvenienced them by asking them to participate in the observation.

'I do think that I have begun to understand more the benefit of being in the study compared to being outside of it, and to hear about how this difference in care is articulated to participants when they are given information about the study. The language barrier is of course a huge shortcoming, but I do feel that there will be value in being able to contextualise some of the findings from the interviews within these documented observations.'

As I have stated, there were significant shortcomings to this approach, such as the language barrier discussed above, but these observations were instrumental in allowing me to take a step back, consider how the AMBITION-cm trial was situated within routine care, and formulate my conclusions. They appeared to be minimally inconvenient to those being observed, with my personal concerns about the methodology and my multi-positionality at least not being articulated by them.

I have acknowledged that my position as both an insider within the trial but also an outsider culturally, created a complex ethnographic space. One must also consider the potential benefits of positionality. My role within the AMBITION-cm trial can also be considered a strength as my extensive knowledge of the clinical condition under investigation, the complexities and nuance of the trial, and HIV care in both sites helped to shape this ethnographic study and provided an ability to contextualise the data. I acknowledged that although I see this as predominantly a strength, there are valid critiques of clinician researchers that having 'insider' knowledge can also lead to assumptions which may prevent

adequate clarifications or the discussion of contrary positions, both from researcher and participant (McNair et al., 2008).

The analysis

Although I led on the analysis within the following research papers, they did not come entirely from me. Throughout the research process I met regularly with members of the team, particularly Neo Moshashane and Georgina Nabaggala, who collected data from trial participants and next-of-kins. We used these meetings to discuss the latest interviews, any challenges with data collection, and emergent findings from the data. These discussions were hugely valuable and helped to clarify any questions or challenges I had in interpreting the data and to develop follow-up questions for subsequent interviews. As a result, preliminary themes began to emerge thanks to the help of this core team, and these later formed the formal analyses presented hereafter. In addition, the wider research team also fed back on each analysis and manuscript.

Having discussed both positionality and reflexivity, the LEOPARD protocol manuscript is presented. This is followed by the results which includes recruitment into LEOPARD, an overview of the AMBITION-cm trial findings for context, and then three results papers which are each summarised and then presented in turn.

RESEARCH PAPER THREE: THE LIVED EXPERIENCE OF PARTICIPANTS IN AN AFRICAN RANDOMISED TRIAL (LEOPARD): PROTOCOL FOR AN IN-DEPTH QUALITATIVE STUDY WITHIN A MULTISITE RANDOMISED CONTROLLED TRIAL FOR HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS

Summary of Findings

The following protocol paper summarised the methods of the paper however there is significantly more detail in the preceding pages.

Importance of Findings

This paper facilitates transparency with regards to the methods utilised in this study.

Dissemination and Impact

This paper was published in *BMJ Open* in April 2021 (Lawrence et al., 2021d).

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1800328	**Title**	Dr
First Name(s)	David		
Surname/Family Name	Lawrence		
Thesis Title	The Lived Experience of Participants in an African Randomised Trial (LEOPARD)		
Primary Supervisor	Prof Joseph Jarvis		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Open		
When was the work published?	05/04/2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	DSL conceived the project, developed the methodology, wrote the initial manuscript and trial protocol and is the Chief Investigator for the study. KT, AS and ZM are social scientists based at each of the three African sites. GH is a social scientist in South Africa and contributed to the study design. DN is a social scientist in Malawi and contributed to the study design. DM and CN are the AMBITION and LEOPARD principal investigators at the Kampala and Harare sites respectively. TH and JNJ are co-Chief Investigators of the AMBITION study. JS and JNJ jointly supervise DSL. All authors reviewed and approved the final manuscript.

SECTION E

Student Signature	[redacted]
Date	01/09/2022

Supervisor Signature	[redacted]
Date	01/09/2022

BMJ Open

The Lived Experience Of Participants in an African RandomiseD trial (LEOPARD): protocol for an in-depth qualitative study within a multisite randomised controlled trial for HIV-associated cryptococcal meningitis

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► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-039191).

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ABSTRACT

Introduction Individuals recruited into clinical trials for life-threatening illnesses are particularly vulnerable. This is especially true in low-income settings. The decision to enrol may be influenced by existing inequalities, poor healthcare infrastructure and fear of death. Where patients are confused or unconscious the responsibility for this decision falls to relatives. This qualitative study is nested in the ongoing AMBIsome Therapy Induction OptimisatioN (AMBITION) Trial. AMBITION is recruiting participants from five countries in sub-Saharan Africa and is trialling a novel treatment approach for HIV-associated cryptococcal meningitis, an infection known to affect brain function. We aim to learn from the experiences of participants, relatives and researchers involved in AMBITION.

Methods and analysis We will collect data through in-depth interviews with trial participants and the next of kin of participants who were confused at enrolment and therefore provided surrogate consent. Data will be collected in Gaborone, Botswana; Kampala, Uganda and Harare, Zimbabwe. Interviews will follow a narrative approach including participatory drawing of participation timelines. This will be supplemented by direct observation of the research process at each of the three recruiting hospitals. Interviews will also take place with researchers from the African and European institutions that form the partnership through which the trial is administered. Interviews will be transcribed verbatim, translated (if necessary) and organised thematically for narrative analysis.

Ethics and dissemination This study has been approved by the Health Research Development Committee, Gaborone (Reference: HPDME:13/18/1); Makerere School of Health Sciences Institutional Review Board, Kampala (Reference: 2019–061); University of Zimbabwe Joint Research Ethics Committee, Harare (Reference: 219/19), and the London School of Hygiene and Tropical Medicine (Reference: 17957). Study findings will be shared with research participants from the sites, key stakeholders at each research institution and ministries of health to help inform the development and implementation of future trials. The findings of this study will be published in journals and presented at academic meetings.

Trial registration Registered at www.clinicaltrials.gov: NCT04296292.

Strengths and limitations of this study

- ► There has been no previous qualitative study conducted in a low-income setting which has aimed to explore the experience of individuals who enrol into a clinical trial for the management of a life-threatening illness.
- ► We plan to collect data from trial participants, their next of kin and researchers working on a multisite clinical trial and by doing this we can elicit a broad range of perspectives and experiences that can inform the improvement of this and similar trials in the future.
- ► By adopting a multisite approach, we can compare and contrast experiences across different settings to understand which are shared and which are unique to a particular context.
- ► The study team are from multiple social and behavioural science disciplines meaning that interpretation of the data will be informed by a range of social theoretical perspectives.
- ► This study is taking place in a single clinical trial and will collect data from individuals in Botswana, Uganda and Zimbabwe only which means that the results may not be broadly generalisable.

INTRODUCTION

Since the start of the HIV epidemic our knowledge and understanding of the epidemiology and management of HIV and its numerous complications has exponentially increased. This knowledge has been produced through

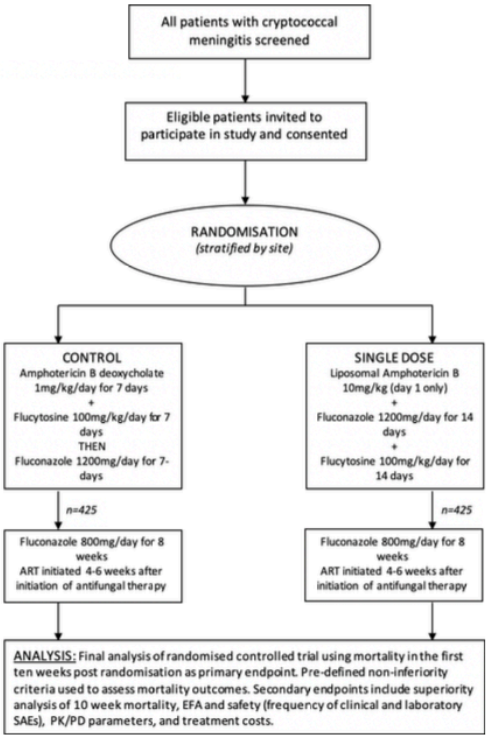

Figure 1 AMBITION Trial schema. ART: antiretroviral therapy, EFA: Early Fungicidal Activity, SAEs: Serious Adverse Events, PK/PD: Pharmacokinetics/Pharmacodynamics

the conduct of clinical research which would not be possible without the willing consent of participants.[1 2] Although antiretroviral therapy (ART) programmes have expanded dramatically and AIDS-related deaths have reduced, there were still an estimated 940 000 people who died from AIDS in 2017.[3] In individuals with advanced HIV disease the search for superior treatment options for fatal opportunistic infections continues.

The AMBITION Trial

The AMBIsome Therapy Induction OptimisatioN (AMBITION) Trial is a phase-III multicentred randomised controlled trial recruiting patients with HIV-associated cryptococcal meningitis (CM)[4] (figure 1). CM is a fungal infection of the brain that occurs most frequently in severely immunocompromised individuals with a CD4 count of less than 100 cells/uL.[4] There are approximately 223 000 incident cases of CM globally, with 73% of these occurring in sub-Saharan Africa. Annual global deaths are estimated at 180 000 and CM is responsible for roughly 15% of all AIDS-related deaths.[5] The nature of the infection means that roughly 40% of patients present with confusion[6] and some with a significantly reduced level of consciousness.

AMBITION is testing a new treatment for CM, a single, high dose of a less toxic, liposomal form of amphotericin, and is recruiting 850 participants from eight hospitals across five African countries: Botswana, Malawi, South Africa, Uganda and Zimbabwe. The decision-making capacity of potential participants is assessed by the clinical team who determine if the individual is able to understand the information around the trial, retain that information, weigh up the information to make a decision and communicate that decision. Patients consent for themselves if deemed to have decision-making capacity and if they do not, for example, if they are confused or comatose, then a surrogate will do so on their behalf. Participants are followed up daily during their initial inpatient admission (roughly 2 weeks) and then fortnightly as an outpatient until they complete the study at 10 weeks. Participants have their medical expenses paid for and receive transport reimbursements to attend outpatient appointments. AMBITION is funded by the European and Developing Countries Clinical Trials Partnership which brings together researchers from institutions in low and middle income countries (LMICs) and Europe.

The AMBITION Trial creates a rich environment for an in-depth qualitative study for a number of reasons.

Why participants are motivated to participate in trials

In routine care, mortality with the best standard of care treatment for CM is roughly 50% at 10 weeks.[7] In recent CM trials using the same regimen mortality is roughly 40%.[6 8] It has been observed that even when using the same drugs as in routine care, trial participants often do better.[7] The reasons for this include having a dedicated research team with more time for patients, better management of drug-induced toxicities and aggressive management of raised intracranial pressure, a common and potentially fatal complication of CM, and, inevitably, some selection of trial participants. Further widening outcomes between routine and trial settings in CM is the fact that the most effective drugs may be unavailable, or only sporadically available, in routine care. Clinical trials are however designed to answer a research question, the findings of which it is hoped will later be of benefit to a larger population. Some individuals may benefit by participating but it is not designed so that everyone will.[9] Despite this it is not uncommon for research participants to expect a personal therapeutic benefit from the treatment they receive, including in placebo-controlled trials.[10 11] Other commonly identified motivators are material benefits including free healthcare and transport reimbursements,[12–14] and altruism is also a factor.[15] In AMBITION it is fair to expect that all participants will benefit, compared with routine care. What is not understood is how this impacts both patients and researchers when it comes to motivating to enrol in the trial. Their motivation may be rooted in the economic inequality that exists between the patient and the research institution and which permeates the concept of voluntary participation. Voluntariness is understood as an autonomous choice without material entanglements and the principle of autonomy is often held above others when it comes to consenting for a clinical trial.[16] Research participants who lack agency are therefore subject to 'structural coercion' whereby their social and economic situation drives them into research participation as a means of navigating their

illness and because they may not have any other options to get the care they need or desire.[17] This is polarised when the chance of death is high, such as in CM.

Whom to consent when the patient cannot

In the context of life-threatening illness there are questions about when to obtain consent and who to obtain it from. One option is to commence trial procedures and defer consent until the patient is stable, which was acceptable to 70% of parents in a UK-based emergency paediatric study who felt the process was too much to handle in a stressful situation.[18] These findings are consistent with other studies from the UK.[19–21] The Declaration of Helsinki states that it is acceptable to recruit someone without capacity in best interests[22] and it has been argued that delaying treatment while waiting for consent risks losing out on the potential health benefit of that specific emergency treatment and underappreciating the impact of emergency treatment due to systematically delayed initiation.[23] An alternative is therefore to waiver informed consent completely, as was the approach in a postpartum haemorrhage trial in the UK which found that the perceptions of those who gave consent, had a surrogate, or waived consent were not dissimilar.[11]

Regarding who provides the consent, it is typical for surrogates to consent on behalf of an unwell patient who is confused or comatose. Within CM studies, roughly 40% of participants are confused and if they regain capacity they reconsent for themselves. Research in high-income countries (HICs) has identified that there is generally good concordance between surrogates and patients when it comes to agreeing to consent to both real life and hypothetical trials but that this is reduced in high-risk trials.[24 25] In LMICs multiple actors are often involved in the consent process with partners, parents, older family members and community leaders being consulted,[10 26] particularly in the case of severe illness.[13] This extends the process of gaining consent and can delay recruitment and treatment. According to a systematic review of 21 studies in Africa, only 47% of participants undergoing informed consent understood trial procedures such as randomisation and placebo and only 30% were aware they may not experience a therapeutic benefit of participation.[27] Another review found that understanding is significantly diminished among those who are critically ill.[28] To date there have been no in-depth qualitative studies in LMICs exploring the process of consent from the perspective of an acutely unwell adult or their consenting next of kin.

Participant and next of kin experience

We use the broad term of participant experience to encompass the way that an individual navigates through the scheduled events of a clinical trial as detailed in the protocol. Time is a prominent factor throughout this process. An illness occurs at a specific time in someone's life and the entire trial experience is time bound and shaped by the protocolised schedule of events. A large portion of the ethnographic work exploring participant experience of research in LMICs has elicited data concerning rumours, most commonly blood stealing, which are often dismissed by researchers as expressions of ignorance but are interpreted by social scientists as forms of popular resistance.[29–31] Most ethnographic exploration of rumours has been situated in trials of healthy individuals in trials and less commonly in acute, life-threatening illness. Lumbar puncture, the procedure used to diagnose and treat CM is known to be associated with rumours of causing death.[32] This has not been extensively studied using ethnographic methods but lumbar puncture refusal is common and can be fatal.

In the USA there has been an increasing call to assess clinical trial participant 'patient satisfaction' through the use of surveys or interviews which aim to hear the participant's voice and respond by making local improvement to the trial.[33] In LMICs this approach is less common but the concept of 'good participatory practice' has been developed by the WHO over the years[34] and this involves elements related to the participant experience.[35] No ethnographic work has explored these in the context of acute illness research in sub-Saharan Africa. Research within healthy volunteer studies has found that where poor outcomes such as severe disability or death occur, this has led to the apportioning of blame or the generation of rumours about research studies and institutions.[29 36] An exploration within AMBITION, where poor outcomes are not uncommon, could provide an opportunity to inform and potentially improve the conduct of this trial and others in the future.

Researcher experience

Paul Farmer (2002) wrote that 'researcher and subject are living in different worlds'[37] and it is commonly perceived that there is a mismatch between researcher and participant understanding of the research process.[29] Large, randomised controlled trials like AMBITION employ a large number of individuals from different countries.[38] Clinical researchers interact with individuals and their next of kin throughout the trial timeline[14 26 39 40] and are well placed to comment on the research process, regulatory approvals and implementation of a trial. These individuals can therefore provide a practical insight and suggestions for improvement.[41] As partners in the research process they can reflect on how clinical trials are conceptualised and designed in addition to the benefits and shortcomings of transnational partnerships and how we can optimise these relationships for the benefit of participants.[42] International researchers often have a broad range of experience working in clinical trials and can reflect on the evolution of clinical trials over time. As representatives of institutions which are partners (and often the lead) on grant applications, they often help to steer the clinical trial agenda in the region and are well placed to comment on how trials can be improved.

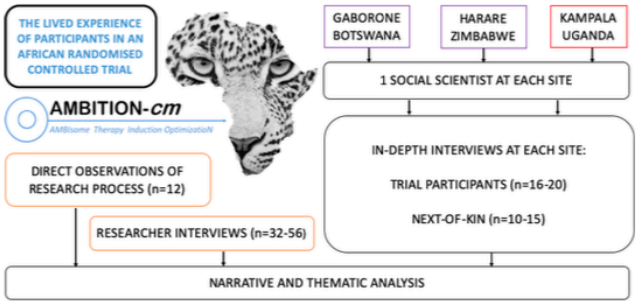

Figure 2 The Lived Experience Of Participants in an African RandomiseD trial (LEOPARD) Study Schema.

Aim and objectives

The aim of this study is to explore the experience of participants, their next of kin and researchers within the AMBITION Trial. By doing this we hope to learn how we can improve the trial experience within AMBITION and future trials for life-threatening illnesses.

Our specific objectives are:

From the perspectives of the participant, next of kin and researcher:

1. To build an understanding of the factors that enhance or diminish a clinical trial experience.

From the perspective of the researcher:

2. To compare the individual researcher's experience of the conceptualisation, development, initiation and implementation of a multicentred clinical trial in Africa.

METHODS AND ANALYSIS

Study design

We propose an in-depth qualitative study entitled the Lived Experience Of Participants in an African RandomiseD trial (LEOPARD). We will adopt a combination of in-depth interviews (IDIs) and direct observations to explore the experience of participants, their next of kin and researchers within the AMBITION Trial (figure 2).

Developing the methodology

The LEOPARD Study was conceived by DSL but the methodology was refined with the valuable input of social scientists from each of the six AMBITION Trial sites. Each social scientist has a particular interest in clinical trials. Over a series of one-on-one discussions and group calls the LEOPARD Study evolved. Having developed a consensus on a methodology it was necessary to determine the feasibility of collecting data from six sites. Recruitment into the LEOPARD Study will take place in Gaborone, Harare and Kampala. The reason for limiting data collection to three sites is to enable in-depth data collection and to avoid simply skimming the surface by diluting down data collection across multiple sites. These three sites represent diverse HIV epidemics, healthcare systems and political contexts which can be explored during data analysis.

Conceptual framework

We will use narrative analysis to explore how the concept of time shapes the experience of a life-threatening illness and a clinical trial. Drawing on Nancy Munn's theory of temporalisation we will look at how time is experienced by different individuals and how the pressure of a life-threatening illness impacts the perception of time as well as the complex decision to enrol (or not) in a clinical trial. By understanding how time and pressure impact the meaning and understanding of events at a time of crisis, we hope to learn how clinical trials can be better tailored to the needs of individuals with life-threatening illnesses. Narrative analysis is more commonly adopted by studies exploring chronic health conditions but the exploration of time is well suited to narrative analysis and a clinical trial, which has a clearly defined temporal structure, provides a rich setting for story-telling.

IDIs with AMBITION Trial participants

The purpose of the IDIs with AMBITION Trial participants is to collect personal accounts of their experience within the trial. Individuals who on entry into the AMBITION Trial were deemed to have decision-making capacity (ie, orientated) and those who were not (ie, disorientated), and therefore underwent surrogate consent, will be approached. All participants in the LEOPARD Study will need to have decision-making capacity to contribute to the IDI, meaning that those who lacked decision-making capacity at baseline will have clinically improved and regained that capacity. We will aim to recruit a maximum of 20 participants from each of the three sites, 60 in total, with a proposed gender balance of 50%–60% male and 40%–50% female which is in line with the epidemiology of CM at the sites. Consecutively eligible individuals will be approached to participate in two IDIs. One will take place at least 6 weeks into the 10-week AMBITION Trial and the other will take place at least 4 weeks after the trial. The reason for this is to allow reflection on the trial when one is both within and outside of it. Interviews will follow a broad interview schedule and the participant will be invited to draw a timeline of the events before, during and after the trial (online supplemental file 1). If individuals can only contribute to one IDI, for example due to worsening health or unavailability, then the data from the first IDI will be retained and analysed.

IDIs with the next of kin of AMBITION Trial participants

The purpose of the IDIs with the next of kin of AMBITION Trial participants is to collect personal accounts from individuals who have cared for and made important decisions about someone with a life-threatening illness. We use the term next of kin as a broad umbrella term to include any individual who may be the legal representative, a caregiver or a surrogate of the participant. This individual will have provided consent for the participant to enrol into the AMBITION Trial even if they may not have been the legally defined next of kin. We will aim to recruit a maximum of 15 individuals from each site, 45 in total,

with no specification for gender. Consecutively eligible individuals will be approached to participate in a single IDI which will take place at least 6 weeks into the AMBITION Trial. At the time of the IDI it will not be necessary for the trial participant to have regained decision-making capacity and these IDIs do not need to be linked to those with participants, although it is anticipated that some will be. Interviews will again follow a broad interview schedule and the participant will be invited to draw a timeline of the events (online supplemental file 2).

IDIs with AMBITION researchers

The purpose of the IDIs with AMBITION researchers is to understand their perspectives on how research is designed and implemented in Africa. Interviews will take place with researchers from each of the research institutions which form the AMBITION consortium. At African sites where trial participants are being recruited we will approach a range of individuals with different roles including senior and junior researchers, research doctors and nurses, laboratory scientists, pharmacists and study coordinators. In addition, individuals who are based at European institutions will be approached. We will aim for a maximum of 12 individuals from each of the three participating African sites and 4 from each of the five European sites. The maximum number of researcher interviews will be 56. Individuals will be conveniently sampled and interviewed on a single occasion, following a broad interview schedule (online supplemental file 3).

Direct observations of AMBITION researchers

A period of 12 months will be spent conducting ethnographic fieldwork at the African sites. The objective of this work is to contextualise the data from IDIs within the broader research environment. As the primary focus is on improving the trial for participants, observations will be largely based in the clinical environment, with emphasis placed on observing clinical staff. A total of four researchers from each of the three African sites will be invited to participate in direct observations. It will be made clear that this is not a method designed to appraise an individual, but an opportunity to spend a defined period of time observing events that take place within the research process. Observations will be coupled with brief questions to those in close proximity to the activity under observation.

Principles of recruitment

Eligible individuals will be approached to enrol in the study by a social scientist. In the case of AMBITION Trial participants and their next of kin, this will be done in the local language by an experienced social scientist at that site. In the case of AMBITION researchers this will be DSL who is part of the AMBITION Trial Management Group in his role as Lead Clinician for the trial. The researcher participant will be assured that they are free to decline participation and are not being interviewed or observed for the purposes of any appraisal or formal evaluation of their role within the team. The purpose of the researcher interviews and observations is to understand the research process and not to criticise individuals. A reflective approach to the research process will be adopted to iteratively refine the data collection methods and the communication skills of the social scientists.

Eligible individuals will be provided with a Participant Information Sheet and given the opportunity to ask questions. If they agree to participate, they will sign an Informed Consent Form and will be given the opportunity to withdraw their consent at any time, without giving a reason. Interviews will take place in a mutually acceptable location, be recorded with a digital voice recorder and notes will be taken during the interview. Observations will not be recorded and field notes will be made after the period of observation has finished.

It is anticipated that this study may identify aspects of the AMBITION Trial that need to be improved. In order to ensure this a formal reporting process will be followed. Each of the individual social science research assistants will report back to DSL. Any urgent issues that relate to trial conduct and Good Clinical Practice will be communicated through the use of direct communication and reflective summaries written on the day of data collection. In addition, weekly meetings will take place between the social scientists and DSL to discuss less urgent issues. These findings will be communicated either urgently to the Trial Management Group or at their weekly meetings, whichever is deemed appropriate. Additional advice may be sought from JS who is independent of the AMBITION Trial. Following this process the team will determine a course of action which may result, for example, in additional training of trial staff or modification of study procedures. This process is of vital importance to ensure that the findings of this study can improve the conduct of the ongoing AMBITION Trial. The confidentiality of the participant will be maintained throughout this process so as not to undermine trust in the study.

Confidentiality

All study documents will be kept on the person of the researcher or in a secure, locked location at all times. All digital documents will be on a password-protected, encrypted computer, backed up regularly and only shared with the study team. Names of interviewees will not be used at any stage of the data collection process. Predetermined identification numbers will be used on data collection forms. Audio recordings will not start until the interviewee has given consent and will not record their name. Pseudonyms will be used throughout. The location of researcher participants will be anonymised because the small number of eligible participants means that stating their location could make it possible to identify them.

Data analysis

Audio recordings will be transcribed verbatim into MS Word, translated into English in a separate second step if necessary, then exported to NVIVO V.11 for coding and

analysis. The first two IDIs from each group of participants will be analysed and discussed to enable iterative refinement of the data collection approach. Similarly, regular meetings will be used to review data, refine data collection tools and assess for data saturation. We will organise the data thematically and analyse it using narrative analysis at the country level by the social science team at each site. All data from AMBITION researchers will be analysed together using thematic analysis which will be performed in six phases: familiarisation with data, initial code generation, searching for themes, reviewing themes, defining and naming themes, and presenting final conclusions. These analyses will then be combined in a meta-synthesis of all data, irrespective of location or informant, to identify any areas of disconnect and, by comparing with country-specific analyses, to assess generalisability of findings.

Patient and public involvement

This protocol has been reviewed by Community Advisory Board members, expert patients and HIV activists from across the African sites. These individuals and groups will continue to be consulted throughout the data collection process and during the dissemination of research findings.

ETHICS AND DISSEMINATION

This study has been approved by the Human Resource Development Council, Gaborone (Reference HPDME:13/18/1); Makerere School of Health Sciences Institutional Review Board, Kampala (Reference: 2019–061); University of Zimbabwe Joint Research Ethics Committee, Harare (Reference: 219/19), and the London School of Hygiene and Tropical Medicine (Reference: 17957). Study findings will be shared with research participants from the African and European sites, key stakeholders at each research institution and ministries of health to help inform the development and implementation of future trials. The findings of this study will be published in journals and presented at academic meetings.

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CHAPTER THREE: LEOPARD RESULTS

Within the following chapter I will summarise the recruitment into the LEOPARD study and then present the results of the AMBITION-cm trial for context.

Summary of recruitment

Between 6th February 2020 and 7th July 2021, a total of 89 individuals were recruited into the study: 38 trial participants, 20 next-of-kin, and 31 researchers (Table 4). Forty-eight (54%) of all participants were female.

Table 4: Number of participants recruited into the LEOPARD study

Category	Gaborone	Kampala	European Partners	Total
Trial participants	18	20		38
Next-of-kin	9	11		20
Researchers	11	9	11	31
Total				89

Trial participants

In Gaborone, 18 trial participants were recruited: 11 male and 7 female (Table 5). Twelve were Motswana and the interviews were conducted in Setswana and six were Zimbabwean with interviews conducted predominantly in English but often intermixed with some Setswana. There was an equal proportion who were decision-orientated and decision-disorientated upon enrolment into the AMBITION-cm trial. Two were educated to primary level, 13 to secondary level and three to tertiary level.

In Kampala, 20 trial participants were recruited: 10 female and 10 male. All participants were Ugandan, and interviews were conducted in Luganda. There was an equal proportion who

were decision-orientated and decision-disorientated upon enrolment into the AMBITION-cm trial. Thirteen were educated to primary level, five to secondary level and two to tertiary level.

Overall, an equal number were randomised to each arm in the trial. Thirty participants took part in two interviews and eight took part in only one. The primary reasons for not being able to participate in a second interview included travel restrictions due to the COVID-19 pandemic or death. Towards the end of data collection, it was difficult to find eligible female participants who were decision-disorientated at baseline because of fewer being recruited into the trial but also particularly poor outcomes. As a result, some of these participants were contacted after they had already completed the trial and a single interview was sufficient to obtain data. The median duration of the initial interviews was 45 minutes (range 20 to 163 minutes), and second interviews were typically much shorter with a median duration of 32 minutes (range 6 to 67 minutes) with interview duration missing for four follow-up interviews.

Next-of-kin

In Gaborone, nine next-of-kin participants were recruited: seven female and two male. In Kampala, 11 next-of-kin participants were recruited: eight female and three male. Of all next-of-kin interviews, 17 were linked to trial participants who also enrolled and three were not. In those cases, in which the next-of-kin was interviewed without being linked to the trial participant, this was typically due to ongoing ill health of the trial participant, including prolonged lack of decision-making capacity, and in one case death. The median duration of interviews was 45 minutes (range 23 – 101 minutes).

Researchers

Due to the limited number of eligible individuals and to preserve anonymity, I present limited demographic data of the researcher participants. Of the 32 individuals recruited 15 (47%) were female. The median duration of the interviews was 53 minutes (range 27 – 112 minutes). All participated in an in-depth interview and of those, three individuals with clinical roles were observed in each recruiting site on one occasion. Observations lasted between roughly two and four hours.

Table 5: Summary of trial participant and next-of-kins (NOK)

	Age	Gender	Nationality	Language of interview	Education Level	Decision-making capacity	Trial Arm	Number of Interviews	NOK Interview	NOK Gender
Gaborone	34	Male	Batswana	Setswana	Secondary	Disorientated	AmBisome	2	Yes	Female
	50	Male	Batswana	Setswana	Primary	Disorientated	AmBisome	2	Yes	Female
	44	Male	Batswana	Setswana	Secondary	Disorientated	Control	2	Yes	Female
	34	Female	Batswana	Setswana	Secondary	Disorientated	Control	1	Yes	Female
	32	Female	Batswana	Setswana	Tertiary	Disorientated	Control	2	Yes	Female
	49	Male	Batswana	Setswana	Tertiary	Disorientated	Control	2	Yes	Female
	35	Male	Zimbabwean	English	Secondary	Disorientated	AmBisome	2	Yes	Female
	44	Female	Batswana	Setswana	Tertiary	Disorientated	AmBisome	1	No	
	34	Male	Zimbabwean	English	Secondary	Disorientated	AmBisome	1	No	
	37	Female	Zimbabwean	English	Secondary	Orientated	Control	1		
	24	Female	Zimbabwean	English	Secondary	Orientated	Control	2		
	42	Male	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	37	Male	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	40	Male	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	47	Male	Zimbabwean	English	Secondary	Orientated	AmBisome	2		
	22	Male	Batswana	Setswana	Secondary	Orientated	Control	2		
	33	Female	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	29	Female	Zimbabwean	English	Primary	Orientated	Control	1		
Kampala	46	Female	Ugandan	Luganda	Primary	Disorientated	Control	2	Yes	Female
	53	Female	Ugandan	Luganda	Primary	Disorientated	AmBisome	2	Yes	Female
	26	Female	Ugandan	Luganda	Primary	Disorientated	Control	1	Yes	Male
	29	Female	Ugandan	Luganda	Secondary	Disorientated	AmBisome	1	Yes	Female
	36	Male	Ugandan	Luganda	Primary	Disorientated	Control	2	Yes	Female
	35	Male	Ugandan	Luganda	Primary	Disorientated	Control	2	Yes	Female
	45	Male	Ugandan	Luganda	Tertiary	Disorientated	Control	2	Yes	Female

	35	Male	Ugandan	Luganda	Primary	Disorientated	AmBisome	2	Yes	Female
	30	Female	Ugandan	Luganda	Secondary	Disorientated	Control	2	Yes	Female
	27	Male	Ugandan	Luganda	Primary	Disorientated	AmBisome	2	Yes	Male
	49	Male	Ugandan	Luganda	Primary	Orientated	AmBisome	2		
	44	Male	Ugandan	Luganda	Primary	Orientated	Control	1		
	24	Male	Ugandan	Luganda	Secondary	Orientated	AmBisome	2		
	46	Female	Ugandan	Luganda	Primary	Orientated	Control	2		
	45	Male	Ugandan	Luganda	Primary	Orientated	Control	2		
	32	Female	Ugandan	Luganda	Secondary	Orientated	AmBisome	2		
	34	Female	Ugandan	Luganda	Tertiary	Orientated	AmBisome	2		
	23	Female	Ugandan	Luganda	Primary	Orientated	Control	2		
	23	Female	Ugandan	Luganda	Primary	Orientated	AmBisome	2		
	30	Male	Ugandan	Luganda	Secondary	Orientated	Control	2		

Note: This table is repeated in Research Paper Six.

AMBITION-CM TRIAL RESULTS SUMMARY

The results of the AMBITION-cm trial are important to help contextualise the LEOPARD results papers, particularly Research Paper Six which focuses on the acceptability of the regimen. Here, I summarise those results.

Trial Population: A total of 1193 individuals were screened and 844 were enrolled and underwent randomisation (Jarvis et al., 2022). Thirty were excluded and 814 were included in the intention-to-treat population. No participants were lost to follow up. Baseline characteristics were similar across groups. The median age was 37 years, 60% were male, 28.5% were decision-disorientated at baseline, and the median CD4 was 27 cells/μL.

Mortality: Ten-week mortality in the AmBisome arm was 24.8% (101/407) and in the control arm was 28.7% (117/407). The primary outcome, absolute difference in mortality at 10 weeks between the AmBisome arm and the control arm was -3.9% and the upper bound of the one-sided 95% confidence interval was 1.2% which was well below the prespecified 10% noninferiority margin ($p<0.001$) (Figure 8 and Figure 9). In the adjusted analysis, which controlled for factors independently associated with mortality, the difference in mortality was -5.71% and the upper bound of the one-sided 95% confidence interval was -1.0, indicating superiority. These findings were consistent across per-protocol analyses.

Figure 8: AMBITION-cm non-inferiority figure. ITT denoted intention-to-treat; PP denotes per-protocol

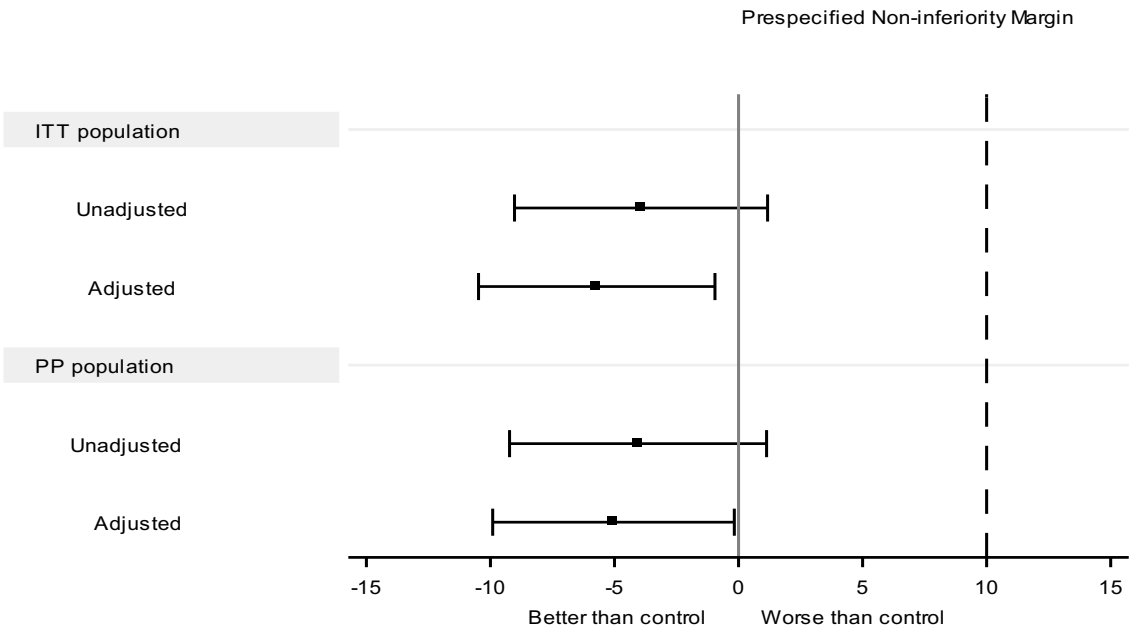
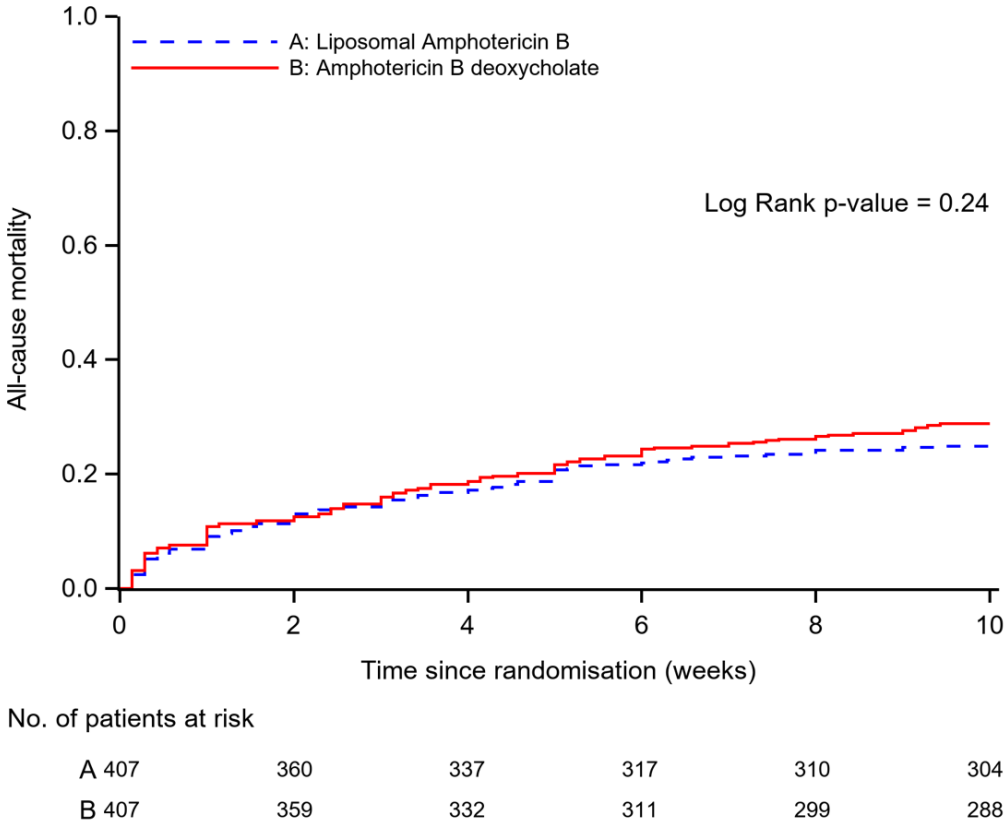


Figure 9: AMBITION-cm Kaplan-Meier survival curves



Safety: During the initial 21 days of treatment there were significantly more adverse events in the control arm (50.0% of participants vs 62.3% ($p<0.001$)). Grade 3 or 4 anaemia developed in 13.3% (56/420) of participants in the AmBisome arm and 39.1% (165/422) participants in the control arm ($p<0.001$). The mean decrease in haemoglobin during the first week was 0.3g/dL in the AmBisome arm and 1.9g/dL in the control arm ($p<0.001$). Blood transfusion was performed in 7.6% (32/420) in the AmBisome arm and in 18.0% (76/422) in the control arm. The mean relative increase in the serum creatinine level from baseline to day seven was 20.2% in the AmBisome arm and 49.7% in the control arm ($p=0.001$)

Conclusions: Single-dose liposomal amphotericin B combined with flucytosine and fluconazole was non-inferior to the WHO-recommended treatment for cryptococcal meningitis and was associated with fewer adverse events. The full results paper is presented in Appendix 11.

CHAPTER FOUR: RESEARCH PAPER FOUR - PATHWAYS TO CARE WITH HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS IN BOTSWANA AND UGANDA: FINDINGS FROM A QUALITATIVE METHODS STUDY

Summary of Findings

This analysis tries to capture the events leading up to becoming diagnosed with cryptococcal meningitis and then being approached to enrol in the AMBITION-cm trial. I have already described the epidemiology of cryptococcal meningitis and the expected ongoing burden as well as the lack of in-depth qualitative methods research exploring the perspectives of those diagnosed with this infection. The aim of this analysis was to describe and learn from individual pathways to care and begin to understand how cryptococcal meningitis could be averted or diagnosed earlier to reduce the chances of death.

In-depth interviews with trial participants and their next-of-kin were the primary source of information for this analysis. Data collected from researchers and during direct observations, as well as my personal experience working on the trial and caring for participants and other PLWH in Gaborone, helped to contextualise these data. Of those 38 trial participants who enrolled in the LEOPARD study, all but one (97%) presented with a headache with a median duration of 14 days (range 3 – 90 days), consistent with the overall trial where 96% of all participants presented with a headache of median duration 14 days (Jarvis et al., 2022). The participants spanned the entire HIV care cascade. Twenty-two participants (58%) had a previous HIV diagnosis and 16 (42%) were newly diagnosed with HIV. Of the 22 with a known HIV diagnosis, 19 had previously received ART and three had never started. Among those 19 on ART, eight (42%) were reportedly adherent and/or had a suppressed viral load; six (32%) stated their adherence was poor and five (26%) had defaulted and stopped taking ART entirely. When tabulating the number of healthcare interactions prior to admission to the

AMBITION-cm recruiting hospital the median number was two visits (range 0-8 visits), and when considering this on a site basis the median was two in Gaborone and three in Kampala.

The headache that develops in cryptococcal meningitis is often the first symptom and it may be quite indolent at first. In some cases, it could persist for days, weeks, or even months before any other neurological symptoms developed. This resulted in the headache often being interpreted by the individual as benign, perhaps due to general physiological imbalance, such as heat or dehydration, or common pathologies such as flu or, where endemic, malaria, and later COVID-19. This was also a common interpretation of healthcare workers. Particularly in situations where the HIV status was unknown or not disclosed by the individual then we were told of long, convoluted pathways, navigating multiple healthcare facilities, medical specialities, cadres of healthcare worker, and excessive out-of-pocket expenses whilst their symptoms continued, worsened and evolved. Several people were sent to psychiatric hospitals, some for outpatient assessments whereas others were admitted, and some visited traditional practitioners such as herbalists or traditional healers. It was often only when additional symptoms, such as collapse, seizures, or confusion developed that hospital level, inpatient care was accessed.

One of the difficulties in being able to recognise meningitis was that almost no participants had ever heard of it before. Those who knew their HIV status had not been told that meningitis was a possible complication of untreated HIV, or that meningitis could develop shortly after starting ART. Those who knew their HIV status tended to visit primary care facilities rather than HIV clinics. A critical step that propelled these pathways to care and the

ultimate diagnosis of cryptococcal meningitis was the recognition of the individual's HIV status and that they were likely to be living with AHD.

Importance of Findings

This is the first, in-depth qualitative methods study to explore pathways to care with cryptococcal meningitis across multiple contexts in sub-Saharan Africa. Within the following research paper, I provide recommendations across critical points in the HIV care cascade that could increase knowledge around cryptococcal meningitis, encourage early healthcare-seeking, and ultimately lead to improved outcomes.

Dissemination and Impact

This paper has been submitted to *SSM Qualitative Research in Health*. In addition, these data are being used to inform ongoing implementation efforts which are described in more detail in the discussion.

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SECTION A – Student Details

Student ID Number	1800328	**Title**	Dr
First Name(s)	David		
Surname/Family Name	Lawrence		
Thesis Title	The Lived Experience of Participants in an African Randomised Trial (LEOPARD)		
Primary Supervisor	Prof Joseph Jarvis		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Where is the work intended to be published?	SSM - Qualitative Research in Health
Please list the paper's authors in the intended authorship order:	David S Lawrence, Agnes Ssali, Neo Moshashane, Georgina Nabaggala, Lebogang Maphane, Thomas S Harrison, David B Meya, Joseph N Jarvis and Janet Seeley
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This project was conceived by myself with support from Prof Janet Seeley and Prof Joseph Jarvis. I developed the methodology which was refined by all members of the team. I collected data from researchers and Neo Moshashane and Georgina Nabaggala collected data from trial participants and next-of-kins in Gaborone and Kampala respectively. I performed the analysis and received feedback from Prof Seeley. I wrote the initial draft of the manuscript and all authors commented on and approved the final submission

SECTION E

Student Signature	[redacted]
Date	15/09/2022

Supervisor Signature	[redacted]
Date	15/09/2022

Pathways to care with HIV-associated cryptococcal meningitis in Botswana and Uganda: findings from a qualitative methods study

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Consent to participate: All participants signed a written consent form which was approved by the relevant research ethics committees.

Consent for publication: All participants provided written consent for publication, including the use of anonymised quotes.

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Authors contributions: David S Lawrence: Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Project Administration. **Agnes Ssali:** Conceptualization, Methodology, Formal Analysis, Writing – Review & Editing, Project Administration. **Neo Moshashane:** Formal Analysis, Investigation, Data Curation, Writing – Review & Editing, Project Administration. **Georgina Nabaggala**: Formal Analysis, Investigation, Data Curation, Writing – Review & Editing, Project Administration. **Lebogang Maphane:** Data Curation, Project Administration. **Thomas S Harrison**: Methodology, Writing – Review & Editing, Supervision. **David Meya:** Methodology, Resources, Writing – Review & Editing, Supervision. **Joseph N Jarvis:** Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Funding acquisition. **Janet Seeley:** Conceptualization, Methodology, Formal Analysis, Resources, Writing – Original Draft, Supervision.

ABSTRACT

HIV-associated cryptococcal meningitis remains a key driver of AIDS-related mortality. Mortality is twice as high in those who present later to care and with severe symptoms such as confusion. We embedded a qualitative methods study within a randomised controlled trial with the aim of understanding pathways to care. We conducted in-depth interviews with trial participants and surrogate decision makers and analysed data thematically. We interviewed 58 individuals. Pathways to care were prolonged because headaches were disregarded by participants and healthcare workers as a common occurrence with a broad differential diagnosis of predominantly benign aetiologies. There was also a lack of awareness of cryptococcal meningitis, and it was often after HIV was diagnosed or disclosed that the pathway accelerated, resulting in hospital admission. We outline key recommendations to reduce mortality and argue for the integration of social and behavioural interventions within differentiated service delivery models for advanced HIV disease.

Keywords: HIV; Advanced HIV Disease; Cryptococcal Meningitis; Qualitative Research; Differentiated Service Delivery

INTRODUCTION

An estimated 650,000 people died from AIDS-related complications in 2021 (UNAIDS, 2022). This figure is a 68% reduction from the peak of 2.1 million people who died in 2004 (UNAIDS, 2004), however over the last decade the rate of decline has decreased significantly. In 2020 UNAIDS set a target to reduce annual AIDS deaths to below 250,000 by 2025 (UNAIDS, 2020) but if current trends continue 460,000 people are projected to die of AIDS-related causes in that year. These deaths occur primarily in individuals with advanced HIV disease (AHD) who have a CD4 count of less than 200cells/µL and are vulnerable to potentially fatal opportunistic infections such as tuberculosis and cryptococcal meningitis, and malignancies such as lymphoma (Egger et al., 2002).

There remains a relatively constant population of people living with HIV who are diagnosed with AHD (Carmona et al., 2018). This is an extremely heterogeneous population but can be crudely categorised into two groups. The first are individuals who have AHD upon initial diagnosis of HIV, indicating that a considerable length of time has lapsed between acquiring HIV and undergoing testing. Recent data from South Africa (Carmona et al., 2018), Nigeria (Otubu et al., 2022), and Botswana (Leeme et al., 2021) indicate that roughly 32.9%, 47.6% and 24.8% of people have AHD at diagnosis. The second group are individuals who have been diagnosed with HIV and develop AHD over time. This may be because of a number of factors including imperfect linkage to care; ART toxicity and intolerance; difficulties with adherence; and drug resistance. Data suggest that this is an increasingly large proportion of people with AHD and that it is not uncommon for individuals to move 'backwards' along the care cascade and develop AHD in the process. For example, data from Botswana found that between 2015-

16, 40% of all individuals with a CD4 count <100 cells/µL were new to care compared to 26% in 2018-19 (Lawrence et al., 2021c).

HIV-associated cryptococcal meningitis is the second leading cause of AIDS-related mortality and is estimated to cause 19% of all AIDS-deaths (Rajasingham et al., 2022). As with AHD, the burden of cryptococcal meningitis persists. Recent programmatic data from South Africa and Botswana indicate that the number of cases has stayed relatively constant in recent years (Osler et al., 2018; Tenforde et al., 2017). Cryptococcal meningitis primarily affects people with very advanced HIV disease, typically with a CD4 count less than 100 cells/µL (Lawrence et al., 2019). Meningitis is the most serious manifestation of cryptococcal disease, which is caused by *Cryptococcus spp,* a ubiquitous fungus that enters the lungs through inhalation of spores. In immunocompetent individuals this exposure rarely leads to any disease or impact on health, however among individuals with severely weakened immune systems, such as those with advanced HIV disease, the fungus can spread throughout the body, including to the brain. This spread is a state called cryptococcal antigenaemia and can be detected by a point of care blood test called a cryptococcal antigen (Jarvis et al., 2009). Screening the blood of people with advanced HIV provides the opportunity to identify the presence of *Cryptococcus* in the blood to attempt to avert its onward spread, and many high-prevalence countries have national screening programmes (Greene et al., 2021). If meningitis does occur the prevailing symptom is headache, and this can be followed by a myriad of other symptoms including confusion, seizures, and coma. Left untreated, cryptococcal meningitis is uniformly fatal. Death can arise from the direct impact of the fungus on the brain but also from impedance of the normal flow of fluid around the brain which leads to raised intracranial pressure and can result in coning, in which the brainstem is pushed down through the base

of the skull. Cryptococcal meningitis must be diagnosed with a lumbar puncture in which a needle is inserted into the bottom of the spinal column to obtain cerebrospinal fluid and the same procedure is also warranted, often daily, to reduce raised intracranial pressure.

Outcomes among individuals diagnosed with cryptococcal meningitis have historically been very poor with roughly 70% of patients dying within a year (Gaskell et al., 2014; Longley et al., 2008; Nussbaum et al., 2010; Rothe et al., 2013). There have been significant advances in recent years following two landmark trials which have demonstrated that mortality rates below 30% are possible. The ACTA trial ultimately led to the World Health Organisation (WHO) in 2018 adopting a treatment regimen of a week of intravenous amphotericin B deoxycholate given with oral flucytosine as their recommended first-line treatment regimen (Molloy et al., 2018). Observational data from South Africa found the mortality gains in the trial to also be possible in routine care settings (Mashau et al., 2022). Following this the AMBITION-cm trial found a single, high dose liposomal amphotericin-based regimen to be non-inferior to the ACTA regimen (Jarvis et al., 2022) and, due to the added convenience of a single intravenous regimen, this was adopted by WHO as the first-line regimen in 2022 (World Health Organisation, 2022).

Despite the improved outcomes observed in recent clinical studies, the case fatality rate is still high compared to other opportunistic infections (Mabunda et al., 2014) and the epidemiological data suggest that cryptococcal meningitis will remain a significant contributor to mortality in the coming years (Rajasingham et al., 2022). To date there has been very limited information on the pathways to care of those individuals diagnosed with cryptococcal meningitis, primarily because of the severity of the infection and the poor

outcomes (Link et al., 2022). Qualitative methods research can provide valuable insights into the lived experience of individuals diagnosed with cryptococcal meningitis that could be used to improve care and outcomes across the HIV care continuum. First, these individuals have already had HIV for a number of years and have either not been tested and/or been maintained on effective ART. Exploring and learning from their experience of living with HIV and developing AHD can inform approaches to care that stretch far beyond cryptococcal meningitis. Second, in the case of cryptococcal antigenaemia there is a window of opportunity for healthcare systems to intervene and prevent meningitis which may not always be realised, and qualitative research could help highlight areas for improvement in healthcare delivery. Third, cryptococcal meningitis typically causes what begins as a mild headache that worsens over days and weeks before leading to more severe symptoms such as confusion, seizures and coma. Mortality rates are more than double in those with severe symptoms suggestive of delayed presentation (Jarvis et al., 2022) and qualitative research can explore whether individuals are aware of cryptococcal meningitis and the need to present to care soon after symptoms develop. We conducted a qualitative methods study with patients diagnosed with cryptococcal meningitis and their caregivers to begin to understand their pathways to care and identify recommendations to avert mortality.

METHODS

We embedded an ethnographic study entitled The Lived Experience Of Participants in an African RandomiseD trial (LEOPARD) within the AMBITION-cm trial at the Gaborone, Botswana and Kampala, Uganda sites (Lawrence et al., 2021d). In Botswana the participants were recruited at Princess Marina Hospital and in Kampala at Kiruddu Hospital. AMBITION-cm is described in more detail elsewhere (Jarvis et al., 2022) and was a non-inferiority phase-

III trial of a single, high-dose of AmBisome given with 14 days of flucytosine and fluconazole in comparison to the WHO defined standard of care: 7 days of amphotericin B given with 7 days of flucytosine and followed by 7 days of fluconazole. AMBITION-cm recruited 844 participants from eight hospitals in five countries: Botswana, Malawi, South Africa, Uganda, and Zimbabwe. The AMBITION-cm regimen was found to be non-inferior in terms of averting all-cause mortality and was also associated with significantly fewer adverse events. It has since been recommended as the first-line treatment regimen for cryptococcal meningitis by the World Health Organisation (World Health Organisation, 2022).

We conducted in-depth interviews (IDIs) and direct observations, collecting data from three categories of individuals: trial participants, surrogate decision makers (SDMs) who provided consent for the trial in cases where potential participants lacked decision making capacity, and researchers working on the trial. This paper draws on data from trial participants and SDMs only. Pathways to care with cryptococcal meningitis was one of the core areas of enquiry for the LEOPARD study.

Consecutively eligible trial participants were approached to participate in two in-depth interviews. We aimed to recruit a maximum of 20 participants from each site (Kampala and Gaborone), 40 in total. We included individuals who upon entry into the trial were deemed to have decision making capacity (i.e., decision orientated) and those who were not (i.e., decision disorientated). We anticipated 30% of all trial participants to be decision disorientated at baseline but aimed for this group to make up half of all participants in this qualitative methods study. At the time of enrolment into LEOPARD all individuals must however have regained decision making capacity to consent for the IDI. In line with the

epidemiology of cryptococcal meningitis we aimed for 50-60% of participants to be male (Lawrence et al., 2021a). The first IDI took place at least six weeks into the ten-week trial and the other at least four weeks after the final trial appointment. Secondly, consecutively eligible surrogate decision makers were approached to participate in a single in-depth interview at least six weeks after having provided consent for a trial participant who was decision-disorientated at baseline. We aimed to recruit a maximum of 15 individuals from each site, 30 in total, with no specification for gender. Additionally, we conducted direct observations of the research process, including the informed consent process and the administration of study drugs. The direct observations occurred after they had reached hospital so were used to contextualise the severity of the illness rather than contributing significantly to an analysis of pathways to care.

Interviews followed a topic guide tailored to each group of participants and were conducted in Setswana or English in Botswana and Luganda in Uganda. The topic guides explored the experience of developing cryptococcal meningitis (or caring for someone who had), being approached and deciding to enrol in the trial, and the experience whilst in the trial. All interviews were audio-recorded. Interviews were transcribed and translated, and field notes were made. These data were then entered into NVivo 12 and analysed using thematic analysis (Braun & Clarke, 2006). Thematic analysis involved six steps: familiarisation with data, initial code generation, searching for themes, reviewing themes, defining and naming themes and presenting final conclusions. In addition, we extracted data from the participant IDIs and summarised their pathways to care with a focus on their HIV and ART history, how long they had been symptomatic with cryptococcal meningitis, and the various interactions they had

with healthcare services whilst symptomatic and prior to their admission to the AMBITION-cm trial hospital.

The research group was composed of Author1 who is an HIV clinician and was the lead clinician for the AMBITION-cm trial. Author1 conducted direct observations. Author4 conducted IDIs in Uganda under the supervision of Author2 and Author9, all of whom were independent of the trial. Author3 was also independent of the trial and conducted IDIs in Botswana under the supervision of Author1 and with administrative support from Author5. The study was approved by the Human Resource Development Council, Gaborone (HPDME: 13/18/1); Makerere School of Health Sciences Institutional Review Board, Kampala (REF: 2019-061), Uganda National Council for Science and Technology (REF: SS386ES) and the London School of Hygiene and Tropical Medicine (REF: 17957).

RESULTS

Between January 2020 and June 2021, we recruited a total of 58 individuals. Thirty-eight trial participants (18 in Gaborone, 20 in Kampala) and twenty SDMs (9 in Gaborone, 11 in Kampala). Of the 38 trial participants who took part in an IDI, 17 (45%) were female, and half were decision-disorientated at baseline. 20 were Ugandan, 12 Motswana, and six Zimbabwean. All but one (97%) presented with a headache with a median duration of 14 days (range 3 – 90 days), consistent with the overall trial where 96% of all participants presented with a headache of median duration 14 days. Twenty-two participants (58%) had a previous HIV diagnosis and 16 (42%) were newly diagnosed with HIV when they were admitted with cryptococcal meningitis, compared to the main trial where 30% of participants were newly diagnosed with HIV. Of the 22 with a known HIV diagnosis, 19 had previously received ART

and 3 had never started. Among those 19 on ART, 8 (42%) were reportedly adherent and/or had a suppressed viral load; 6 (32%) stated their adherence was poor and 5 (26%) had defaulted and stopped taking ART entirely. When tabulating the number of healthcare interactions from the onset of symptoms to admission to the AMBITION-cm recruiting hospital the median number was 2 visits (range 0-8 visits).

Suspecting the headache is serious

'Just a simple headache, an everyday one'

Male participant, Gaborone

One of the challenges in recognising the life-threatening diagnosis of cryptococcal meningitis was that, for many participants, headaches were a common and everyday phenomenon. The headaches were often described as starting off as quite mild, and potentially being attributed to dehydration, the weather, or stresses in life such as relationship difficulties and money worries. As a result, they were often managed by drinking plenty of water or taking simple analgesia kept in the house or sourced from local pharmacies and clinics, or herbal preparations that were rubbed on the head. The headaches would initially respond to these, at least during the day, and then frequently became worse at night when the participants were lying down. For some participants this relatively indolent presentation could go on for weeks and weeks, becoming more irritating but not always much more severe or signalling a serious underlying pathology. Some participants described going back and forth to the same clinics every week or two for a healthcare worker to review their symptoms and prescribe

them more, or stronger, analgesia and this was true of both those who were aware and unaware of their HIV status. In these cases, it was only when the symptoms evolved and, for example, they developed double vision, had seizures, or collapsed, that they were prompted to seek health from larger health centres or hospitals.

When considering pathological causes of the headache participants developed their own differential diagnosis which was often broad such as flu, malaria which is common in Kampala but not in Gaborone, and later in the study, COVID-19. These were pathologies they had regularly encountered and could also explain the fevers which commonly accompanied the headache. This self-diagnosis could be managed by visiting pharmacies which sell antimalarials and a variety of flu remedies without the need for a clinic consultation or prescription which would help save time and money. One of the difficulties in being able to recognise meningitis was that almost no participants had ever heard of it before. Some of those who had heard of meningitis had not identified it as something they were at risk of developing with one female participant in Kampala telling us that *'I am an adult, not a child. I hear that children are the ones who suffer from meningitis'*. Only one male participant in Kampala had suspected he had meningitis having been hospitalised many years ago for another reason and seeing a case on the same ward who *'was all straight and stiff as a dead body, so whenever my neck became tight, my thoughts went to that man'* and this prompted him to seek urgent medical attention.

In both locations, but more so in Kampala, we also found a small number of examples in which the headache was attributed to witchcraft and having been bewitched. This was most commonly in cases in which the participant's behaviour had changed, perhaps as a result of

confusion or hallucinations. In one scenario, a male participant in Kampala had fallen ill during a trip to his ancestral clan shrine and his symptoms were misinterpreted as possession and he was severely beaten with a stick by his relatives. The belief that witchcraft was the cause prompted the use of traditional medicine, either obtained from the house or from a traditional healer and in the scenario described above the traditional healer recognised that the presentation was likely related to advanced HIV disease and diverted the participant to a hospital. We also commonly encountered individuals who did not express any concerns about witchcraft but did use a combination of biomedical and traditional medicines to try and alleviate their symptoms, as they would typically for other symptoms, and sometimes visited a traditional healer after several unsuccessful trips to a biomedical facility.

Suspecting the headache is related to HIV

"They sent me away from the health facility. They even took me to [a psychiatric hospital], thinking that maybe I had run mad. So, I stayed [there]. There were some who used to … wonder and ask me, saying, "You seem not to be a mad patient like others."

Female participant, Kampala

The majority of participants had never heard of meningitis and therefore this was not commonly considered as a potential diagnosis. In some of these scenarios the HIV status was undiagnosed and therefore unknown to all, in some the diagnosis was known only by the participant, and in others all parties were aware. Those who did not know their HIV status were also often for the first-time experiencing symptoms of untreated infection including weight loss and skin changes. Some wondered if these changes and their headache could be

related to undiagnosed HIV infection, and this was sometimes combined with suspicion or knowledge that their partner was also living with HIV. In these scenarios several participants used this as a prompt to go and test and this new diagnosis often triggered consideration of HIV-related pathology by clinicians. Those who knew their HIV status but were aware that they were either not on treatment at all or had been taking it infrequently did not commonly express to our team that they had considered their headache and associated symptoms to be related to HIV, although this might have been the case. In addition, nobody said that they had been told by a healthcare worker that a headache could be a serious consequence of untreated HIV. In several of these scenarios, the participants did not disclose their HIV status to healthcare workers when visiting facilities with their headache and were often tested further down the pathway, for example when they were finally admitted to hospital. Others went and tested at clinics, seeking confirmation of their diagnosis, but indicating that it was their first time to test. Finally, those who were on treatment did not say that they had been told a headache could be a serious complication of HIV. Those who had recently been started on treatment also did not indicate that they had been told that a headache could emerge shortly after starting treatment and that this and could be a potentially fatal complication.

Most of our participants (all except three) had encounters with healthcare workers during the course of their symptoms and prior to reaching hospital. In one case there had been at least eight separate attendances. Quite often a potential cause for the headache was not offered by healthcare workers and in others there were a number of alternative diagnoses considered, including one female participant in Kampala who was told she had *'on and off malaria'*, multiple male participants in Gaborone who were given *'migraine pills'*, and a female participant in Kampala who was told she could not have HIV because she was *'not very*

small'. This lack of a diagnosis led to some participants enduring long, convoluted pathways, navigating multiple healthcare facilities, medical specialities, cadres of healthcare worker, and excessive out-of-pocket expenses whilst their symptoms continued, worsened and evolved. Several people were sent to psychiatric hospitals, some for outpatient assessments and others were admitted, including the participant quoted above. Here we present the pathway to care for one male participant in Kampala.

'He was working away from home and developed fevers and a headache. Thinking he had developed malaria he went to a clinic in Kitende for some treatment. He took the treatment and carried on working but the headache persisted. He then started his journey back home but stopped mid-way at Salama and went to another clinic where he was diagnosed with typhoid and given some intravenous treatment for a day. He went home to Masajja and started a new job for two days but started feeling even weaker so went to another clinic, thinking that perhaps it was a very severe case of malaria. At that next clinic in Masajja he was diagnosed with brucellosis and given a dose of intravenous treatment. He went back to work but then became confused and lost consciousness. He recovered to an extent but the next day he slept all day and was taken to the same clinic in the evening for another dose of treatment for brucellosis, and again the day after. His family came to see him and took him to a clinic in Salama but they had a problem in the lab and could not do any tests, so he went to another clinic and was given some more intravenous treatment before going home. That night he struggled to sleep, and the pain became more severe: he pulled out his intravenous line, fell down and his eyes rolled to the back of his head. The family resolved to take him to the hospital the next day. That next day they looked for a suitable facility in Salama but failed to get one and ended up at a hospital in Bunga where he was admitted for 36 hours. It was as

he became more unwell that he was transferred to Kiruddu. At this point he had a severe headache and intermittent confusion. He describes this entire process as taking a month. He was diagnosed with HIV in 2005 by community testing services. Initially he doubted the result. Two years later he went to another facility and tested positive again. He never started treatment and was tested again at Kiruddu. He did not mention the HIV status to anyone during this entire process until he went to Kiruddu.'

It was common to hear that patients moved between these multiple facilities whilst their health deteriorated and it was often after they developed symptoms of severe infection, such as confusion, collapse, seizures, or coma that the diagnosis of meningitis was considered. What was clear however was that upon recognition of advanced HIV disease and meningitis the pathway moved much faster, and participants described that they were rushed to hospitals, with the AMBITION-cm recruitment hospitals being clearly recognised as the appropriate facility for patients to be transferred. In Kampala in particular, it was very clear that Kiruddu Hospital was the specialist centre to manage meningitis and all other hospitals referred participants here. In Gaborone it was typically the case that participants were sent to Princess Marina Hospital but there were some scenarios in which they first presented to private hospitals in extremis but after the diagnosis had been made, they were informed about the likely length and cost of the hospital admission and instead had to transfer to the government facility.

Missed opportunities in HIV care

We identified several ways that HIV care had missed the opportunity to prevent cryptococcal meningitis from occurring or encourage early health-seeking behaviours. As discussed, only one of the participants who knew they were living with HIV had mentioned that they knew meningitis could be a potentially serious complication of untreated infection. No participants mentioned having received any specific information or education about meningitis whilst accessing HIV care. In addition, we found that only one of the participants had attended their usual HIV clinic whilst seeking care for their headache. In this instance a female participant in Kampala was told that her symptoms were likely due to taking her ART at night and was advised to change to morning dosing. It was only after the symptoms became more severe and the participant was brought back to the clinic in a coma that she was transferred to hospital.

Several participants had very recently initiated ART and developed their headache within the first few months of starting treatment. Despite this they often presented to other healthcare facilities, rather than their HIV clinics, when they developed symptoms and they did not report having been told that cryptococcal meningitis and other infections such as tuberculosis can sometimes only develop shortly after treatment is initiated. There were also two instances where participants were diagnosed with HIV whilst suffering from a headache but were started on ART rather than being investigated and managed for cryptococcal meningitis.

Finally, the Zimbabwean participants who were recruited in Gaborone were, at the time of the study, not able to access free ART in Botswana and so either had to pay in Botswana or

travel to Zimbabwe to access it for free. One of our female participants explained that due to stock outs in Zimbabwe she had not been able to access her usual ART regimen and had been put back on a regimen which she had previously stopped due to side-effects. When the same side-effects occurred, she stopped the regimen and eventually developed cryptococcal meningitis.

DISCUSSION

In this qualitative methods study of participants in a clinical trial for HIV-associated cryptococcal meningitis we found that pathways to care were prolonged for several reasons. First, headaches are a common complaint, typically without severe consequences, and are often attributed to environmental factors such as hydration and psychological wellbeing. Where headaches are caused by biomedical aetiologies, including infections, the differential diagnosis is broad and there are multiple therapeutic options that can be easily accessed. Second, people living with HIV are not well informed about the possibility for headaches to signify a serious underlying pathology in the context of AHD and so meningitis is very rarely suspected. Third, healthcare workers who do not specialise in HIV, do not always suspect meningitis as the cause of a headache and this is much harder if they are unaware of their patient's HIV status. Finally, HIV clinicians do not always inform patients about meningitis, particularly around the time of ART initiation, and can sometimes cause harm by prescribing ART to patients with symptoms of meningitis.

There is an urgent need to recognise cryptococcal meningitis as early as possible. As we have discussed the absolute mortality risk in the AMBITION-cm trial was more than twice as high in those who were diagnosed whilst suffering from confusion or reduced consciousness. The

ubiquity of headaches and their broad differential diagnosis can lead to cognitive biases among healthcare workers which were observed within this study. We observed multiple alternatives bias in which the number of possible aetiologies considered by healthcare workers can be overwhelming and is subsequently simplified to a smaller, manageable subset with which they are familiar (Redelmeier & Shafir, 1995). This has previously been described as a common challenge when managing individuals with headaches and can lead to a lack of consideration of other, potentially more serious pathologies (Gottschalk, 2019).

Within our data we observed that many of the participant's pathways to care were quite similar, in that the standard approach seemed to be to advise hydration and provide simple analgesia, then consider common pathologies such as flu, malaria or raised blood pressure, then think of another, one by one, almost in a syndromic, trial-and-error manner. This is likely a tried and tested approach which works for the majority of individuals but when less commonly encountered pathologies occur, as is the case in this study, it can lead to vertical line failure in which there is a lack of lateral thinking or a consideration of 'what else could this be?' (Croskerry, 2002). Finally, we assume that as healthcare workers are likely to see many individuals with headaches, in the majority of cases the symptom is self-limiting or responsive to commonly prescribed treatments. This can lead to posterior probability error in which if the previous approach has worked many times before then it will likely work in this scenario too (K. Hansen, 2021). These heuristics are common in HIV medicine and are certainly not limited to our geographical context, having been described in encounters elsewhere (Deming et al., 2019).

A critical step that propelled these pathways to care and the ultimate diagnosis of cryptococcal meningitis was the recognition of the individual's HIV status and that they were likely to be living with AHD. This can be achieved with regular HIV testing but also requires recognition that people living with HIV can move in both directions along the care cascade and therefore those who are or who have previously been receiving ART can develop AHD. Data from Botswana show that this is an increasingly large proportion of people with AHD and we anticipate it will continue to grow over time (Lawrence et al., 2021c). Recognition of AHD is more difficult in situations of non-disclosure of HIV status, a phenomenon we observed within this study. There is extensive research that has explored the concept of non-disclosure and demonstrated an association with negative outcomes (Akilimali et al., 2017; Arrivé et al., 2012). Within this study we observed evidence of non-disclosure to family and friends and also to healthcare workers. Reasons given for non-disclosure to healthcare workers have included concerns around confidentiality and stigma (Greeff et al., 2008) as well as not feeling that disclosure was necessary in a particular context (Agne et al., 2000). In addition, some of our participants showed evidence of having not yet accepted their HIV status, having gone back to test on multiple occasions, sometimes without informing healthcare workers that they had tested positive in the past. Again, this is a well described phenomenon (Horter et al., 2017; Nam et al., 2008; Wringe et al., 2009).

We have identified a number of key foci for educational interventions that can help facilitate the prevention, identification, and management of cryptococcal meningitis. First, patients and their friends and family need to know about the potentially severe complications of untreated HIV disease so that they can be aware that a headache may not be so 'simple' for them and that certain symptoms that develop shortly after ART should prompt rapid

presentation to a HIV clinic or hospital. The information that they receive, how it is communicated, and using which methods, needs to be developed by communities of people living with HIV in order to be effective and there are several examples of best practice in this area (AfroCAB, 2021; Differentiated Service Delivery, 2022). Second, healthcare workers who are not HIV specialists need to know how to recognise advanced HIV disease, both clinically but also by using rapid diagnostic tests which should be made available to them. Third, healthcare workers at HIV clinics needs to ensure that their clients are aware of cryptococcal meningitis and that ART prescribing is done safely, in the absence of any symptoms that could suggest meningitis, and with adequate safety-netting should those symptoms develop.

When the diagnosis of AHD is made or known a whole new differential diagnosis gains prominence along with a new syndromic approach to diagnosis and management. Differentiated service delivery models for HIV care have gained traction since 2015 but have typically focused on innovative ways to deliver care to stable outpatients (Grimsrud et al., 2016). Differentiated service delivery models for AHD specifically have only started to gain prominence in recent years and thus far primarily focus on the availability of a package of rapid diagnostic tests for CD4 count, cryptococcal disease and tuberculosis, coupled with therapeutics to prevent and treat these infections (Differentiated Service Delivery, 2019). These programmes adopt a hub-and-spoke model with local centres implementing the majority of the package and then referring to inpatient units when acute care is required. Significant progress has been made by these programmes in last few years, particularly with cryptococcal disease. A partnership between Clinton Health Access Initiative and Unitaid has provided diagnostics and antifungal medications, including flucytosine and liposomal amphotericin, to countries with a high incidence of cryptococcal meningitis (Unitaid, 2021),

and early observational data are promising (Clinton Health Access Initiative & Unitaid, 2022). This acknowledgement of the differentiated service needs of people living with AHD is extremely welcome and this research study can inform the future development of such approaches. First, we observed a clear centralisation of knowledge and expertise around cryptococcal meningitis, insomuch that once the diagnosis was considered it was often clear that participants needed to be urgently referred to central locations. However, participants were regularly moved from one hospital to another to initiate treatment, putting considerable time and distance between themselves and their first dose of antifungal medication. In addition to skilling up healthcare workers around AHD at all facilities there is a need to decentralise care so that more hospitals are equipped with the skills and resources to offer rapid, high-quality care. This would work in synergy with the hub and spoke model. Second, differentiated service delivery models for AHD have thus far been almost entirely biomedical in nature, providing the essential diagnostics and therapeutics but overlooking the sociological context of AHD, particularly among individuals who have known their HIV diagnosis for some time. There is an urgent need to develop and integrate evidence based social and behavioural interventions into these programmes as a standard. When combined with effective diagnostics and therapeutics these can be life-saving interventions that prevent the persistence or recurrence of AHD and ultimately reduce mortality.

There are limitations to this study. The trial participants were very unwell with a life-threatening neurological infection, even those who were decision-orientated at baseline, so it is likely there was some recall bias as a result. This is particularly true for some trial participants who had their pathways to care narrated back to them by other people who had escorted them as they simply had no memory. In addition, we observed inconsistencies

between what was recorded in trial documents by the AMBITION-cm research team and collected through the in-depth interviews, particularly in terms of HIV and ART status, suggesting that some participants knew their HIV status and/or had been prescribed ART before. Within some interviews we also observed that participants were not always comfortable talking to us about their previous or current ART adherence. We therefore conclude that the findings of this analysis are also subject to the same response bias. Finally, all data collected in Setswana or Luganda were translated to English so the nuance of some testimony will have been lost, however each interview was discussed within the core team to try and reduce this.

CONCLUSION

We found that pathways to care with cryptococcal meningitis were prolonged because headaches were often disregarded as an everyday occurrence and had a broad differential diagnosis of predominantly benign aetiologies. There was a lack of awareness of the disease among participants and healthcare workers and it was typically only when a diagnosis of HIV was made or disclosed that the diagnostic pathway accelerated and resulted in hospital admission. We have outlined key recommendations to prevent, diagnose and manage cryptococcal meningitis and argued for the integration of social and behavioural interventions into differentiated service delivery models for advanced HIV disease.

ACKNOWLEDGEMENTS

We are greatly indebted to the individuals who participated in this study, particularly those who were recovering from a severe illness. We thank all of the research and routine care staff at each site who helped care for the participants and co-facilitated this research, particularly

during the COVID-19 pandemic. Thanks to expert patients and Community Advisory Board members across the sites for their important feedback on the design and methodology of this study. Finally, we acknowledge Dr Agatha Bula, Dr Graeme Hoddinott, Dr Zivai Mupambireyi and Dr Deborah Nyirenda for their early comments and input to the study design and data collection tools.

References: The references for this paper are incorporated into the main bibliography of the thesis.

INTERLUDE – A BRIEF NOTE ON PARTICIPANT TIMELINES

'I am not good at art!'

Male participant, Kampala

'I will explain everything, but I cannot draw a picture'

Female participant, Gaborone

'I would not like to tell you a lie that I can draw a sketch map but what I can do is explain in words'

Male participant, Kampala

When devising the methods for this study, and with the concept of time in mind, I had wanted to supplement the IDI discussions with some visual representations of the individual's pathways to care by asking them to draw timelines. Timelines can be used to develop the discussion and elicit further meanings and associations (Bagnoli, 2009). However, as the representative quotes given above suggest, there was not much uptake. The rare occasions that timelines were drawn they were typically composed of lists of healthcare facilities where a participant had visited in the run up to their hospital admission but when reviewing these alongside the transcription, they were useful in helping to structure the discussion. Two examples are shown overleaf. Given the extremely low uptake they did not make a significant contribution to the resultant papers and reveal more about my educational bias in terms of appropriate methods than the participants' ability to embrace this task.

Figure 10: Timeline drawn by a female participant in Kampala

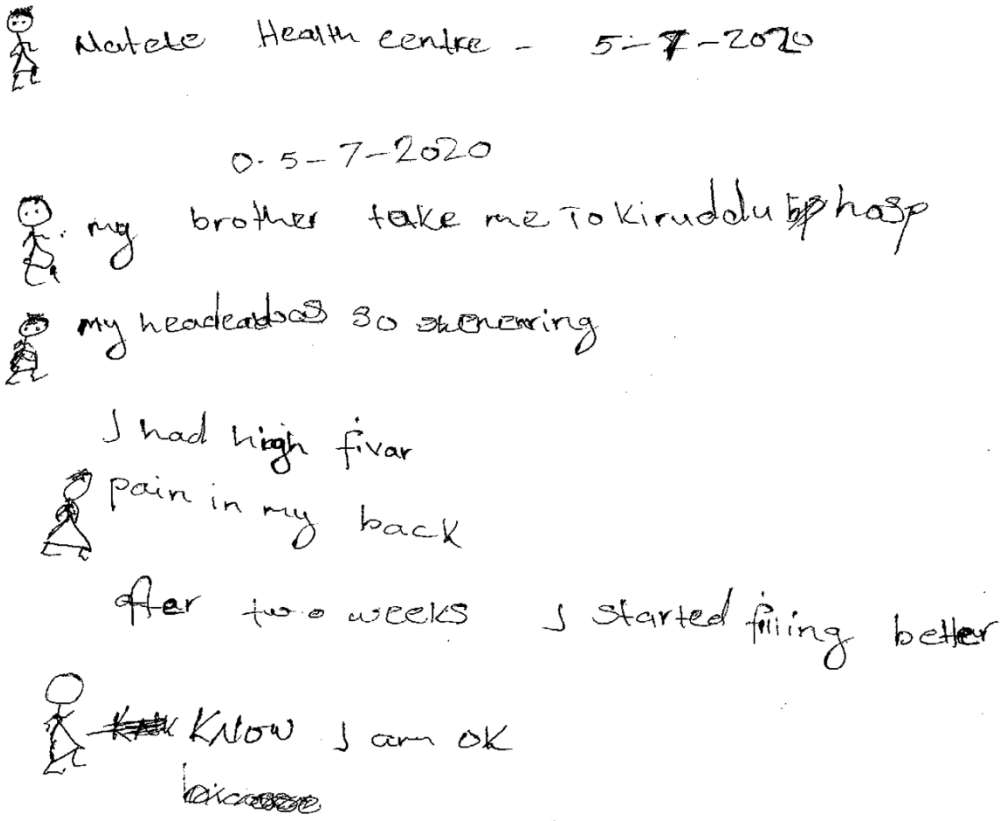
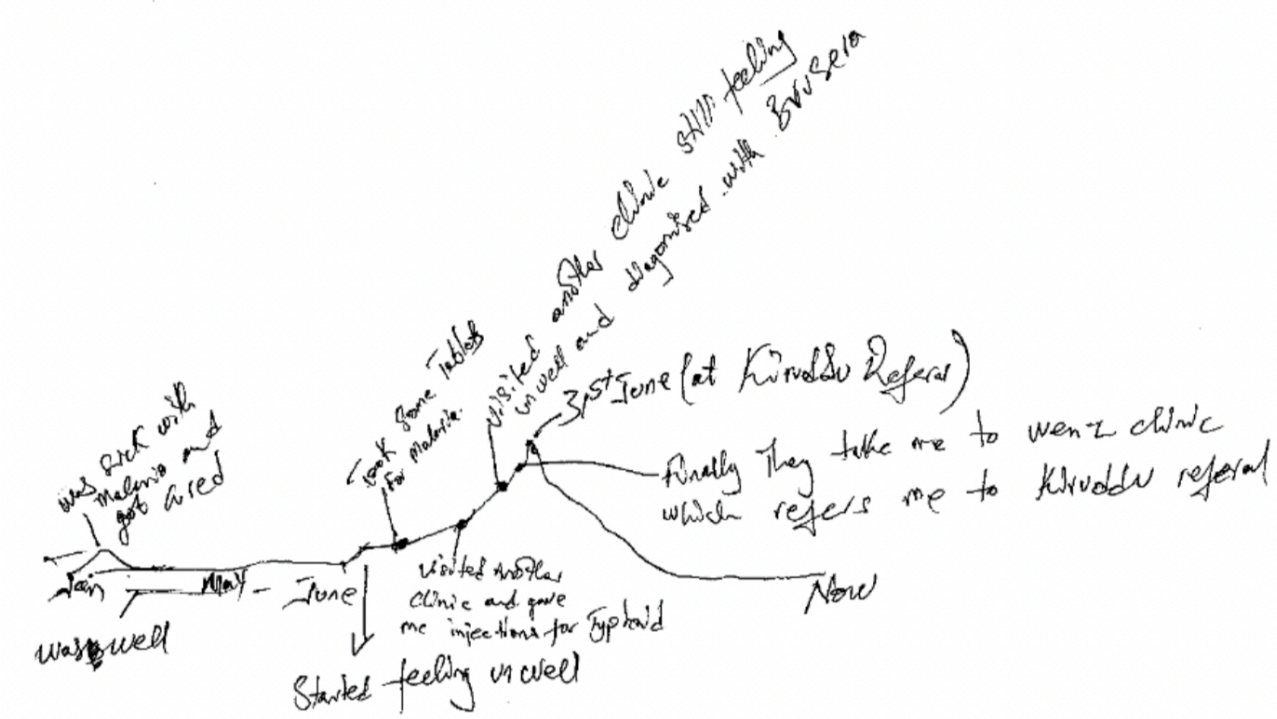


Figure 11: Timeline drawn by a male participant in Kampala



CHAPTER FIVE: RESEARCH PAPER FIVE - DECISION MAKING IN A CLINICAL TRIAL FOR A LIFE-THREATENING ILLNESS: THERAPEUTIC EXPECTATION, NOT MISCONCEPTION

Summary of Findings

The previous paper described pathways to care with cryptococcal meningitis up to the point when individuals had been admitted to hospital and a diagnosis had been reached. This next paper draws on that context and explores in detail the decision-making process around the AMBITION-cm trial. The following analysis draws on the full dataset and forms a central argument to this entire thesis.

The severity of the illness is intrinsically linked to their ability to understand, retain, weight-up and communicate information around trial participation. This was demonstrated in the critical interpretive synthesis and is evident in the following analysis. In addition to the life-threatening nature of the illness one must also consider the potential physical, cognitive, and emotional impacts of having potentially visited multiple healthcare facilities before finally being admitted to hospital and receiving a diagnosis. The diagnosis itself is made after a lumbar puncture and this paper discusses at length the concerns around lumbar punctures that were shared by participants and their next-of-kin, the most common being that they were associated with and could lead to death.

When considering how individuals made decisions to enrol into the trial, we found that previous knowledge and experience of clinical research was limited and that understanding around core concepts such as standards of care and randomisation were lacking. Those who provided consent did not explicitly state that they were aware that the standard of care in the AMBITION-cm trial was superior to that which would be routinely available, nor did they

focus heavily on the financial benefits such as having hospital bills paid for and travel expenses reimbursed. Instead, we found that decisions to enrol were made on an expectation of high-quality care and trust in the research team to offer trial participants the best possible chance of survival. Hesitation was mostly around the lumbar punctures and many expressed fear and sometimes held the conviction that they would die if they agreed to consent, however, despite this, they did. These decisions were often informed by interactions with research teams, routine care staff, and in Kampala, other AMBITION-cm participants, and their relatives. The decisions were often made to the detriment of personal relationships, with some avoiding discussions with selected family members, hiding their decision from loved ones, or being criticised or even abandoned if they consented.

Participants consistently spoke highly of the research teams. They remembered an extensive discussion which had culminated in the signing of a consent form and that this had involved papers containing the information but very few referred back to these documents. In one instance we found that even after the completion of the trial, a participant was unaware they were part of a research study. Across all participant groups we received feedback that the consent documents were too long and detailed.

The interpretation of these findings was that rather than consenting to join the trial based on a therapeutic misconception, these decisions were made based on a clear consensus that the trial was likely to result in the best possible outcome, a concept we term the therapeutic expectation and which we justify further by applying to the wider literature. We also consider the therapeutic expectation in the context of structural coercion and demonstrations of agency witnessed in the study.

Importance of Findings

This was a unique ethnographic study which recruited individuals who were suffering with a life-threatening neurological infection and had been approached to enrol in a clinical trial. The interpretation of these primary data has led to the generation of a novel concept that challenges the therapeutic misconception and which acknowledges the agency and expectations of prospective clinical trial participants.

Dissemination and Impact

This interpretation was developed over multiple iterations. The first was presented at the Qualitative Health Research Network Conference in March 2021 (Lawrence et al., 2021b) (Appendix 6) and later at the EDCTP Forum in October 2021. The following paper was published in *Social Science & Medicine* in May 2022.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1800328	**Title**	Dr
First Name(s)	David		
Surname/Family Name	Lawrence		
Thesis Title	The Lived Experience of Participants in an African Randomised Trial (LEOPARD)		
Primary Supervisor	Prof Joseph Jarvis		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Social Science & Medicine		
When was the work published?	25/05/2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This project was conceived by myself with support from Prof Janet Seeley and Prof Joseph Jarvis. I developed the methodology which was refined by all members of the team. I collected data from researchers and Neo Moshashane and Georgina Nabaggala collected data from trial participants and next-of-kins in Gaborone and Kampala respectively. I performed the analysis and received feedback from Prof Seeley. I wrote the initial draft of the manuscript and all authors commented on and approved the final submission.

SECTION E

Student Signature	[redacted]
Date	01/09/2022

Supervisor Signature	[redacted]
Date	01/09/2022

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Decision making in a clinical trial for a life-threatening illness: Therapeutic expectation, not misconception

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ABSTRACT

Potential participants for clinical trials which aim to define treatments for life-threatening conditions are often extremely unwell. When exploring why individuals participate in clinical trials one common observation is a misplaced expectation of personal benefit - a therapeutic misconception. The care offered in some clinical trials is of a higher standard than is routinely available and this has led to criticism around the freedom of choice to enrol - structural coercion. We embedded an ethnographic study within a randomised controlled trial for HIV-associated cryptococcal meningitis in Gaborone, Botswana and Kampala, Uganda. We aimed to gain an understanding of decision-making around the trial and how this was impacted by the study design and broader social context. We conducted in-depth interviews with trial participants, surrogate decision makers and researchers, combined these with direct observations and analysed data using thematic analysis. Between January 2020 and June 2021 we interviewed 89 individuals. We found previous exposure to and awareness of clinical research was limited, as was understanding of the trial objectives and design. Through observations and engagement with healthcare facilities decision-makers were able to identify the trial as providing the best possible chance of survival. Hesitation and reluctance were mostly due to fear of lumbar punctures which was sometimes based on rumours but often based on tragic personal experience. Despite fear, and sometimes conviction that they would die, individuals agreed to consent, often against the wishes of family members. Reassurance and confidence came from trust in routine care staff and the research team but also from fellow participants and their surrogates. We argue that participants made informed decisions based on a therapeutic expectation from the trial and that rather than being the result of structural coercion this was an informed and voluntary choice.

1. Introduction

An individual who has been hospitalised in an emergency may be suffering from significant physical symptoms such as pain and confusion as well as emotional distress and fear brought on by their unfolding experience. In this context, diagnostic procedures and interventions for life-threatening illnesses need to be initiated without delay to facilitate prompt management and improve the chance of survival. These treatments need to be defined through clinical trials. Conducting clinical trials of treatments and therapies for illnesses which are acutely life-threatening and require emergency hospitalisation is challenging. In the setting of a clinical trial the enrolment and randomisation of participants may lead to delays in the initiation of an intervention, delaying the benefit to the patient but also potentially resulting in an under-

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measurement of efficacy had the treatment been started sooner.

There has been much debate surrounding the ethics of clinical trial participation, particularly in terms of why individuals decide to join, how freely they give their consent, and how much they understand from the informed consent process. This debate is often polarised when participants are deemed vulnerable because of biomedical, social or economic reasons. At the centre of this process is an individual, often surrounded by family and/or friends, who needs and wants the best care available. Clinical trials can offer a route to access novel therapies which, despite being yet unproven, may be more efficacious than the standard of care and are primarily designed to answer a research question, the findings of which it is hoped will later be of benefit to a larger population. Trial designs often require that among those participating some individuals will not receive a new treatment (Molyneux et al., 2004). Despite this, research participants may expect a personal therapeutic benefit of participation, including in placebo-controlled trials, and this is often a key motivator behind participation (Behrendt et al., 2011; Corrigan, 2003; Houghton et al., 2018; Kenyon et al., 2006; Leach et al., 1999), a concept termed the therapeutic misconception (Appelbaum et al., 1987).

In certain circumstances however there is reason to believe that participation may be of benefit for all participants, regardless of whether they receive the experimental or control treatment. There is no universal definition to determine the nature of a control arm (Benatar and Singer, 2000; Council for International Organization of Medical Sciences, 2002; World Medical Association, 2013) but it is argued that it should be the treatment already proven to be most effective. Comparison with a placebo when effective treatment(s) exist, or comparison with a treatment already proven inferior, results in a lack of equipoise which is both unethical but also bad science. In reality however, the most effective, proven treatment may not be routinely available in a certain setting and in this context the treatment in the control arm may be better than the routinely available care.

In addition to the potential impact of the treatments being investigated in a trial, research participants regularly have access to additional benefits including dedicated research teams who may have more capacity to provide intensive medical care than routine care staff, ancillary care benefits that might otherwise not be available, and financial reimbursements and incentives. The extent of ancillary care that clinical trials can and should provide is poorly defined and often constrained by funding but can lead to researchers having to navigate complex dilemmas when faced with the extensive needs of their participants (Nkosi et al., 2020). There are similar concerns around financial reimbursements which may be criticised for being too low, and therefore not adequately valuing the time and contribution of participants, or too high and causing undue influence and/or impacting household financial dynamics (Molyneux et al., 2012; Nyangulu et al., 2019).

As a result, in settings where resources are limited and the scientifically proven best therapies are not available then it can be expected that due to this combination of an enhanced standard of care, a dedicated research team, ancillary care, and financial reimbursements then all participants will benefit, providing the experimental intervention does not cause harm. This clear benefit of participation, particularly when alternative options are limited or inferior, has been criticised for creating an 'empty choice' for potential participants when considering whether to enrol (Kingori, 2015; Lavery et al., 2013).

Voluntariness is understood as an autonomous choice without material entanglements and the principle of autonomy is often held above others when it comes to consenting for a clinical trial (Geissler et al., 2008). However, the design of a trial and the informed consent process make assumptions about choice and autonomy that can be at odds with the lives of some individuals (Marsland and Prince, 2012) and neglect to appreciate that decisions may be made under conditions of poverty. Fisher argues that this constitutes a lack of agency and that participants are subject to 'structural coercion' whereby their social and economic situation drives them into research participation as a means of navigating their illness when they lack other options to get the care they need or desire (Fisher, 2013).

We embedded an ethnographic study within a randomised clinical trial for a life-threatening neurological infection which recruited participants across southern and east Africa. The trial provided a context to explore expectations and agency around the decision-making process from the perspective of participants, surrogate decision makers, and researchers. We aimed to gain an understanding of decision-making around the trial and how the study design and broader social context impacted that process.

2. Methods

2.1. Study setting: the AMBITION trial

The AMBIsome Therapy Induction OptimisatioN (AMBITION) trial was a phase-III multi-centred randomised controlled trial recruiting patients with HIV-associated cryptococcal meningitis (CM) (Jarvis, 2022). CM is a fungal infection of the brain that occurs most frequently in people living with HIV (Lawrence, 2019) and is the second leading cause of AIDS-related mortality, after tuberculosis (Rajasingham et al., 2017). As CM is a neurological infection almost all patients present with a headache and roughly 40% present with confusion (Molloy et al., 2018). In severe cases, patients may be comatose.

The AMBITION trial recruited participants from eight hospitals across five African countries: Botswana, Malawi, South Africa, Uganda and Zimbabwe. The trial tested a novel treatment regimen against the WHO recommended standard of care and was a non-inferiority trial because the new regimen was expected to be as effective as the standard of care whilst being easier to administer and associated with fewer side effects. It was anticipated that ten week mortality would be roughly 30% in each arm. During the trial the available treatment at the AMBITION trial sites was not the WHO recommended first-line treatment for CM in resource-limited settings and the drugs that were available were associated with a mortality of between 40 and 70% (Azzo et al., 2018; Gaskell et al., 2014; Longley et al., 2008; Nussbaum et al., 2010; Rothe et al., 2013). As a result the standard of care within the trial was superior to the routinely available treatment.

Observational data consistently demonstrate that outcomes in CM trials are better than when using the same drugs in routine care (Tenforde, 2020). The reasons for this include having a dedicated clinical research team with more time to care for patients, better monitoring and correction of drug-induced toxicities and aggressive management of raised intracranial pressure. Raised intracranial pressure is a common and potentially fatal complication of CM which is treated with serial lumbar punctures whereby a needle is inserted through the back into the sub-arachnoid space to drain off excess cerebrospinal fluid.

The trial recruited individuals hospitalised with CM. Prospective participants had already undergone a lumbar puncture to make the diagnosis and were then approached by a researcher and informed about the trial using a participant information sheet. Patients consented for themselves if able and if they were disorientated or comatose then a surrogate decision maker, usually a spouse or relative, consented on their behalf. When disorientated patients regained decision making capacity they were approached to consent for themselves. In cases where the person providing consent was illiterate a thumbprint was used and a witness observed the process and countersigned the form. Participants were followed up daily during their initial inpatient admission (roughly two weeks in duration) and then fortnightly as an outpatient until they completed the ten week study. Throughout the study, participants had medical expenses paid for and received transport reimbursements for outpatient appointments. In Gaborone, citizens of Botswana are entitled to free care in a government hospital but this is not the case for non-citizens. In Kampala, hospital care in government facilities always attracts a cost.

The AMBITION trial recruited 844 participants between January

2018 and February 2021. Four participants withdrew consent, none were lost to follow-up. The trial observed a mortality rate of 24.8% in the single dose arm, compared to 28.7% in the control arm. The single-dose regimen was deemed non-inferior and in an adjusted analysis was superior. In addition, there were significantly fewer adverse events in the single-dose arm.

2.2. Participants and sampling

We embedded an ethnographic study within AMBITION. We collected data from three groups: trial participants, surrogate decision makers, and researchers. The study primarily took place at the trial sites in Gaborone, Botswana and Kampala, Uganda but researchers from across the trial consortium, including African and European collaborating institutions also contributed. The Botswana and Uganda sites were selected as they provided a contrast among the AMBITION sites in terms of location and healthcare systems.

2.2.1. In-depth interviews with AMBITION trial participants

Consecutively eligible trial participants were approached to participate in two in-depth interviews (IDIs). We aimed to recruit a maximum of 20 participants from each site, 40 in total, and consecutive sampling would have resulted in the highest chance of recruiting this sample given the severity of the underlying illness and the anticipated mortality. We included individuals who upon entry into the trial were deemed to have decision making capacity (i.e. orientated) and those who were not (i.e. disorientated). We anticipated 30% of all trial participants to be disorientated at baseline but aimed for half of all participants in this qualitative study to have been disorientated as we were interested in exploring the experiences of this group. Upon enrolment into the ethnographic sub-study all individuals must have regained decision making capacity. We aimed for roughly 50–60% of participants to be male, in line with the epidemiology of cryptococcal meningitis. The first IDI took place at least six weeks into the ten-week trial and the other at least four weeks after the final trial appointment. The second interview was conducted to enable the research team to review the content of the first interview and formulate follow-up questions as well as capture the participant's reflection on the trial after completion. If trial participants could only contribute to one IDI, for example due to worsening health or unavailability, data from the first IDI were retained and analysed.

2.2.2. In-depth interviews with surrogate decision makers

We use the term surrogate decision maker as a broad umbrella term to include any individual who may be the legal representative, next-of-kin, or a caregiver of the participant. This individual will have provided written consent for the participant to enrol into the trial. We aimed to recruit a maximum of 15 individuals from each site, 30 in total, with no prior specification for gender. Consecutively eligible individuals were approached to participate in a single IDI at least six weeks into the trial. At the time of the IDI it was not necessary for the trial participant to have regained decision-making capacity and these IDIs did not need to be linked to those with participants, although it was anticipated that most would be.

2.2.3. In-depth interviews with AMBITION researchers

Single interviews took place with researchers from the two sites and the broader AMBITION trial consortium. In Botswana and Uganda, where trial participants and surrogate decision makers were being recruited, we purposively approached a range of individuals with different roles including senior and junior researchers, research doctors and nurses, laboratory scientists, pharmacists, and study coordinators. Our sample size was 12 for each site. In addition, we purposively sampled up to 12 researchers from across a number of European institutions. The maximum number of researcher interviews was therefore 36.

2.2.4. Direct observations

Direct observations took place at the two sites (Bernard, 2017). As the primary focus was on the trial participant experience, observations were largely based in the clinical environment, with emphasis placed on observing clinical staff and their interactions with participants, for example by witnessing the consent process or the administration of study medication.

2.3. Data collection

Eligible individuals were identified by Author1 and approached to enrol in the study by a social scientist. In the case of trial participants and surrogate decision makers, this was conducted in the local language by an experienced social scientist at that site: Setswana in Botswana by Author3 and Luganda in Uganda by Author4. In the case of interviews and direct observations with researchers, Author1 approached potential participants directly and collected data. Eligible individuals were provided with a Participant Information Sheet and given the opportunity to ask questions. Those who agreed signed an Informed Consent Form. If the participant was illiterate a thumbprint was used and the process was verified by a witness who was independent of the AMBITION trial and this study. Interviews followed broad interview schedules and were recorded with a digital voice recorder. Notes were made during and after the interviews, including reflective summaries made by the interviewer. Observations lasted up to 4 h, had a clearly defined start and end time, and were not audio-recorded. Each participant took part in a maximum of three observations. Field notes were made after the observation.

2.4. Data handling and analysis

All study documents were securely stored in keeping with local guidelines. Audio recordings were transcribed verbatim into MS Word, translated into English in a separate second step if necessary, then exported to NVivo 12. Regular meetings enabled the rapid review of data to allow for data collection tools to be refined and preliminary themes to be generated. Data were analysed together using thematic analysis performed in six phases: familiarisation with data, initial code generation, searching for themes, reviewing themes, defining and naming themes and presenting final conclusions (Braun and Clarke, 2006). A refutational analysis was used to help determine the generalisability of themes and any geographical variations in conclusions. When presenting primary data related to trial participants, we state the gender and whether they consented for themselves at baseline ("self--consent") or required a surrogate for consent due to impaired decision-making capacity ("proxy-consent"). The location, role, and gender of researcher participants is omitted because of the small number of eligible participants.

2.5. Positionality

Author1 led this ethnographic study and was also the Lead Clinician for the AMBITION trial, based full-time in Gaborone and travelling regularly to Kampala to provide oversight and supervision. Author1 collected data from researchers through IDIs and it was made clear that these were voluntary, anonymous, confidential, and did not form any type of appraisal of an individual's performance but were motivated by a desire to understand in-depth the complexity of decision-making around the trial. Direct observations, also conducted by Author1, were clearly defined periods of time with starting and stopping points. Author 6 and Author 8 were the Chief Investigators for the AMBITION trial and Author 7 was the Principal Investigator for the Kampala site however none was involved in data collection for this study. Author3 and Author4 conducted IDIs and Author 2 and Author 9 provided supervision and support of this process, with all being independent of the trial and employed by different research institutions from where the trial was recruiting participants, in an effort to overcome potential bias.

2.6. Ethical considerations

This study was approved by the Human Resource Development Council, Gaborone (HPDME:13/18/1); Makerere School of Health Sciences IRB, Kampala (REF: 2019–061), and the London School of Hygiene and Tropical Medicine (REF: 17,957). It was anticipated that the study may identify aspects of the trial that need to be improved. In order to ensure this a formal reporting process was adopted (Lawrence, 2021).

The protocol was reviewed by Community Advisory Board members, expert patients and HIV activists from across the AMBITION sites, including those where this ethnographic study did not take place. These individuals and groups continued to be consulted throughout the data collection process.

3. Results

Between January 2020 and June 2021 we recruited a total of 89 individuals - 38 trial participants, 20 surrogate decision makers, and 31 researchers. Of the 38 trial participants, 18 were in Gaborone and 20 in Kampala. Follow-up interviews were conducted with 29 of the 38 with the main reasons for not conducting a second interview being either that the participant had died or logistical challenges caused by the COVID-19 pandemic. 55% of participants were male and 50% were individuals who were disorientated at baseline. We interviewed 20 surrogate decision makers: 9 in Gaborone and 11 in Kampala. A total of 31 researchers were interviewed: 11 from the Gaborone site, 9 from the Kampala site, and 11 from the various European collaborating institutions. Initial interviews varied in duration from 20 to 163 min with a median duration of 52 min.

3.1. Pathways to care and suffering with cryptococcal meningitis

> 'I was at work doing some cleaning when I developed a headache. At first I took it lightly and just went home to go and rest. I called my mother and told her I have a headache but I will be fine. I took it as a simple headache, an everyday headache. But the headache started to become worse over some few days and so my girlfriend told me to go to this private clinic in town. I went there and they gave me an injection for the pain, though I don't know what it was exactly, but I could feel that it wasn't the right treatment. Then next day I went to a clinic in a private hospital and they gave me some painkillers, some migraine pills. When I got home I took those but then things changed and my head was aching in a way I didn't know. That means I was taken by some people that live at home to the hospital. Now I couldn't even talk straight. When I got to that private hospital they checked me over and they asked my mother for a down-payment on an admission before they could proceed any further. They asked for 40,000 Pula (US$3500)! That was a down payment and after I was admitted there would be a balance to pay on top of that. Or they said they could just do some tests for 4,000 Pula (US$350). So my family went home and found my wallet and some other money and they paid the first 4,000. During that time I then became worse and I can't remember well but I was told that I became confused and because there was not enough money they decided to send me to the government hospital instead. So I am told that we went there in the car and reached the accident and emergency that side where we spent the night before the doctors worked on me in the morning and found the meningitis'
>
> Male participant, self-consent, Gaborone

All participants were suffering with a headache that had lasted for at least several days but it was not uncommon for this to have become progressively severe over weeks or, in extreme cases, more than a month. Individuals commonly self-medicated with simple analgesics and visited multiple healthcare facilities in the preceding days including pharmacies, traditional healers, local clinics and rural hospital facilities. In one instance a disorientated participant had been admitted to a psychiatric hospital for several weeks before being transferred to a medical facility.

For many participants their physical health had worsened during this time and they gradually became weaker and began to suffer more severe symptoms of meningitis. The immense pain and disorientation caused by the illness often resulted in severely distorted perceptions of what was happening, including persecutory delusions and visual hallucinations. Some were comatose by the time they reached the hospital.

> 'I used to see the ward in which I was as a small round yellow circle which I thought in my mind to be a mortuary in which they had put us. For the whole week I used to see that building as having been thatched with grass from bottom to top but on top of it, there was burning fire and I used to wonder whether the fire would not burn us … I used to dream finding myself in my village standing amidst dead bodies or I would dream seeing wild animals chasing me or snakes. There was one time when I dreamt falling down in a deep pit, then I would suddenly wake up in terror … I never saw a corner in the ward I was sleeping in, instead I used to see a round, small sort of building so I asked my sister whether they had brought me into a traditional healer's shrine. She would keep silent, maybe she knew the state of my mind.'
>
> Male participant, proxy-consent, Kampala

As a result participants and their surrogates had already undergone long and drawn out journeys from the start of their illness to the point where they were diagnosed with cryptococcal meningitis and approached to join the trial.

3.2. Recollection, understanding and expectations of the trial

> Interviewer: What motivated you to agree?
>
> Respondent: I was sick.
>
> I: Did you not see that you can get help somewhere else or you felt pressure of getting help from [the AMBITION team]?
>
> R: I realised that at the hospital we are many … so it takes time for them to come and help you.
>
> I: Is that the only thing you were looking at?
>
> R: Yes madam.
>
> Female participant, self-consent, Gaborone

The majority of participants who were orientated at baseline recalled being invited to participate. None reported having been part of a research study before and for most there was little or no awareness of what clinical research was. For example, that clinical trials are designed to answer a specific question and that there is an inherent uncertainty around the outcome. This was apparent when asking participants about clinical research in general but also about the AMBITION trial specifically, for example, what it was trying to achieve and how. We observed a limited understanding of the concept of randomisation and that the trial was comparing two different treatment regimens. Those who were aware tended to be orientated and suffering from milder symptoms.

In no case did any participant demonstrate an awareness that the antifungal medication offered within the trial was superior to that available in the routine care setting. When asked what they understood to be the alternatives to enrolment, participants spoke more broadly around outcomes and the general standard of medical care and attention they would receive rather than the biological efficacy of the treatments.

This expectation of high quality care was the most prevailing factor behind agreeing to join the trial. At the root of this was trust in the healthcare professionals who had interacted with the participant. Participants felt that there was a lot of information to digest during the informed consent process and that they were not necessarily in the best

physical or mental state to fully understand and retain this information but they accepted that the level of professionalism and expertise that emanated from the research team filled them with confidence. This was often bolstered by the input of the routine care team who had discussed the trial with the participant, referred to the trial team, and in many cases advised that it would be the best option for them. In fact, some patients had been transferred to that specific hospital on the expectation that they may be able to be enrolled into the trial, so this recommendation extended to other, non-participating hospitals too. Additionally, in the Kampala site where there were often several trial participants being treated on the same, open ward it was common for those already recruited and their surrogates to encourage new patients and those who were hesitant to sign up for the trial.

> 'Yet there were some [surrogate decision makers] who refused to have water removed from their patients and the patients died and yet they were not in a worse condition than our patient. What was amazing was that our patient was in a far worse condition than others but when they removed the water she stabilized!'
>
> Female surrogate decision maker, Kampala

This aspect of peer influence was particularly apparent in situations whereby individuals had initially expressed reluctance or declined to join the trial but after witnessing the difference in the intensity of care and hearing from individuals in similar situations they changed their minds and enrolled. In extreme circumstances, patients and their surrogates had witnessed patients dying from cryptococcal meningitis and this had heightened their fear further.

3.3. Overcoming the fear of lumbar punctures

> 'At first I refused and told them in these words "My friends I pray you do not remove water from my back". This was because some time ago they had brought my father to Mulago and they removed water from his back and he died later. So I too thought I was going to die.'
>
> Female participant, proxy-consent, Kampala

When considering whether or not to join the trial the most frequently cited concern by far related to the lumbar punctures that were required to monitor the participants' response to treatment and also to manage the common complication of raised intracranial pressure. Almost all participants had prior awareness of lumbar punctures and either knew or had heard of someone who had previously had a lumbar puncture and subsequently died. There was a widespread interpretation that lumbar punctures directly led to death. In addition, at the Kampala site in particular there were also fears that they could cause infertility, impotence and physical deformities. Yet despite this fear all of the individuals ultimately consented to the trial, including the lumbar punctures

> Interviewer: Did you, did you have any choice in all of this?
>
> Respondent: Yes, I did. I did. But also I didn't because the way I was feeling I needed whatever help I could get. I needed to have those headaches gone.
>
> I: What motivated you to take part in the study?
>
> R: Umm like I'm saying I needed the help. I needed the medical attention. And also the doctors that I was under, that I worked with, were very friendly. It was personal to them somehow.
>
> Female participant, proxy-consent, Gaborone

This aspect of the decision making process often involved discussions with friends and relatives, both in cases where participants consented for themselves or where a surrogate made the decision. On several occasions participants found themselves in extremely difficult situations whereby those they consulted strongly discouraged them from consenting to lumbar punctures (and therefore the trial). Participants and surrogate decision makers therefore faced a complex situation whereby they and/or those they had consulted had a strong conviction that consenting to the lumbar punctures and the trial would ultimately kill them. One reason given for consenting despite these grave concerns was that their physical condition and severe state of illness resulted in an expectation that they were already likely to die, regardless of being in the trial. In addition, when considering the alternatives to being in the trial they felt that enrolment was their best chance at survival. This was often supported by the trust and influence of healthcare professionals and sometimes, as described above, the influence of other participants and surrogates in the vicinity. As a result individuals described handing themselves over to the research team and putting their faith in both them and God.

3.4. Making decisions with and without others

> 'I was there in deep thoughts and undecided, the papers were there because [the nurse] had given them to me … I was lying on the bed unable to sit and the head paining me until I said to my sister in law "This life belongs to me, in case I die you know the clans of my children and their fathers, you will take them there". My sister in law asked "What, have you signed? So now what are we to expect after the men have removed the water from your back." My small daughter was also present and said "Those doctors are going to turn you into a laboratory mouse." And my brother rang me and said "They are going to test on you all sorts of useless medicines they have and eventually [you will] die. I told them that even if I become a laboratory mouse and come out alive I would have won. My brother who is in the army said "I have given up and I am not involved in these matters, I shall come for the burial. If she dies let me know but I am not going to give you even a single coin." He never rang again and never came back to the hospital [until] he came to fetch me after I had been discharged.'
>
> Female participant, self-consent, Kampala

Where shared decision making was taking place participants and surrogates described strategically consulting specific members of the family who they felt were likely to agree with them and avoiding others that may not. In situations whereby there was a difference in opinion it was not uncommon for the decision maker to hide their decision from those they consulted. Where there were disagreements these could lead to difficult confrontations including relatives saying that participants were condemning themselves to death, threatening to not contribute towards funeral expenses and in several instances announcing the death of the individual to the family and friends despite them ultimately surviving.

> 'At that time they announced me dead. In the village there was someone who had died and many mourners were coming from the burial to our home and gathered there. When I came out of [the] coma … I heard people saying that I had died and I asked that "is it true I had died?" I could not understand what they were talking about.'
>
> Female participant, proxy-consent, Kampala

Although some decision making appeared to be extremely complex and at times distressing there were some participants for whom the decision appeared relatively simple. In some cases we observed ambivalence towards the trial with participants saying that they were indifferent to participation or distracted by being too unwell to fully appraise the situation. The decisions made in these instances were interpreted to be mainly based on trust in healthcare professionals, sometimes in the absence of a comprehensive understanding of the trial and what was involved. Some participants mentioned concerns around experimentation and being used as guinea pigs but this was not common and was never expressed as the prevailing concern.

Interviewer: Was it because the treatment was expensive, which encouraged you to [enrol]?

Respondent: No. What I wanted above all other things at that time was to get cured. I had surrendered my life to God and I said to God "Let the doctors do what they want, provided it can cure me." So I did not bother about all those things. If money was needed those attending to me would look for it.

Female participant, self-consent, Kampala

Participants consistently spoke highly of the research teams who had approached them and cared for them during the trial. They remembered that there had been an extensive discussion which had culminated in the signing of a consent form and that this had involved papers containing the information which they had been given a copy of to keep. Some participants were illiterate so had a witness present. Very few participants ever referred back to these documents. In one instance we found that even after the completion of the trial a participant was unaware they were part of a research study.

When asked about the informed consent process most participants did not suggest any areas for improvement and no participants said that they felt the research team placed them under pressure to sign. The main suggestion that was made was to provide less information as the volume and depth provided was too much to handle at such a difficult time.

All of the participants who required surrogate consent later consented to the trial when they regained decision-making capacity and they all agreed with the actions that were taken by their surrogate decision maker.

Interviewer: Oh so when you woke up you found that they have signed for you …

Respondent: Yes …

I: How did you feel about their decision?

R: No it was a great decision because when you are sick, you seek help.

Male participant, proxy-consent, Gaborone

Not all surrogates reported having ever discussed making this decision with the participant but in all instances where a conversation had taken place there was agreement that this was the right choice.

3.5. The researcher desire to help

The interviews with researchers at the sites highlighted that there was a real urge to recruit patients into the trial. This was driven by a desire to offer the best care available and based on an understanding that the trial gave patients the best chance of survival. No researchers expressed being placed or feeling under pressure to recruit participants to meet targets but they did want to complete recruitment into the trial so that the results could be analysed and potential policy changes could be made to improve care in the future. Researchers struggled when faced with individuals who were not recruited due to meeting an exclusion criteria or those who declined participation, most commonly due to lumbar puncture refusal. At both sites doctors had witnessed poor outcomes among those who declined.

'Most of them [who declined] died in the two weeks and then those who don't die, most of them relapse, they keep coming back so that's what happens. They miss their doses, when you look at their drugs, their raised [intracranial pressure] is not adequately monitored, toxicity of drugs is not greatly monitored and treated, so it just becomes a bit of a mess.'

When discussing the trial within the context of the routine care setting there was an awareness by the research team that those individuals who would otherwise have had to pay for their care could have been induced into participation. However the clear medical benefits of taking part were identified as being the main driver. The researchers were consistently clear to point out that they did not over-emphasise the financial benefits of participation when approaching individuals to consent. Specifically, when asked researchers did not feel that this amounted to coercion but for some it was felt that the low standards of routine care left participants with no legitimate alternative but to participate.

'We know by GCP (Good Clinical Practice) if someone does not participate in the study that it shouldn't change, sort of, the care that you should give them as a clinician but this is not the case for our situation. They will certainly get suboptimal care if they do not participate, you know, not because I'm just fighting them [to enrol] in the study, but because they just, you know, they are not in the study so they won't get the benefits of having investigations done free of charge and at my site our patients pay out of pocket for almost everything … What I'm trying to really illustrate is that, that clause that is in many consent forms, if you do not participate in the study it will not affect the standard of care. No, here it does, structurally it does [and] they will get to know through their interactions with the study team during the consent process but also from the ward staff [and] the non-study staff.'

For researchers it made sense from their clinical perspective for patients to be enrolled into the trial and the ancillary care and financial components were an additional benefit which also impacted on their health and wellbeing.

4. Discussion

The purpose of this study was to gain in-depth perspectives on the decision-making process for a clinical trial when an individual is suffering from a life-threatening illness. In summary, we found that previous exposure to and awareness of clinical research was limited, as was understanding of the trial objectives and design but through observations and previous engagement with healthcare facilities decision-makers were able to identify the trial as providing the best possible chance of survival. Hesitation and reluctance were mostly due to fear of lumbar punctures which was sometimes based on rumours but often based on tragic personal experience, having known someone who had died during an illness that required one. Despite fear, and sometimes conviction that they would die they agreed to consent often to the detriment of personal relationships, with some avoiding discussions with selected family members, hiding their decision from loved ones, or being criticised or even abandoned if they consented. Reassurance and confidence in their decision came from trust in routine care staff and the research team but also from the personal testimonies of other participants and their surrogate decision makers.

The participants that contributed to this study were all extremely unwell when they or a surrogate made the decision for them to enrol in the trial and these decisions were often made in the context of protracted pathways to care, severe pain and fear of death. For some, their illness had progressed, causing confusion and disordered perceptions such as hallucinations. We found that the primary motivator for enrolment was survival rather than material gain from financial reimbursements. The therapeutic misconception is based on the notion that clinical research is not designed to benefit all participants (Appelbaum et al., 1987) and when exploring why individuals consent for clinical research this concept is often used to describe misplaced expectations of a personal gain resulting from participation (Kearns et al., 2020; McCann et al., 2010; Norris et al., 2019) however, despite being widely used in the literature this concept has not always been considered appropriate by social scientists (Molyneux et al., 2005). In this study we found a clear consensus that the trial was likely to result in the best possible outcome, a concept we term the therapeutic expectation. In our study we spoke

exclusively to survivors and their surrogate decision makers who described an almost binary choice between life and death, participation and exclusion. This was a sentiment that was shared to an extent by the research team who had observed worse outcomes among those who declined to enrol. The reality in routine care is more nuanced than this but differences between outcomes have been observed in multiple contexts when comparing clinical trial and observational, routine care data (Tenforde, 2020; Carls et al., 2017). Of course outcomes in clinical trials cannot be compared with routine data in real-time so a therapeutic expectation may not be possible in all trial contexts, particularly when using novel therapies and in early-phase studies where there is limited clinical data from human participants from which to draw expectations. However in the AMBITION trial the greatest expectations were in the time, attention and resources available from the research team compared to the routine care facilities. In addition, compelling phase II data and the use of antifungal drugs that have been widely used and tested in other settings meant there was little uncertainty around the clinical efficacy of both regimens, at least that neither would be worse than the alternatives available (Jarvis, 2018).

Our observations arose from this particular context where there was clear consensus that the trial was expected to benefit all participants because of the superior treatments that were on offer. In many trial settings this may not be the case or is not so apparent however we believe that therapeutic expectations can exist in subtler forms. In trials where the standard of care is the same as would be routinely available there are often added benefits of having a dedicated research team, ancillary care and financial reimbursements which can collectively be therapeutic (Nkosi et al., 2020). Even in observational studies where no treatments are administered participants can benefit from these other interventions and, more broadly, by being part of a research community individuals can feel that they have an extra layer of care or protection from the research infrastructure (Henderson et al., 2020). Although for some the prospect of being diagnosed with HIV-associated cryptococcal meningitis and depending on clinical research to save your life may seem an unlikely or abstract notion, the fear and uncertainty particularly at the start of the COVID-19 pandemic may provide a relatable context. Placebo-controlled vaccine trials were inundated with volunteers who as well as being driven by a desire to contribute to science were also comforted by the possibility that they may have received an effective vaccine or at least that they were part of a cohort or community that was keeping an even closer watch over them, for example to determine if they developed COVID-19 or adverse side effects (Wentzell and Racila, 2021).

In this study we also aimed to explore if decision-makers were aware and influenced by this difference in the clinical efficacy of the trial defined standard of care and the treatment available in the routine care setting. We found that although there was internal debate amongst researchers the decision-makers themselves had not noted this difference and instead were more focused on the quality and intensity of care they received. This is likely due to the complexity in explaining and understanding the expected and observed outcomes of different treatments in the context of having had no prior experience with clinical research and being acutely unwell. We found that in general the understanding and comprehension of the clinical trial, including core concepts such as randomisation, was low and it was difficult to disentangle research from routine care which is consistent with other published literature (Molyneux et al., 2005; Snowdon et al., 1997). One could argue that given this low level of understanding the informed consent process itself must have been fatally flawed. However, we found that all participants felt that they had received all the information they wanted, had the opportunity to ask questions, did not want any more information, and were not put under pressure to enrol. The informed consent process was observed on multiple occasions and all the information was relayed in a way that was felt to have satisfied a Trial Monitor or ethics committee. The reality was that the broader context made it incredibly difficult to convey novel and complex concepts during an unfolding emergency.

In settings where the routine standard of care is not optimised individuals being approached to enrol in research studies have often been described as being subject to structural coercion, whereby their 'vulnerability', socioeconomic situation and the quality of routine care available to them induces them into participation (Fisher, 2013). Although we acknowledge that this is one interpretation of these data and the AMBITION trial, the therapeutic expectation provides a lens to reconsider structural coercion which we feel can underestimate and overlook individual agency. Structural coercion is applied in situations which present an individual as someone who would rather not join a research study but who consents because of structural circumstances beyond their control. In the absence of structural coercion, or given a free choice, the default approach suggests that this individual would otherwise decline to be in the study and therefore the act of enrolling is seen as passive in nature whereas the act of declining is active. This may be the case in some scenarios, particularly where the therapeutic expectation is less (Nyirenda et al., 2020). However, agency can be demonstrated by remaining within a power imbalance (Mannell et al., 2016) and agentic responses do not need to have positive, 'active' outcomes (Pells et al., 2016). As Kabeer (1999) has described, agency is about more than observable action and can involve a number of strategies including bargaining, negotiation and manipulation, all of which were observed among our participants as they navigated the decision-making process, one which led to the majority of individuals consenting but also to some declining enrolment. When considering therapeutic expectation, and reflecting on the testimonies of our participants, we conclude that the decision to enrol in the AMBITION trial (or not) was often an extremely active choice. In the opinion of enrolled participants and the researchers approaching them this was a sensible decision made in the best interest of their health. This was particularly true when patients were initially hesitant or reluctant to enrol but got to witness first-hand the level of care that was provided (or not) to other patients and participants on the wards. These individuals made a particularly informed decision when faced with the true alternative to participation. Where there is a clear therapeutic expectation we argue that the decision to enrol should not simply be attributed to structural coercion.

4.1. *Limitations and strengths of the study*

This was, to our knowledge, the first in-depth ethnographic study to explore the lived experience of patients suffering with a life-threatening neurological infection who had been approached to enrol in a clinical trial. We recruited a broad range of participants from two country settings and were able to identify common themes and nuances across both sites. These data and interpretations are limited by the fact that we only recruited individuals and surrogates who had survived to six weeks into the trial and did not interview any surrogate decision makers after the death of a participant. This was an active choice to avoid causing emotional distress. We also did not interview anyone who had declined to participate. In addition, we acknowledge the positionality of members of the research team, including Author1 in their role as Lead Clinician for the AMBITION trial, and how this may have caused some desirability bias and a Hawthorne effect. We aimed to overcome this by forming a research group including social scientists external to the trial and emphasising that the clearly delineated data collection for this study was not a form of appraisal. We also consider the authors' positionality as a strength as their extensive knowledge of the clinical condition under investigation and the complexities and nuance of the trial helped to shape this ethnographic study and provided an ability to contextualise the data. All data collected in Setswana or Luganda were translated to English so the nuance of some testimony will have been lost however each interview was discussed within the core team to try and reduce this.

4.2. Recommendations

We have identified key recommendations for further research as well as bioethical considerations for future clinical trials. First, we recommend wider public engagement around clinical trials to improve literacy and comprehension around core research concepts. Second, further research is required to explore alternative methods of delivering the informed consent process that take into account the complexity of clinical trials, the severity of the disease under investigation and participant (il)literacy. This will require engagement with the public, patients and ethical review committees to determine what is both ethically and legally acceptable and may require an iterative process to evaluate understanding from participants in the early stages of a trial. Third, research to understand the perspectives of those who decline to participate in clinical trials should be conducted and it should also be considered whether sensitively conducted research with bereaved family members could take place. Finally, we advocate for further in-depth qualitative research studies to explore the lived experience of individuals involved in clinical trials for other life-threatening illnesses and in other contexts.

Credit author statement

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Declaration of competing interest

None.

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CHAPTER SIX: RESEARCH PAPER SIX - THE ACCEPTABILITY OF THE AMBITION-CM TREATMENT REGIMEN FOR HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS: FINDINGS FROM A QUALITATIVE METHODS STUDY OF PARTICIPANTS AND RESEARCHERS IN BOTSWANA AND UGANDA

Summary of Findings

The hypothesis of the AMBITION-cm trial was that the single, high-dose AmBisome regimen would be as clinically effective, less toxic, cost-effective, and simpler to administer in comparison to the standard of care. The AMBITION-cm trial results demonstrated non-inferiority in averting all-cause mortality and a significantly reduced toxicity profile. As a separate piece of work, I also led on the economic analysis which demonstrated the AMBITION-cm regimen to be cost-effective (Muthoga et al., 2022) (Appendix 7). LEOPARD therefore offered the opportunity to consider the acceptability of the AMBITION-cm regimen in comparison to the control regimen from the perspective of both participants and the researchers who were administering it.

This final paper centres on this question and draws on data collected from trial participants and researchers who provided direct clinical care to those participants. As discussed in the previous paper, the trial participants were severely unwell, and the comprehension of the trial was limited. In addition, there were typically multiple other treatments given during the hospital admission, so it was difficult to disentangle these from the specific antifungal regimen and of course, they each only received one of the two regimens so cannot speak about both. Where participants were aware, there was a general preference for the AmBisome regimen, due to an aversion to having multiple intravenous doses.

Most of the data which contributed to this analysis therefore came from researchers who expressed an overwhelming preference for the AmBisome regimen. The regimen took longer to prepare on day one but resulted in overall less time administering intravenous medication, managing issues with intravenous cannulas such as thrombophlebitis, and fewer toxicities to monitor and manage. This was felt to be particularly worthwhile in terms of anaemia because blood transfusions were often difficult to access. The main drawback of the regimen was the extended duration of the flucytosine in the AmBisome regimen, 14 days instead of seven, as it was given four times a day, including at night, however this was not felt to be an insurmountable challenge.

Importance of Findings

The single, high-dose AmBisome regimen was highly acceptable to both participants and researchers in the clinical trial. These findings compliment the clinical efficacy and safety data from the clinical trial to support widespread implementation of the regimen.

Dissemination and Impact

I was invited to present these findings in confidence to the World Health Organisation Guideline Writing Committee in February 2022, along with other sub-study data from the trial. The resultant judgements were that the intervention was acceptable to all stakeholders and probably feasible. These were then incorporated into the revised WHO treatment guidelines for cryptococcal meningitis which were published in June 2022, the relevant excerpts of which are included in Appendix 8 (World Health Organisation, 2022). In addition, these findings were presented as a poster at the International AIDS Conference 2022 in Montreal, Canada (Appendix 9). The following paper is in press at *PLOS NTDs*.

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SECTION A – Student Details

Student ID Number	1800328	**Title**	Dr
First Name(s)	David		
Surname/Family Name	Lawrence		
Thesis Title	The Lived Experience of Participants in an African Randomised Trial (LEOPARD)		
Primary Supervisor	Prof Joseph Jarvis		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
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Where is the work intended to be published?	PLOS NTDs
Please list the paper's authors in the intended authorship order:	David S Lawrence, Agnes Ssali, Neo Moshashane, Georgina Nabaggala, Lebogang Maphane, Thomas S Harrison, David B Meya, Joseph N Jarvis and Janet Seeley
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This project was conceived by myself with support from Prof Janet Seeley and Prof Joseph Jarvis. I developed the methodology which was refined by all members of the team. I collected data from researchers and Neo Moshashane and Georgina Nabaggala collected data from trial participants and next-of-kins in Gaborone and Kampala respectively. I performed the analysis and received feedback from Prof Seeley. I wrote the initial draft of the manuscript and all authors commented on and approved the final submission

SECTION E

Student Signature	[redacted]
Date	15/09/2022

Supervisor Signature	[redacted]
Date	15/09/2022

The acceptability of the AMBITION-cm treatment regimen for HIV-associated cryptococcal meningitis: findings from a qualitative methods study of participants and researchers in Botswana and Uganda

Short title: Acceptability of the AMBITION-cm regimen for cryptococcal meningitis

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ABSTRACT

Background: The AMBITION-cm trial for HIV-associated cryptococcal meningitis demonstrated that a single, high-dose of liposomal amphotericin (AmBisome) plus 14-days of oral flucytosine and fluconazole was non-inferior in terms of all-cause mortality to 7-days of amphotericin B deoxycholate and flucytosine followed by 7-days of fluconazole (Control). The AmBisome regimen was associated with fewer adverse events. We explored the acceptability of the AmBisome regimen from the perspective of participants and providers.

Methods: We embedded a qualitative methods study within the AMBITION-cm sites in Botswana and Uganda. We conducted in-depth interviews with trial participants, surrogate decision makers, and researchers and combined these with direct observations. Interviews were transcribed, translated, and analysed thematically.

Results: We interviewed 38 trial participants, 20 surrogate decision makers, and 31 researchers. Participant understanding of the trial was limited; however, there was a preference for the AmBisome regimen due to the single intravenous dose and fewer side effects. More time was required to prepare the single AmBisome dose but this was felt to be acceptable given subsequent reductions in workload. The AmBisome regimen was reported to be associated with fewer episodes of rigors and thrombophlebitis and a reduction in the number of intravenous cannulae required. Less intensive monitoring and management was required for participants in the AmBisome arm.

Conclusions: The AmBisome regimen was highly acceptable, being simpler to administer despite the initial time investment required. The regimen was well tolerated and associated with less toxicity and resultant management. Widespread implementation would reduce the clinical workload of healthcare workers caring for patients with HIV-associated cryptococcal meningitis.

Key words: HIV; cryptococcal meningitis; acceptability

AUTHOR SUMMARY

The AMBIsome Therapy Induction OptimisatioN (AMBITION-cm) clinical trial found that a single, high-dose, intravenous liposomal amphotericin B (AmBisome) based regimen for HIV-associated cryptococcal meningitis was non-inferior to the WHO recommended first-line treatment which includes seven daily doses of intravenous amphotericin B deoxycholate. The AmBisome regimen was also associated with fewer adverse events. In addition to the clinical efficacy data it is important to consider how acceptable the AmBisome regimen was from the perspectives of those who received the regimen as well as the healthcare workers administering it. To do this we conducted a qualitative methods study of in-depth interviews with AMBITION-cm trial participants, surrogate decision makers, and researchers working on the trial. These interviews were combined with direct observations of the research process and analysed thematically. The trial participants were often severely unwell and therefore the understanding of the trial was limited; however, the AmBisome regimen was generally preferred due to the single intravenous dose and fewer side effects. Researchers strongly preferred the AmBisome regimen which took less time to administer overall and was also associated with fewer side effects. We conclude that these findings complement the efficacy data from the clinical trial to support widespread implementation of the regimen.

BACKGROUND

HIV-associated cryptococcal meningitis remains a significant driver of AIDS-related mortality. There are an estimated 152,000 cases of cryptococcal meningitis each year, the majority of which occur in sub-Saharan Africa (Rajasingham et al., 2022). Cryptococcal meningitis is estimated to be responsible for 112,000 deaths annually and is the cause of 19% of all AIDS-related deaths. The burden of cryptococcal meningitis persists despite widened access to antiretroviral therapy (ART), with recent programmatic data from South Africa and Botswana indicating that the number of cases has stayed relatively constant in recent years (Osler et al., 2018; Tenforde et al., 2017). Cryptococcal meningitis primarily affects people with advanced HIV disease, typically with a CD4 count less than 100 cells/μL, and there remains a relatively constant population of people living with HIV who are diagnosed with advanced disease either as a result of delayed diagnosis or treatment failure due to difficulties with adherence and/or drug resistance (Carmona et al., 2018; Leeme et al., 2021).

Outcomes among patients diagnosed with cryptococcal meningitis are often poor. This is due to factors including presenting to care with severe disease, inadequate antifungal therapy, and drug-related toxicities. Cryptococcal meningitis has historically been treated with high-dose oral fluconazole monotherapy which is widely available but associated with high mortality: over 50% at ten weeks and over 70% within a year (Gaskell et al., 2014; Longley et al., 2008; Nussbaum et al., 2010; Rothe et al., 2013). Ten week mortality outcomes can be improved to roughly 40% in clinical trial settings when combining fluconazole with 14 daily doses of intravenous amphotericin B deoxycholate (amphotericin B) (Beardsley et al., 2016; Molloy et al., 2018) but this regimen is notoriously toxic and prolonged courses often lead to renal impairment, electrolyte disturbances, anaemia and thrombophlebitis (Ahimbisibwe et

al., 2019; Bicanic et al., 2015). An alternative antifungal, flucytosine, which is given for seven to fourteen days in four daily oral doses has been proven to be superior to fluconazole as a partner drug for amphotericin B (Molloy et al., 2018). The enhanced antifungal effect of flucytosine permits a reduction in the duration of amphotericin B from 14 to seven days, mitigating but not eliminating amphotericin-related toxicities (Molloy et al., 2018). These toxicities can be further reduced when managing patients with intravenous fluid administration both before and after each daily amphotericin B infusion, and oral potassium and magnesium supplementation, but they cannot not be eliminated. The administration of seven days of amphotericin B and the pre-emptive medication, as well as the monitoring and management of drug-related toxicity, remains complex and require intensive time and resources from healthcare professionals, as well as contributing to poor outcomes among patients.

Liposomal amphotericin (AmBisome, Gilead Sciences Inc) is associated with fewer drug-related toxicities (Adler-Moore et al., 2019; Groll et al., 2019; Hamill et al., 2010) and has been proven to be well suited to single, high-dose administration in both cryptococcal meningitis (Jarvis et al., 2018) and other infections (Gubbins et al., 2009; Sundar et al., 2010). The AMBIsome Therapy Induction OptimisatioN (AMBITION-cm) trial was a non-inferiority phase-III trial of a single, high-dose of AmBisome given with 14 days of flucytosine and fluconazole in comparison to the World Health Organisation defined standard of care: 7 days of amphotericin B given with 7 days of flucytosine and followed by 7 days of fluconazole (Lawrence et al., 2018). AMBITION-cm recruited 844 participants from eight hospitals in five countries: Botswana, Malawi, South Africa, Uganda, and Zimbabwe. A total of 814 participants were included in the intention-to-treat analysis, 407 in each arm. The ten-week

mortality was 24.8% (101/407% CI 20.7-29.3%) in the AmBisome arm and 28.7% (117/407, 95% CI 24.4-33.4%) (Jarvis et al., 2022). The absolute difference in 10-week mortality risk between the AmBisome arm and control arm was -3.9% and the upper limit of the one-sided 95% confidence interval for this mortality risk difference was 1.2%, indicating non-inferiority. When adjusting for factors independently associated with mortality the AmBisome regimen was found to be superior. In addition, the AmBisome regimen was associated with significantly fewer adverse events including anaemia requiring blood transfusion, thrombophlebitis and electrolyte abnormalities. Based on the trial findings, the World Health Organization updated their guidelines in early 2022 to recommend the single, high-dose of AmBisome given with 14 days of flucytosine and fluconazole as first-line therapy in resource limited settings (World Health Organisation, 2022).

Having proved the clinical efficacy, it is essential to consider the potential barriers and facilitators to real-world implementation of the AmBisome regimen. We conducted a qualitative methods study with the aim of understanding the acceptability of the AmBisome regimen compared with the standard of care from both the participant and the researcher perspective.

METHODS

We embedded an ethnographic study entitled The Lived Experience Of Participants in an African RandomiseD trial (LEOPARD) within the AMBITION-cm trial at the Gaborone, Botswana and Kampala, Uganda sites (Lawrence et al., 2021d). Through LEOPARD we aimed to understand the experience of participating in the AMBITION-cm trial from a range of different perspectives. We conducted in-depth interviews (IDIs) and direct observations,

collecting data from three categories of individuals: trial participants, surrogate decision makers (SDMs) who provided consent for the trial in cases where potential participants lacked decision making capacity, and researchers working on the trial. The qualitative methods study focused on several key aspects of the trial including decision-making around entry into the trial, the informed consent process, and the broader dynamics of the transnational research partnership within which the trial was conducted. In addition, we aimed to understand the acceptability of the intervention with a particular focus on participants, SDMs and those researchers who were directly providing clinical care.

Consecutively eligible trial participants were approached to participate in two in-depth interviews. In-depth interviews provide the opportunity for the conversation to flow, to ask follow-up questions, probe for additional information, and circle back to key questions later. In general, this approach provides richer, more in-depth data than structured interviews. We aimed to recruit a maximum of 20 participants from each site, 40 in total. We included individuals who upon entry into the trial were deemed to have decision making capacity (i.e., decision orientated) and those who were not (i.e., decision disorientated). We anticipated 30% of all trial participants to be disorientated at baseline but aimed for half of all participants in this qualitative study to have been disorientated. At the time of enrolment into LEOPARD all individuals must have regained decision making capacity. We aimed for roughly 50-60% of participants to be male, in line with the epidemiology of cryptococcal meningitis. The first IDI took place at least six weeks into the ten-week trial and the other at least four weeks after the final trial appointment. Secondly, consecutively eligible surrogate decision makers were approached to participate in a single in-depth interview at least six weeks after having provided consent for a trial participant. We aimed to recruit a maximum of 15 individuals

from each site, 30 in total, with no specification for gender. Finally, we purposively selected a range of researchers working on the trial to participate in a single in-depth interview. We approached individuals with different roles including senior and junior researchers, research doctors and nurses, laboratory scientists, pharmacists and study coordinators. Our sample size was 12 for each site: 12 in Botswana, 12 in Uganda and 12 affiliated to collaborating European institutions, 36 in total.

Interviews followed a topic guide tailored to each group of participants (Supplementary Information). The trial participant and surrogate decision maker topic guides explored the experience of developing cryptococcal meningitis (or caring for someone who had), being approached and deciding to enrol in the trial, and the experience whilst in the trial. The researcher topic guide focused on the day-to-day experience working on the trial and broader impressions of the AMBITION-cm trial and global health research in general. All interviews were audio-recorded. Additionally, we conducted direct observations of the research process, including the informed consent process and the administration of study drugs. Interviews were transcribed and translated, and field notes were made. These data were then entered into NVivo 12 and analysed using thematic analysis (Braun & Clarke, 2006). Thematic analysis involved six steps: familiarisation with data, initial code generation, searching for themes, reviewing themes, defining and naming themes and presenting final conclusions. Within this analysis we focus specifically on data from participants and those researchers who were providing direct care to trial participants as they had hands-on experience of providing the two different treatment regimens. When presenting data, the location, role, and gender of researcher participants is omitted because of the small number of eligible participants.

The study was approved by the Human Resource Development Council, Gaborone (HPDME: 13/18/1); Makerere School of Health Sciences Institutional Review Board, Kampala (REF: 2019-061), Uganda National Council for Science and Technology (REF: SS386ES) and the London School of Hygiene and Tropical Medicine (REF: 17957). Written informed consent was obtained from all participants.

RESULTS

Between January 2020 and June 2021, we recruited a total of 89 individuals (Table 1) – 38 trial participants (18 in Gaborone, 20 in Kampala), 20 SDMs (9 in Gaborone, 11 in Kampala) and 31 researchers (11 in Gaborone, 9 in Kampala and 11 from European collaborating institutions). Forty-eight (54%) of the participants were female. Initial interviews ranged in duration from 20 to 163 minutes with a median duration of 52 minutes.

Table 1: Summary of trial participants and surrogate decision makers (SDMs).

	Age	Gender	Nationality	Language of interview	Education Level	Decision-making capacity	Trial Arm	Number of Interviews	SDM Interview	SDM Gender
Gaborone	34	Male	Batswana	Setswana	Secondary	Disorientated	AmBisome	2	Yes	Female
	50	Male	Batswana	Setswana	Primary	Disorientated	AmBisome	2	Yes	Female
	44	Male	Batswana	Setswana	Secondary	Disorientated	Control	2	Yes	Female
	34	Female	Batswana	Setswana	Secondary	Disorientated	Control	1	Yes	Female
	32	Female	Batswana	Setswana	Tertiary	Disorientated	Control	2	Yes	Female
	49	Male	Batswana	Setswana	Tertiary	Disorientated	Control	2	Yes	Female
	35	Male	Zimbabwean	English	Secondary	Disorientated	AmBisome	2	Yes	Female
	44	Female	Batswana	Setswana	Tertiary	Disorientated	AmBisome	1	No	
	34	Male	Zimbabwean	English	Secondary	Disorientated	AmBisome	1	No	
	37	Female	Zimbabwean	English	Secondary	Orientated	Control	1		
	24	Female	Zimbabwean	English	Secondary	Orientated	Control	2		
	42	Male	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	37	Male	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	40	Male	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	47	Male	Zimbabwean	English	Secondary	Orientated	AmBisome	2		
	22	Male	Batswana	Setswana	Secondary	Orientated	Control	2		
	33	Female	Batswana	Setswana	Secondary	Orientated	AmBisome	2		
	29	Female	Zimbabwean	English	Primary	Orientated	Control	1		
Kampala	46	Female	Ugandan	Luganda	Primary	Disorientated	Control	2	Yes	Female
	53	Female	Ugandan	Luganda	Primary	Disorientated	AmBisome	2	Yes	Female
	26	Female	Ugandan	Luganda	Primary	Disorientated	Control	1	Yes	Male
	29	Female	Ugandan	Luganda	Secondary	Disorientated	AmBisome	1	Yes	Female
	36	Male	Ugandan	Luganda	Primary	Disorientated	Control	2	Yes	Female
	35	Male	Ugandan	Luganda	Primary	Disorientated	Control	2	Yes	Female
	45	Male	Ugandan	Luganda	Tertiary	Disorientated	Control	2	Yes	Female

	35	Male	Ugandan	Luganda	Primary	Disorientated	AmBisome	2	Yes	Female
	30	Female	Ugandan	Luganda	Secondary	Disorientated	Control	2	Yes	Female
	27	Male	Ugandan	Luganda	Primary	Disorientated	AmBisome	2	Yes	Male
	49	Male	Ugandan	Luganda	Primary	Orientated	AmBisome	2		
	44	Male	Ugandan	Luganda	Primary	Orientated	Control	1		
	24	Male	Ugandan	Luganda	Secondary	Orientated	AmBisome	2		
	46	Female	Ugandan	Luganda	Primary	Orientated	Control	2		
	45	Male	Ugandan	Luganda	Primary	Orientated	Control	2		
	32	Female	Ugandan	Luganda	Secondary	Orientated	AmBisome	2		
	34	Female	Ugandan	Luganda	Tertiary	Orientated	AmBisome	2		
	23	Female	Ugandan	Luganda	Primary	Orientated	Control	2		
	23	Female	Ugandan	Luganda	Primary	Orientated	AmBisome	2		
	30	Male	Ugandan	Luganda	Secondary	Orientated	Control	2		

Three male surrogate decision makers were interviewed without being linked to a trial participant due to the ill health of the trial participant: two in Gaborone and one in Kampala.

The perspective of participants: Most participants had long, convoluted pathways through care leading to their diagnosis of cryptococcal meningitis. The vast majority had a headache at the time of diagnosis, and they had often navigated through multiple healthcare facilities prior to reaching the AMBITION-cm site hospital. During this time, they had experienced a gradual deterioration in health and mental status, common to cryptococcal meningitis, such as the development of disturbing hallucinations, seizures, confusion and reduced consciousness. As a result, we found that the decision to enrol in the trial was predominantly motivated by fear of death, an acknowledgement that the trial was their best chance of survival, and trust in the research teams. This subject has been discussed in more detail elsewhere (Lawrence et al., 2022). The levels of comprehension around the trial aims and design were relatively low and participants found it difficult to disentangle the different parts of their treatment. For example, when asked if they knew that some *'were given one yellow bottle [of amphotericin] while others were given seven'*, one 37 year old male participant in Gaborone responded saying *'I did not know about that'* whilst a 48 year old female participant in Kampala explained they *'did not know because there was a time when I had lost my senses'* and a 35 year old male participant in Kampala said that *'the truth is that I may have been unconscious'*. This resulted in a limited amount of primary data around the acceptability of the AmBisome regimen directly from trial participants and instead we had to rely more on the testimonies of the researchers who also made this observation:

> *Interviewer: Do you think that the patients appreciate that there is a difference between the treatments that are on offer? That there's the control arm and then there's the single dose arm?*

Researcher: I doubt they appreciate, they notice that, I doubt. I think they notice more the interactions than the actual medicine.

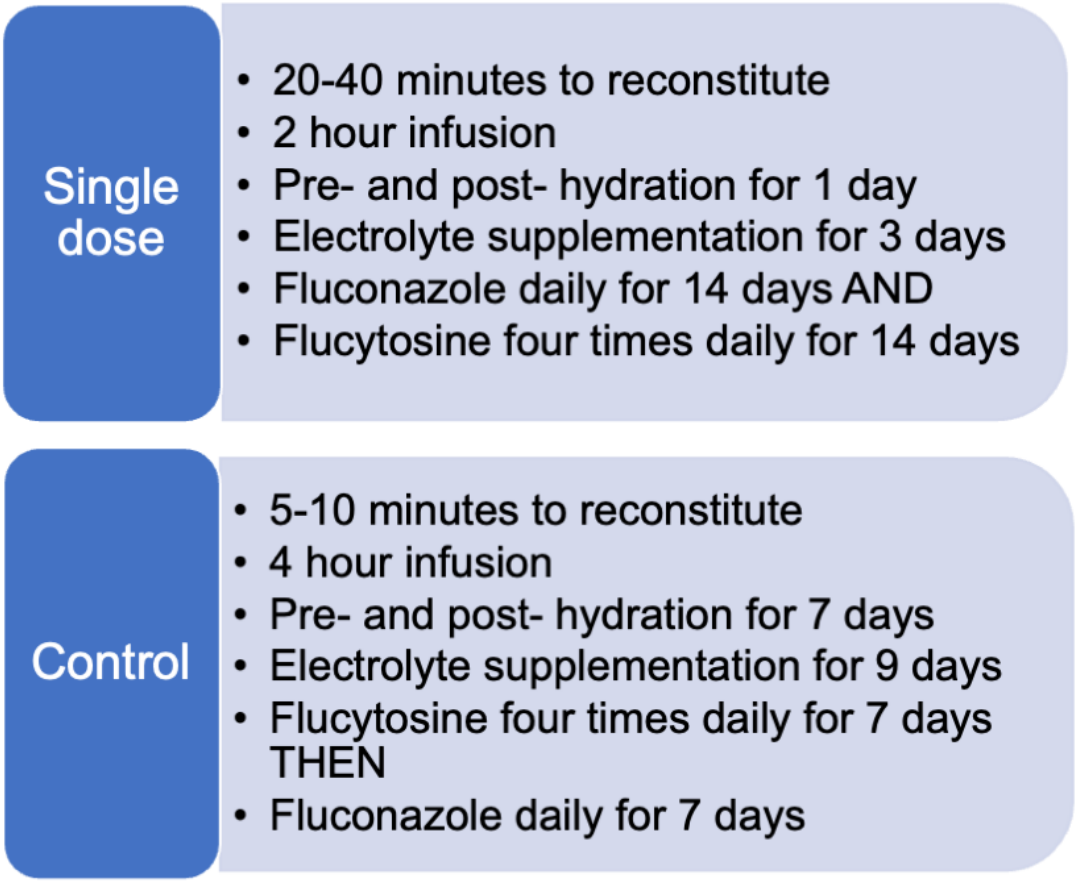
We found a general preference among participants for the AmBisome dose arm, due to an aversion to having multiple intravenous doses as described by a doctor who said '*they think they would have the drip in only for one day … so they'd rather have the single dose over the seven'*. When considering if there were any concerns about only getting one dose versus the seven offered in the control arm, albeit of a different formulation, there was one mention from a doctor of potential concerns as this arm was sometimes referenced as being the *'experimental arm'* within the trial and therefore carrying an element of uncertainty. Nevertheless, they felt that most participants had confidence in the single dose, and this was confirmed by several participants in Kampala who were managed on an open ward and able to see the progress of others in the trial. For example, one 32 year old female participant felt that *'the one bottle works quickly because I realised that the others who were given the seven bottles could take some time to respond to the treatment'* and a 23 year old female participant had a similar observation:

'I noticed that others who were getting seven bottles lacked strength and were very weak and were being supported when walking and I, who had received one bottle, was stronger than my colleagues. So, I did not long for the seven bottles because my health condition improved quickly but those patients who received many bottles still had a weak health condition.'

Although the trial itself did not find a difference in the duration of hospitalisation between arms, participants were highly motivated by fewer intravenous infusions and the potential prospect of shorter admissions and therefore being able to get back to work and/or other household responsibilities. One doctor told us that trial participants *'don't doubt the one dose'* and thought that having the single dose meant that *`they would get to leave hospital maybe day eight. Because the ones who get a single dose sometimes think they will go home soon after they get the AmBisome.'*

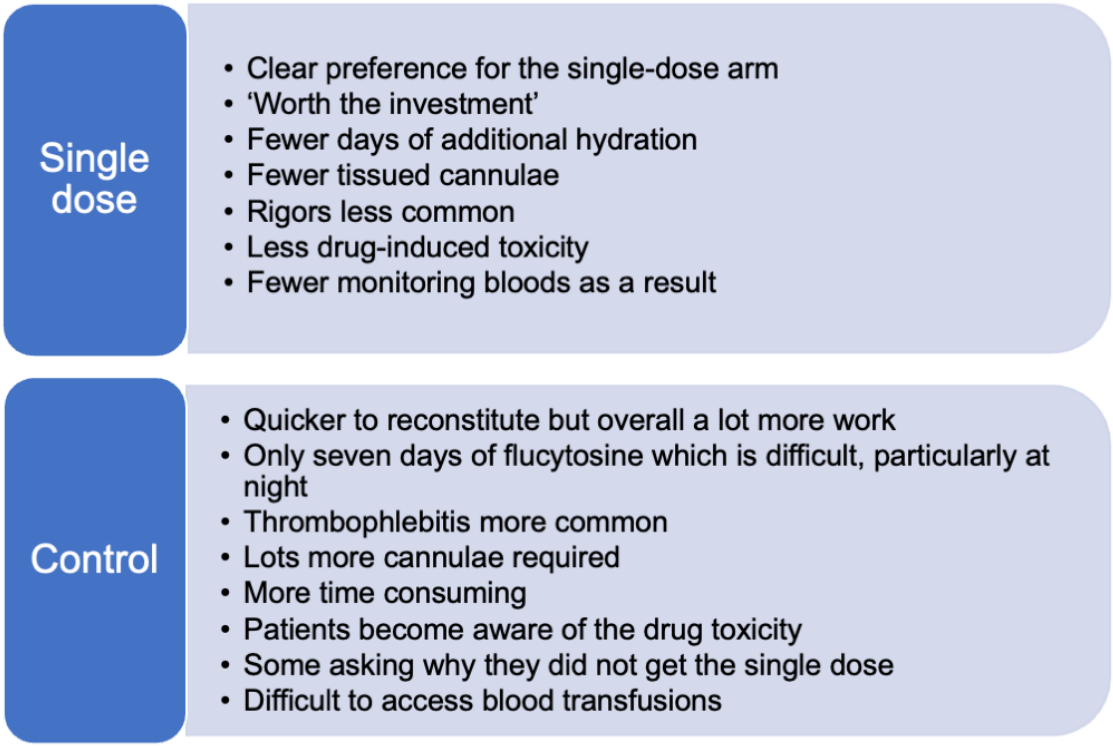
Researcher observations on administration of the two treatment regimens: There were significant differences between the two regimens in terms of the medication given and the time required to do this (Figure 1). Researcher participants found that the single, high-dose of AmBisome took longer to reconstitute. On average 12 vials were used per participant and reconstitution was reported to take between 20 and 40 minutes. The infusion ran over two hours and had to be preceded and followed by a litre of intravenous normal saline. Participants received twice daily doses of oral potassium supplementation and a daily dose of magnesium supplementation for each day they received amphotericin, so three days in the single-dose arm. In addition, fluconazole was given daily and flucytosine 6 hourly for 14 days.

Figure 1: A summary of how each of the two treatment regimens were administered



In comparison, in the control arm the conventional amphotericin B deoxycholate took roughly 5 to 10 minutes to reconstitute and was given over a four-hour infusion. The pre- and post-hydration was required for the seven days of amphotericin therapy and the oral electrolyte supplementation for nine. With regards to the oral antifungals, the 6 hourly flucytosine was only given for seven days and was followed by seven days of fluconazole.

Figure 2: Feedback on the administration and toxicity of the two treatment regimens



Researcher perspectives on managing the two treatment regimens: Drawing on the experience of the research teams looking after participants there was a clear preference for the AmBisome arm (Figure 2). It was felt to be worth the time investment of the initial efforts to prepare the large number of vials. A nurse told us:

> *'I like the single dose because it's less work … it means you give them medication one day and unlike putting ampho[tericin B] every day for 7 days, and ampho[tericin] also has its own dynamics, you need to pre-hydrate every day … sometimes you come to the hospital and you find that the patient is not pre-hydrated, now you start pre-hydrating first, sometimes you come to the hospital, the cannula has tissued, you need*

to start to putting in cannulae, you know all those dynamics of giving ampho[tericin] on the daily.'

While individual doses of conventional amphotericin were easier to reconstitute than AmBisome doses, the seven-day course and the issues with fluids and intravenous lines were felt to overshadow this. One drawback of the single-dose arm was that the 6 hourly dosing of flucytosine (given for 14 days in the single-dose arm compared to 7 days in the control arm) was found to be inconvenient for participants who had to set alarms in the night or remind one another to take their dose, and so the shorter duration of flucytosine in the control arm was a positive as described here by a nurse:

'I wouldn't have liked it (the flucytosine), especially that 4am dose, but these patients came to cope with it because we had explained to them how complicated the disease is, how missing doses would cause them problems and stuff like that, how it was dangerous to miss doses, then the side effect profile, what would happen. So many of them actually welcomed the idea of taking doses as prescribed and they actually got to figure out how to liaise within themselves. They made kind of a system within themselves that was motivated by the study nurses that they would remind each other'

With regards to toxicity and management, the researchers consistently stated that they observed fewer cases of amphotericin induced rigors in the single-dose arm. As was later proven with the formal trial analysis they also observed less drug-induced toxicity and were pleased to have less work managing individuals who developed toxicities. In general, participants treated with the control arm were found to be more time consuming.

Researchers also found that it was very difficult to access blood transfusions which were required more frequently in the control arm.

> *'Less admin, less side-effects, because the patients would be having rigors, then I will have to deal with it (laughs) but if it's, you know, I have to deal with the toxicities, write lots of adverse events, so, it's less work for me if it's AmBisome, it's nicer for the patient also. I don't have to be changing cannulas on the patient every other day so it's really nice for everyone. The nurses don't have to stay here long, waiting for the 4 hours of amphotericin. We love AmBisome.'*

When asked if the participants noticed any difference between the arms in terms of toxicity, researchers in Kampala said that some participants in the control arm became aware of the toxicity they experienced and attributed this to the yellow amphotericin, as described by this research doctor.

> *'Of course, most of them if they get the control they would be like, "Oh I wish I had gotten a single dose", especially if they get phlebitis like on day three and they start saying, "Oh I wish I had gotten one dose of this yellow medicine" … because they notice that people who get a single dose, their arms are never swollen.'*

These findings were consistent with the primary trial analysis which found that thrombophlebitis requiring antibiotic therapy was more common in the control arm and from the perspective of researchers this added to the list of recurring problems with intravenous lines.

DISCUSSION

We found that the single, high-dose AmBisome regimen was acceptable to both participants and researchers within the AMBITION-cm trial. The AmBisome regimen was more time consuming to prepare on day one, but this was felt to be a worthwhile investment because of the additional time required to administer the additional doses of amphotericin B deoxycholate and to avert and manage amphotericin-related toxicity. Participants in the control arm were observed to suffer more regularly from amphotericin induced rigors and thrombophlebitis which often required a lot of medical input, particularly in terms of intravenous access. In addition to the health impact on participants, the increased drug-related toxicity observed in the control arm was time consuming for researchers to manage, required additional resources, and was sometimes difficult to resolve, particularly in terms of the limited availability of blood for transfusions.

The AMBITION-cm trial was well staffed and resourced with external funding. In routine care settings with a high incidence of HIV-associated cryptococcal meningitis healthcare workers are often caring for large numbers of patients with a range of complex medical conditions. In addition, healthcare facilities may not always have access to the resources required to both avert and manage drug-related toxicities. As a result, we believe it is reasonable to assume that the challenges encountered by our research team when managing participants in the control arm would be amplified in routine care settings. There is extensive evidence demonstrating that outcomes of individuals diagnosed with cryptococcal meningitis are worse in routine-care settings compared to within clinical trials, even when receiving the same antifungal treatment regimen (Tenforde et al., 2020). Although the reasons behind this are multi-factorial, the time, expertise and resources required to avert and manage

amphotericin-related toxicity is a key driver of this difference. One key rationale behind the AMBITION-cm trial regimen was to identify an effective but also safe and easier to administer treatment for cryptococcal meningitis. This study complements the main trial efficacy data in that respect and demonstrates that the single, high-dose AmBisome regimen was much simpler to administer and manage. When considering widespread implementation within stretched healthcare systems the true benefits of the AmBisome regimen are therefore also likely to be amplified.

There are limitations to this study. Participants were purposively recruited following a sampling matrix based on gender and severity of infection at baseline, but these results are not intended to be fully representative or generalisable. The participants and SDMs themselves had their own unique experience being treated with one arm so it was clearly not possible to fully explore their preferences for one over another. In addition, due to the severity of their unfolding, life-threatening illness participants found it difficult to disentangle the different parts of their treatment which made it challenging to elicit their perspectives on the different arms. We therefore relied heavily on the data collected from researchers. Finally, we acknowledge the positionality of the research team, including DSL as the Chief Investigator of this study and the lead clinician of the AMBITION-cm trial, and how this may have resulted in some desirability bias and a Hawthorne effect during data collection. We aimed to overcome this by forming a research group including social scientists external to the trial who collected the data from participants and SDMs in Gaborone and Kampala.

In conclusion we found that the single, high-dose AmBisome regimen was highly acceptable to both participants and researchers in the clinical trial. These findings compliment the clinical efficacy data from the clinical trial to support widespread implementation of the regimen.

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References: The references for this paper are incorporated into the main bibliography of the thesis.

CHAPTER SEVEN: DISCUSSION

This was a unique ethnographic study embedded within a clinical trial for a life-threatening illness. The trial participants who contributed were recovering from a severe, potentially fatal infection and their next-of-kins had supported them through this arduous process. They had been cared for by highly dedicated and competent researchers working on the trial and I was privileged to learn from their collective experiences. The data and analyses presented have broad relevance spanning implementation science, health education, community engagement, bioethics, and anthropology, and have already contributed to policy change. In this discussion I will consider each of my objectives in turn, the implications of the analyses presented within this thesis, and the inter-relation between them. In doing so I will describe the contribution this thesis makes to the literature, highlight areas for further research, and outline the potential application of this work.

Objective One: Cryptococcal meningitis trials meta-analysis

My first objective was to perform a meta-analysis exploring how representative and inclusive clinical trials for cryptococcal meningitis are, from both the participant and the researcher perspective. I found that the geographical location of clinical trials had broadly evolved in line with the epidemiology but that some high-incidence countries had not been the location of recruitment sites. In addition, relapse and severe cases of cryptococcal meningitis were under-represented. Relapses account for roughly 10% of hospital admissions with cryptococcal meningitis. As superior antifungal regimens become increasingly available, we can expect to see more people surviving their initial admission with cryptococcal meningitis and therefore we may see more readmissions with relapse although this may not be the case given the high antifungal activity of these superior regimens. Historically, patients suffering

with a relapse of cryptococcal meningitis have been excluded from clinical trials because of the possibility of having acquired fluconazole resistance during previous treatment which would be a confounding factor if fluconazole formed part of an intervention. In routine care however these patients are often managed with the same treatment regimen as those with a first episode of cryptococcal meningitis and I therefore argue they should be included in future clinical trials and factored into adjusted analyses.

The aggregated data in the meta-analysis allow convenient comparison between previous trials and the AMBITION-cm trial. For example, of all participants recruited into the most recent trials published after 2010, 38% were female, 43% ART experienced, and 30% with reduced baseline GCS, and for each of these characteristics there had been a significant increase over time. This compares with 40%, 64%, and 29% respectively within AMBITION-cm which further highlights the increasing number of ART-experienced individuals who are developing cryptococcal meningitis. When comparing the AMBITION-cm data with the composite reference of observational data these are highly comparable except from severe cases which are more commonly observed in routine care settings, roughly 50%, which likely represents the severity of illness, difficulty in obtaining consent, and at times insensitivity of approaching the relatives of someone who is actively dying to enrol in a trial.

The data from the meta-analysis can also be used when calculating sample sizes and estimating withdrawal rates and loss to follow-up which were roughly 1% and 2% respectively across all trials. This also highlights how remarkable it was that no participants were lost to follow-up in the AMBITION-cm trial, particularly considering the COVID-19 pandemic,

something that was highlighted in an editorial published alongside the main trial manuscript (Moosa & Lessells, 2022).

When considering authorship in clinical trials there is still significant work to do. Recent trends have identified that over the last three decades, as clinical trial locations moved from HICs to LMICs, more female authors were named however senior positions such as first and last author were increasingly taken by authors who were not nationals of any recruiting location. The AMBITION-cm trial was consistent with other trials published since 2010 in which of the 42 named authors, 12 (29%) were female, and the first, second and final authors were all British men, me included. This is consistent with broader reviews of global health research in Africa in general which has found that indigenous researchers are frequently 'stuck in the middle' (Hedt-Gauthier et al., 2019; Mbaye et al., 2019). For example, Hedt-Gauthier and colleagues found that among general health-related studies published between 2014-2016 just 54% of authors were from the country of the paper's focus and this was 52.9% among the first author. Overall, in this meta-analysis we found this to be 70% and 59% respectively which is marginally better. There is no doubt that our disciplines need to work much harder to address this inequality and I acknowledge the authorship of the published paper itself lacks the diversity we aspire to.

Finally, I have referenced similar papers which have explored authorship in research but to my knowledge this was the first analysis to consider inclusion and representation from both the participant and researcher perspective and apply this to a specific illness. I believe it is a relatively simple methodology that can be used by researchers exploring other illnesses, both for benchmarking but also as a form of ongoing monitoring.

Objective Two: Critical Interpretive Synthesis

My second objective was to conduct a critical interpretive synthesis of qualitative data relating to participation in a clinical trial when an individual was suffering from a life-threatening illness. This resulted in the development of a synthetic construct which situated the life-threatening illness as an overarching factor impacting all aspects of trial participation, particularly the decision-making process. The key themes presented within that synthetic construct can be considered in the context of the data and analyses presented from the LEOPARD study.

Compared to most papers included in the review the symptoms experienced by AMBITION-cm trial participants were more severe and the risk (and possibly fear) of death were higher. None of the included qualitative studies was embedded within clinical studies of pathologies with expected mortality rates as high as AMBITION-cm, and most did not involve the central nervous system. This highlights further how unique the LEOPARD study was. The overwhelming impact of the underlying illness on the experience of the trial was profound. Consistent with the review, we found that knowledge and previous experience of research and familiarity with concepts such as equipoise and randomisation were low. The decision to enrol in AMBITION-cm was made based on expectations of high-quality clinical care and the best possible chance of survival, which was often made by considering the contrast between routine and research care, however differentiating between the two once in the trial was often difficult. The study-specific factors that were most frequently discussed were the huge potential benefit of survival and the most significant risk was felt to arise from lumbar punctures however, again, the severity of the illness amplified the benefits and even participants who felt the lumbar punctures would kill them took the risk. The additional

benefits of participation, particularly with regards to ancillary care and financial reimbursements, were not prioritised. The added challenges in making decisions highlighted within the synthetic construct were also clearly manifest in the LEOPARD data. These included difficulties in understanding the aims and objectives of the study, understanding and retaining information, and remembering what had happened. When considering the recommendations made by LEOPARD participants, very few were suggested however shorter and more concise consent documents were discussed.

The data from the LEOPARD study complement the critical interpretive synthesis and I have outlined how they fit well within the synthetic construct, whilst also contributing new data from a particularly unwell group of individuals. In addition, there was a paucity of data from LMICs included in the review, and no data obtained from adult participants, which this study goes a short way to address. Ultimately, this work demonstrates the power and influence that researchers hold and the great responsibility they have to provide unbiased information that does not unduly influence or pressure individuals into participation.

Objective Three: Pathways to care

My third objective was to explore pathways to care with cryptococcal meningitis and identify recommendations to avert mortality. Given the high mortality of cryptococcal meningitis and the worse outcomes among individuals who present with more severe disease, averting infection and encouraging early care-seeking are essential. The analysis found that the often subtle, everyday nature of the headache, the broad differential diagnosis, and the lack of awareness around meningitis led to cognitive biases which contributed to the protracted pathways to care described by trial participants and their next-of-kins. These data are

consistent with broader literature exploring pathways to care among PLWH hospitalised in the Democratic Republic of the Congo and Kenya which identified that people with AHD frequently slip through the cracks when accessing outpatient healthcare facilities (R. Burns et al., 2022).

This analysis identified a need for education aimed at both PLWH and healthcare workers to emphasise that a headache in the presence of newly diagnosed or ineffectively managed HIV could potentially be fatal. Patient facing materials needs to be developed by communities of people living with HIV in order to be effective and there are several examples of best practice in this area I have highlighted (AfroCAB, 2021; Differentiated Service Delivery, 2022), however there is a gap with regards to this specific issue of headache. Similarly, given the concerns around lumbar punctures described in the subsequent paper, patient facing materials need to be developed which use real-life testimonies to increase confidence and uptake. These materials are currently being developed as part of a Centers for Disease Control and Prevention (CDC) funded project of which I am co-Principal Investigator with Prof Joseph Jarvis. Individuals with lived experience of AHD, including cryptococcal meningitis, will attend a series of workshops where they are invited to share their experiences, discuss which kinds of communication strategies and messages they feel they may respond to, and co-produce educational materials which we will pilot, refine, and roll out in Botswana, Malawi, Uganda, and Zimbabwe.

This research has similarly identified gaps in knowledge among healthcare workers. The CDC project will begin to address these in those same four country settings through a rolling series of face-to-face trainings delivered across a broad geographical area, focusing particularly on

junior doctors who regularly rotate through hospitals and outpatient clinics, and a virtual repository of videos, job-aids and slide decks. This may go some way to highlight the significance of a headache in the context of AHD, but it will not be able to target all cadres of healthcare workers across different facilities. Within this analysis I identified that the turning point in the pathways to care was the identification and recognition that someone had untreated HIV which then led to rapid referral, usually to hospital. This turning point is dependent on testing for HIV and/or disclosing a known HIV status. An in-depth discussion of the literature exploring facilitators and barriers to HIV testing in sub-Saharan Africa is beyond the scope of this thesis however from the patient's perspective commonly identified themes include perceived low risk of HIV acquisition; the opportunity cost of testing; stigma, and lack of confidence in healthcare systems and providers (Musheke et al., 2013). An increasing proportion of individuals who present with cryptococcal meningitis are ART-experienced, 64% in the AMBITION-cm trial, and amongst LEOPARD participants we observed multiple instances of non-disclosure of HIV status, a phenomenon which has been shown to be associated with negative outcomes (Akilimali et al., 2017; Arrivé et al., 2012). Some individuals did not disclose their HIV status to non-HIV specific healthcare workers, and we were told of very few individuals seeking specialist HIV care when suffering from a headache. When revisiting the LEOPARD dataset there are no more data exploring this in but based on personal experience as a HIV clinician in Botswana my hypothesis is that PLWH are typically only seen for scheduled HIV outpatient appointments, usually at six-monthly intervals, and it is not common for them to present to HIV clinics for unscheduled appointments, instead attending outpatient clinics that offer more of a drop-in service. This can be the focus of further research to consider how PLWH access HIV outpatient clinics (or not) when they are feeling unwell.

There were striking gender differences within both AMBITION-cm and LEOPARD. In contrast to the wider HIV epidemic which affects significantly more women (UNAIDS, 2022), in AMBITION-cm, 60% of participants were male and this was broadly in-line with the composite reference of observational data presented in the meta-analysis (Adeyemi & Ross, 2014a, b; Meiring et al., 2016; Patel et al., 2018; Tenforde et al., 2017). This is also consistent with extensive data that more broadly demonstrate men to be disproportionately diagnosed with AHD (Carmona et al., 2018; Drain et al., 2013; Lahuerta et al., 2014; Nash et al., 2016; Osler et al., 2018). The reasons for this are exceptionally complex but can be superficially explained from a health-systems perspective as being due to men testing later (Hlongwa et al., 2020; Musheke et al., 2013); women of reproductive age accessing HIV testing more often through sexual and reproductive health services (Worku et al., 2022), and pregnant women accessing antenatal testing and prevention of mother to child transmission programmes (Awopegba et al., 2020).

An ad-hoc analysis exploring gender differences within the AMBITION-cm trial in more detail identified that of 490 men recruited to the trial, 32.4% (159/490) presented with reduced baseline GCS. Overall mortality among men was 26.3% (129/490). Among those with normal baseline GCS mortality was 19.0% (63/331) and for those with reduced baseline GCS mortality was 41.5% (66/159). Of 324 women recruited to the trial, 22.5% (73/324) presented with reduced baseline GCS. Overall mortality among women was 27.5% (89/324). Among those with normal baseline GCS the mortality was 19.9% (50/251) and for those with reduced baseline GCS mortality was 53.4% (39/73). These data highlight that significantly more men presented later to care (p=0.023) and outcomes among women who presented with severe disease appeared to be worse, however this difference was not statistically significant,

possibly due to smaller numbers and/or confounding factors (p=0.227). This was also manifest in the recruitment of the LEOPARD study which struggled to identify female trial participants who were decision-disorientated and survived, although I acknowledge this was not a fully representative sample. While the LEOPARD data were not analysed using a specific gender framework, and this could be an area for future focus, one of the reasons for potentially poorer outcomes among women admitted with abnormal baseline GCS could be related to the impact of caregivers who provide bedside care, assisting with feeding, hygiene, and drug adherence. The importance of caregivers has been well described and it has been observed that those who present to hospital alone often have worse outcomes (Kwizera et al., 2020) although this has never been assessed through a formal analysis and would be difficult to approach methodologically and ethically. My experience within AMBITION-cm was that caregivers were often spouses and male participants were more typically supported by partners who maintained a near constant presence at the bedside. I explored this further by considering the site where caregivers were most active on the wards, Uganda. The mortality among male participants who had a reduced GCS at baseline was 39.5% (30/76) and among females the mortality was 65.5% (19/29). I acknowledge how small these numbers are and therefore no truly meaningful conclusions can be made, however I think this may provide a potential sociological explanation for these possible differences which could warrant closer observation and further research.

Gender should be one factor considered when developing differentiated service delivery (DSD) models for HIV care and approaches tailored to men and masculinities have demonstrated good uptake (Mukumbang, 2021). As I have discussed within the fourth research paper, DSD models for HIV care have predominantly focused on innovative ways to

deliver outpatient HIV care (Grimsrud et al., 2016) and models for AHD specifically have focused more on access to diagnostics and therapeutics (Differentiated Service Delivery, 2019). These AHD DSD models have generated promising data (Clinton Health Access Initiative & Unitaid, 2022) but I argue that they have been too biomedical in nature, providing the essential diagnostics and therapeutics but overlooking the sociological context of AHD. Further research is needed to develop and integrate evidence based social and behavioural interventions into these programmes as a standard. When combined with effective diagnostics and therapeutics these can be life-saving interventions that prevent the persistence or recurrence of AHD and ultimately reduce mortality. This thesis provides valuable data for the development of such an approach and in future work I intend to use my findings to develop a research proposal in which participatory methods can be utilised to design, implement, and evaluate a holistic DSD model for AHD that addresses the complex biomedical and sociological needs of this patient group.

Objective Four: Decision Making

My fourth objective was to begin to understand decision-making around the AMBITION-cm trial and how the study design and broader social context impacted that process. This analysis was contextualised within the severity of the disease and the long, convoluted pathways to care that were described in the previous paper and I have already discussed the synergy between my analysis and the synthetic construct developed within the critical interpretive synthesis. This paper ultimately led to the formulation of a concept termed 'therapeutic expectation' which describes an overall expectation of benefit resulting from participation. It is presented not as an antonym of therapeutic misconception but rather as an alternative to it. The therapeutic misconception is, in my opinion, a hierarchical, paternalistic concept that

assumes the researcher knows more than the participant who is making decisions based on flawed comprehension. The therapeutic expectation goes some way to flatten this hierarchy. The setting of the AMBITION-cm trial allowed this concept to emerge given the clear differences between the antifungals in the standard of care arm and those available in routine care. I had grappled with this difference from a bioethical and philosophical perspective and discussed how this in part prompted this thesis, but the data from LEOPARD did not suggest this was what drove the therapeutic expectation, rather it arose from trust in healthcare workers and a clear consensus that the trial was likely to result in the best possible outcome when faced with a real risk of death. One could argue that the therapeutic misconception still arises in other clinical studies in which the differences between the standard of care and what is offered in routine care are less stark, but I have argued that it can exist in subtler forms where having a dedicated research team, ancillary care, and financial reimbursements could collectively be therapeutic (Nkosi et al., 2020), and even in observational studies that create a sense of community and an extra layer of care or protection from the research infrastructure (Henderson et al., 2020).

Within the discussion of this paper, I outlined how the therapeutic expectation may still be considered to be operating alongside and within structural coercion and argue that the therapeutic expectation provides a lens to reconsider structural coercion which as a concept can underestimate and overlook individual agency. I also discuss further and provide examples, drawing particularly on feminist literature, of how agency is about more than observable action (Kabeer, 1999), can involve bargaining, negotiation and manipulation, and that agentic responses do not need to have positive or 'active' outcomes (Pells et al., 2016). These demonstrations and manifestations of agency within a restrictive environment are well

documented, particularly among women, including those in abusive and coercive relationships (Mannell et al., 2016), when trying to access sexual and reproductive healthcare (Thompson, 2005), and when gender inequality intersects with other medical disciplines such as oncology (Banerjee, 2019). However 'agency-within compliance' has been demonstrated elsewhere, including in healthy eating choices among individuals diagnosed with obesity in Guatemala (Yates-Doerr, 2012) and strategies employed by Danish women with hair loss induced by chemotherapy (H. P. Hansen, 2007).

There were clear demonstrations of agency within the AMBITION-cm trial. Most notably, that there were individuals who declined to consent to the trial and others who made an initial decision and then changed their minds, by enrolling or withdrawing. However, agency was also demonstrated by participants and surrogate decision makers who bargained with friends and family, included certain family members in the discussion (and omitted others), and sought approval from influential family members, including one occasion I witnessed when the ancestors were consulted in a side-room on the medical ward in Gaborone. These were all agentic strategies to facilitate enrolment into the trial.

One particular phenomenon that also warrants further discussion is how some trial participants and surrogate decision makers on the wards in Kampala encouraged other potential participants to enrol, including those who had initially declined or expressed reluctance to join. This has not been well described before and is likely unique to the context in which individuals were being managed on open wards where other participants are staying and where caregivers are often present and significantly involved in day-to-day care. A HIV prevention trial of a microbicide in South Africa did find that some participants had co-

enrolled in other prevention trials and that in some cases this had been influenced by 'peer-pressure' which was framed negatively in the discussion (Karim et al., 2011). Whereas within this study I interpret the encouragement of other individuals to join the trial more as a form of biological citizenship (Petryna, 2004), in which the shared diagnosis of cryptococcal meningitis, or shared proximity to the diagnosis in the case of surrogate decision makers, resulted in the development of a connection between individuals and the resultant encouragement to join the trial was a form of advocacy and a demonstration of agency.

Researchers have a duty to identify a therapeutic expectation and to understand where it has come from. In essence, they need to both manage expectations and meet them. Some expectations may be unrealistic and based on a misunderstanding of the trial and this study did find such issues with comprehension, particularly around the objectives of the trial and the concept of randomisation, which was consistent with the critical interpretive synthesis. This was further demonstrated in the poor recollection of the informed consent process which was criticised by the different groups of participants as being excessively long and overly detailed, with too much information provided on consent documents that were rarely referred to. Research procedures need to be adapted to ensure that maximal comprehension of the pertinent information can be attained. A large body of research has specifically explored retention of information during the consent process in various research settings, both qualitatively and quantitatively, and found it to be generally poor (Afolabi et al., 2014; Tam et al., 2015; Vischer et al., 2016; Vischer et al., 2017), and I have already outlined the additional challenges with comprehension when suffering from a life-threatening illness. Innovative methods that have been tested include the use of videos (Hoffner et al., 2012; Weston et al., 1997), pictures and audio tapes (Vallely et al., 2010), assessing comprehension

using questionnaires (Gikonyo et al., 2008; Molyneux et al., 2007), and approaching consent as a continuous process (Klykken, 2021; Vallely et al., 2010). These methods have not been widely used in clinical trials for hospitalised patients suffering from a life-threatening illness and specific research is warranted.

One proactive method is to conduct rapid ethical assessments which collect predominantly qualitative data from prospective participants prior to finalising trial documents to broadly guide research preparation and inform the consent process before a study commences (Bond et al., 2019; Gebremariam et al., 2018; Negussie et al., 2016). In one cluster-randomised trial in Ethiopia a rapid ethical assessment was associated with higher levels of recruitment and retention into a HPV sero-prevalence study and resulted in greater comprehension of the informed consent process (Addissie et al., 2016). Again, these have not been conducted prior to trials for life-threatening illnesses but given the particularly complex bioethical issues posed by such research then rapid ethical assessments would be particularly suited for future trials, including in cryptococcal meningitis, and may pre-emptively address some of the challenges with comprehending information that observed in LEOPARD. In addition, one must consider that novel approaches to consent need to be approved by research ethics committees which may be reluctant to remove information that has been deemed essential by Good Clinical Practice (European Medicines Agency, 2017). This has been documented as a source of tension between researchers and committee members who try to balance providing essential information without overwhelming prospective participants (Ssali et al., 2020). With this in mind, as part of ongoing work I have some funding in place to conduct a workshop with research ethics committee members in Botswana to discuss which novel forms of consent would be acceptable from their perspective.

Although it is important to manage expectations, and good informed consent can help, the therapeutic expectation itself will still exist. As a result, researchers need to be conscious of the expectations of their participants and surrogate decision makers who, in the case of AMBITION-cm, trustingly placed their lives in the hands of researchers based on this expectation. I saw and experienced within AMBITION-cm the great burden of responsibility held by the research teams who worked tirelessly to care for their participants, going above and beyond, particularly during the COVID-19 pandemic. The LEOPARD study was conceived with the aim of understanding how the trial could be improved but the feedback from trial participants and next-of-kins was overwhelmingly positive and this was exemplified by the zero loss to follow-up. Instead, these data were much more useful in describing how individuals with cryptococcal meningitis and their next-of-kins navigated this extraordinarily complex experience.

Objective Five: Acceptability

My final objective was to explore the acceptability of the AMBITION-cm regimen compared with the standard of care from both the participant and the researcher perspective. This was a generally simpler task as the AMBITION-cm regimen had been designed with this in mind: The single intravenous dose was expected to be less toxic and much easier to administer overall. The safety data from the trial confirmed lower rates of all adverse events, including anaemia, raised creatinine, electrolyte abnormalities, and thrombophlebitis requiring antibiotic therapy. Data from researchers supplemented this with subjective testimonies of reduced amphotericin-related rigors and far fewer issues with intravenous cannulas, a constant source of frustration on medical wards. Overall, the regimen was less time

consuming and arduous to administer and the reduced toxicity made participant management simpler. These data confirm the hypothesis that the regimen would be acceptable and were integrated into the acceptability and feasibility judgments of the updated WHO guidelines (World Health Organisation, 2022). Having established acceptability within the trial there is also a need to generate data from a more routine-care setting. I am therefore co-investigator of an implementation study of the AMBITION-cm regimen, in partnership with Médecins Sans Frontières as part of an NIHR-funded Global Health Research Group, which will explore the feasibility and acceptability of implementing this regimen in the Democratic Republic of Congo, Guinea, and Mozambique.

Having established efficacy, safety, and acceptability, the next step is therefore implementation and to increase access to antifungals and ensure healthcare workers are adequately trained on how to administer this regimen. A crucial step to facilitate access is for individual countries to integrate the regimen into their treatment guidelines. To date, this has happened in Botswana, eSwatini, Malawi, Uganda, Zimbabwe. As a result, the AMBITION-cm regimen is already being given in routine care using antifungals supplied through the Unitaid and Clinton Health Access Initiative (CHAI) AHD programme. To support this, and as part of the CDC funded project, we have developed training videos for healthcare workers outlining how to reconstitute the single, high dose of AmBisome and the safe dosing, administration, and toxicity management of the regimen. In addition, colleagues and I have presented these data at several webinars and in-person training sessions, alongside Ministries of Health and key implementing partners in numerous countries.

The Unitaid/CHAI programme will end in December 2022 and although it may continue in another form there is a need for high-incidence countries to procure antifungals locally. This will now be possible through the Global Fund to Fight AIDS, Tuberculosis, and Malaria, who have added the antifungals to their procurement mechanisms. Reliable access to antifungal drugs across all healthcare sectors is dependent upon registration in country and in most settings neither AmBisome nor flucytosine are registered (Loyse et al., 2013). This is another focus of the CDC project. Finally, the success of the implementation of the AMBITION-cm trial will be dependent on the availability of affordable AmBisome from Gilead Sciences Inc. During the course of the AMBITION-cm trial they committed to making AmBisome available at cost price as part of an expanded access programme (Gilead Sciences Inc, 2018) and following the release of the trial results they emphasised their commitment (Gilead Sciences Inc, 2021). In reality, this access programme has had limited impact so far and so working with Gilead to scale up distribution is essential.

Further Analyses

In addition to meeting my five objectives, the immense body of data generated from this work can also be used for further analyses - although I must thank my supervisors for encouraging me to step away from analysis and actually write the thesis. The interviews with researchers generated considerable discussion around other forms of consent, including research without prior consent, and waivers of consent, an analysis of which would allow further exploration of the bioethical considerations of clinical trials for life-threatening illnesses. In addition, there were many in-depth discussions around what should constitute the standard of care in clinical trials in LMICs, the responsibilities of the trial, and broader discussions around the roles of funders in the context of decolonising global health.

Limitations and Strengths

Each of the papers within this thesis have their own specific discussions on this subject and herein I will summarise the broad, overarching limitations and strengths of this thesis. I have discussed in-depth my positionality and the reflexive approaches that were adopted in an earlier section, and I acknowledge these again here but do not repeat them at length.

Fundamentally this study explored how people decided to enrol themselves or a loved one into a trial, and their experience within it, however I only spoke to those who had consented and survived. By not including people who had declined the study I will have missed contrasting opinions about the trial and research more broadly, as well as the opportunity to explore if there were any differences (or not) in the decision-making process which resulted in someone refusing to participate. This was an active choice. These individuals would have just been diagnosed with cryptococcal meningitis via lumbar puncture, and potentially with HIV for the first time, and likely gone through an extensive series of interactions with healthcare workers up to the point of diagnosis. They had declined the trial and it was felt that in amongst that it would have been unfair and inappropriate to then approach them to participate in a different, but potentially indistinguishable study at that point. Other qualitative methods studies have interviewed those who declined to participate in a clinical trial but not in such an acute setting as AMBITION-cm. I attempted to partially overcome this by discussing this subject with researcher participants who were able to supplement my own experience, and this was useful for the decision-making analysis. Second, I clearly could not interview people who had died in the study, but I also actively decided not to interview relatives of those who had died. Again, this has been done in other studies and could have

contributed valuable data on how bereaved relatives reflect on trials when participants have bad outcomes, but here it was inappropriate and at high-risk of causing severe psychological distress in a recently bereaved individual.

Within my analyses I have discussed on multiple occasions the low levels of comprehension around the trial, poor recollection of events, difficulty disentangling aspects of the trial and research from routine care, and the general overwhelming impact of the underlying illness on the entire experience. Within the acceptability analysis this poor recollection was particularly manifest, as well as the consideration that each participant only experienced one of the treatment arms, resulting in limited data from participants being included in the analysis. The acceptability was therefore determined more from the researcher perspective. This limitation however also pervades the entire thesis, as conclusions made from data collected from trial participants, and to an extent their next-of-kin, was likely subject to these multiple, different but overlapping recall biases. It was challenging to design the study in a way that would mitigate these factors. There was a fine balance to strike between conducting interviews earlier in the trial, where recall bias *may* have been reduced, but also factoring in the severity of the illness and the need for neurological, physical, and psychological recovery, which itself takes time.

The COVID-19 pandemic arrived several weeks after data collection for LEOPARD commenced. As I have described in the methodology, this led to significant delays, fewer eligible participants, difficulties in arranging follow-up interviews, having to conduct interviews online, not being able to visit Kampala during the rest of the study, and fewer direct observations than planned. In addition, it led to considerable personal and professional

challenges throughout this PhD study that I would like to describe further. I remained in Botswana for the first full year of the pandemic and my friends and family overseas were completely inaccessible in a time of unprecedented uncertainty. I was invited to co-chair the Botswana COVID-19 Clinical Guidelines committee and worked with a wide team to curate those and a myriad of other COVID-19 operational protocols alongside Prof Jarvis as advisers to the Presidential Task Force. I co-coordinated a weekly webinar programme for healthcare workers around the country and regularly delivered educational sessions to hundreds of attendees. Along with colleagues at the HIV clinic at Princess Marina Hospital we developed a DSD model for during the pandemic which became a model for HIV clinics across the country and resulted in multi-month prescribing being implemented for the first time, something which continues today. With colleagues, we led several COVID-19 studies, and I was co-Principal Investigator on the research protocol that facilitated the discovery of the Omicron variant. We collected observational data from patients admitted with COVID-19 and tried to launch a site for the WHO Solidarity Trial, however the trial was stopped internationally just as we had prepared import permits for the investigational products. Amongst this I saw the potential overlap between clinical trials for COVID-19 and the LEOPARD study and was awarded a research grant by the WHO Public Health Emergency Preparedness and Response Ethics Network (PEPHREN). This project used similar methods to LEOPARD to interview individuals participating in COVID-19 research studies, those who had declined, and researchers trying to implement protocols. So, whilst LEOPARD was on pause, and I was distracted with predominantly clinical duties, I was still able to conduct qualitative methods research and develop my skills. This was of great value when recruitment into LEOPARD recommenced.

Despite this, there are significant strengths to this work. The meta-analysis adopted a novel approach to considering inclusion and representation in clinical trials for cryptococcal meningitis which can be used for ongoing monitoring within our discipline and easily used by researchers studying other illnesses. The critical interpretive synthesis brought together a diverse range of literature using a modified methodology that is clearly presented and replicable and which was congruous with the findings of ethnographic study. LEOPARD was a unique, multi-site study which collected rich, in-depth data from a group of individuals who were recovering from a life-threatening illness. This is a severely under-researched group, and their views were amplified to make recommendations that can improve care for people at risk of or suffering with AHD. These data have also added to the sparse literature considering bioethical issues in clinical trials for life-threatening illnesses in LMICs and my interpretation led to the conceptualisation of therapeutic expectation which re-centres trial participants and challenges the paternalism of existing concepts. Finally, the acceptability analysis complemented the AMBITION-cm trial findings and contributed to WHO guideline change.

CONCLUSION

This thesis has combined two review methodologies with an ethnographic study to explore the lived experience of those involved in AMBITION-cm, a clinical trial for cryptococcal meningitis. A meta-analysis found that there has been a marked shift in cryptococcal meningitis trials over the course of the HIV epidemic and trials are primarily performed in locations and populations that reflect the burden of disease, but severe and relapse cases are under-represented. Most cryptococcal meningitis trials now take place in LMICs but the research is primarily funded and led by individuals and institutions from HICs. A critical interpretive synthesis of qualitative research identified that individuals suffering from a life-threatening illness who are being invited to participate in clinical research need to be managed in a way that adapts to the severity of their illness and there is a need to tailor research processes, including informed consent, accordingly.

Data from the ethnographic study described pathways to care with cryptococcal meningitis which were prolonged because headaches were disregarded as a common occurrence with a broad differential diagnosis of predominantly benign aetiologies. There was a lack of awareness of the disease among participants and healthcare workers and it was often after HIV was diagnosed or disclosed that the pathway accelerated, resulting in hospital admission. I outline key recommendations to reduce mortality and argue for the integration of social and behavioural interventions within DSD models for AHD. The severity of the underlying illness was essential when considering enrolment into the AMBITION-cm trial, where previous exposure to and awareness of clinical research was limited, as was understanding of the trial objectives and design. Through observations and engagement with healthcare facilities, decision-makers were able to identify the trial as providing the best possible chance of

survival. Hesitation and reluctance were mostly due to fear of lumbar punctures which was sometimes based on rumours but often based on tragic personal experience. Despite fear, and sometimes conviction that they would die, individuals agreed to consent, often against the wishes of family members. Reassurance and confidence came from trust in routine care staff and the research team but also from fellow participants and their next-of-kins. Participants made informed decisions based on a therapeutic expectation from the trial and rather than this being the result of structural coercion it was an informed and voluntary choice.

Finally, the AmBisome regimen was highly acceptable, being simpler to administer despite the initial time investment required. The regimen was well tolerated and associated with less toxicity and resultant management. Widespread implementation would reduce the clinical workload of healthcare workers caring for patients and ongoing advocacy is now more essential than ever to increase access to antifungals and reduce deaths from cryptococcal meningitis.

APPENDICES

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Appendix 1: Research Paper Two Supplementary Material - Search Strategy

LIFE THREATENING	
1	Life threatening
2	Critical care
3	Emergency
4	Exp 'emergency care', 'emergency medicine', 'emergency patient', 'emergency surgery', 'emergency treatment', 'emergency ward', 'pediatric emergency medicine', 'emergency', 'evidence based emergency medicine', 'hospital emergency service', 'obstetric emergency'
5	Death
6	Exp 'brain death', 'fetus death' 'maternal death', 'newborn death', 'sudden cardiac death', 'sudden death', 'sudden infant death syndrome', 'parental death'
7	Meningitis
8	Exp 'bacterial meningitis', 'cryptococcal meningitis', 'meningitis', 'pneumococcal meningitis', 'tuberculous meningitis'
9	Stroke
10	Exp 'cerebrovascular accident'
11	Myocardial infarction
12	Exp 'heart infarction'
13	Pneumonia
14	Exp 'pneumonia'
15	Combine 1-14 OR
CLINICAL STUDIES	
16	trial
17	exp 'Clinical Trial', 'Clinical Trial, Phase I', 'Clinical Trial, Phase II', 'Clinical Trial, Phase III', 'Clinical Trial, Phase IV', 'Randomized Controlled Trial'
18	randomi#ed trial
19	prospective
20	exp 'Prospective Studies'
21	Cohort
22	Exp 'cohort analysis', 'controlled study'
23	Case control
24	Exp 'case control study'
25	Observational
26	Exp 'observational study'
27	Combine 16-26 OR
QUALITATIVE DATA	
28	Qualitative
29	Exp 'qualitative analysis', 'qualitative research'
30	Interview
31	Exp 'interview', 'semi structured interview', 'structured interview'
32	Focus group
33	Exp 'focus group'
34	Ethnograph*
35	Exp 'ethnography'
36	Observation
37	Exp 'non-participant observation', 'observation', 'participant observation'
38	Combine 28-37 OR
EXPERIENCE	

39	Experience
40	Exp ‘experience’, ‘near-death experience’
41	Perspective
42	Feedback
43	Opinion
44	Belief
45	Combine 39-44 OR
Combine	
46	Combine 15 AND 27 AND 38 AND 45

Appendix 2: Research Paper Two Supplementary Material - Data extraction form

BIBLIOGRAPHIC INFORMATION	
Title	
Authors	
Research institutions listed	
Article type (e.g. original research / report)	
Journal	
Publication Year	
Country of setting	
AIMS, METHODS AND PARTICIPANTS	
Name of clinical study in which this was embedded	
Type of study (trial, cohort etc)	
Disease under investigation	
Population under investigation	
Intervention(s) (if applicable)	
Qualitative study aims	
Specific objectives / research questions	
Theoretical and epistemological perspective underpinning the research	
Inclusion criteria	
Exclusion criteria	
Sampling	
Data collection method(s)	
Data collection location (e.g. hospital, clinic, telephone)	
Time period data collected over	
Categories of participants	
Number of participants	
Timeframe in relation to the clinical study (collected in-situ, after the trial etc)	
Data handling methods (transcription, translation, verification etc)	
Data analysis methods	
FINDINGS	
Theme 1	
Summary of theme 1	
Primary data to support theme 1	
Theme 2	
Summary of theme 2	
Primary data to support theme 2	
Theme 3	
Summary of theme 3	
Primary data to support theme 3	
Theme 4	
Summary of theme 4	
Primary data to support theme 4	
Theoretical Development	
Figures/Thematic Networks	
Conclusions	

QUALITY ASSESSMENT	
Are the aims and objectives of the research clearly stated?	
Is the research design clearly specified and appropriate for the aims and objectives of the research?	
Do the researchers provide a clear account of the process by which their findings we reproduced?	
Do the researchers display enough data to support their interpretations and conclusions?	
Is the method of analysis appropriate and adequately explicated?	
Notes on generalisability	
Notes on reflexivity and the role of the researcher	
Were any other potentially useful references listed in the bibliography?	
General thoughts of the reviewers	
Reviewer One	
Date	
Reviewer Two	
Date	

Appendix 3: Research Paper Three Supplementary Material - Participant in-depth interview schedule

AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

The Lived Experience Of Participants in an African RandomiseD controlled trial (LEOPARD)

Participant In-depth Interview Schedule

Note: This is purely a guide for a semi-structured interview and is not a rigid script. The interview should attempt to cover the key themes of enquiry outlined below but the participant should be able to steer the conversation and deviate from these themes if desired.

Introduction:

- General purpose and overview of the study
- Aims of interview
- Why the participant's cooperation is important
- Assurance of confidentiality
- What will happen with the collected information
- Any questions?
- Consent

'The aim of this exercise and series of questions is to understand a little about you and to hear your experience of the trial process from before you were recruited, the consent process, and throughout the trial itself'

Demographics and Background

- Age
- Gender
- Occupation

'At this point I would like you to consider drawing your experience in the trial as a timeline onto this piece of paper. I would like to know how you experienced each of the parts of the trial, one after the other, from just before you joined the trial until today.'

The participant can decline this approach if they wish. If they do want to draw a timeline let them direct the conversation and try to understand their recollection of events. Use prompts to ask follow-up questions as suggested below.

Before the study

- Previous experience with clinical trials, if any
- Previously held perceptions of clinical trials
- General health
- Circumstances in which participant became unwell
- How dis/orientated they were, their recollection of events
- The admission to the hospital, including experience of diagnostic lumbar puncture
- Diagnosis of cryptococcal meningitis and any other illness

Recruitment

- Experience of being approached by the team

LEOPARD Participant Interview Schedule: Version 1.0 (28th June 2018)

- First impressions of the clinical trial
- Thoughts on the participant information sheet

Consent

- How did they decide
- What was their motivation and what were their main concerns
- How long did it take to decide
- Did they feel under pressure to consent and if so, by whom
- With whom did they decide
- Did someone decide on their behalf and if so, what is their recollection of that and how did they feel both around that time and now
- When completing the form did they feel that they knew what they were signing up for
- Is there any way this process could have been improved

Within the trial (inpatient)

- Was anything different after they entered the trial compared to before
- What did they think about the nature, number and frequency of the procedures they had e.g. blood tests and lumbar punctures
- What did they think about the drugs they were receiving particularly the night time doses
- Are there any specific experiences whilst in hospital they would like to discuss
- Were they confused by what was going on at any point
- How was the communication and care from the trial team

Within the trial (outpatient)

- How was the outpatient clinic and did you have any concerns (such as confidentiality, security, cleanliness)
- How was your experience of those outpatient visits
- Did they miss any appointments during the trial and if so, why
- At any time did they consider leaving the trial and if so, why
- What did they think about the transport reimbursement, was it enough, did it play a role in encouraging them to attend outpatient visits
- How did they feel being asked the health economics questions
- Can you summarise the AMBITION trial

For participants that were confused, ask these questions at appropriate moments

- Did they understand what was happening
- If not, when did they begin to understand what was happening
- Did their confusion resolve all at once or did it come and go
- When they were informed they were in a clinical trial, what were their thoughts
- Who provided consent for them when they were confused, have they discussed this with the person/people and how do they feel about this now

For participants that have completed the study, ask these questions at appropriate moments

- How do they feel now they have left the trial
- Have they been back to their usual care provider and if so, how was that experience

Lawrence DS, *et al*. *BMJ Open* 2021; 11:e039191. doi: 10.1136/bmjopen-2020-039191

- What would they like to have seen done differently within the course of the trial
- If they were approached to take part in a clinical trial in the future what would they do and why

Closing:

Is there anything else you think is important that we have not talked about?

- Summarise
- Thank participant
- Provide contacts to participant

Second interview

A second interview will take place after the participant has exited the AMBITION study. During the second interview, spend time reviewing the information that was captured in the first and asking the participant if they have changed how they feel since exiting the study.

Any aspects of this interview schedule that were not captured in the first interview can be addressed in the second.

Lawrence DS, *et al*. *BMJ Open* 2021; 11:e039191. doi: 10.1136/bmjopen-2020-039191

Appendix 4: Research Paper Three Supplementary Material - Next-of-kin in-depth interview schedule

AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

The Lived Experience Of Participants in an African RandomiseD controlled trial (LEOPARD)

Next-of-kin In-depth Interview Schedule

Note: This is purely a guide for a semi-structured interview and is not a rigid script. The interview should attempt to cover the key themes of enquiry outlined below but the participant should be able to steer the conversation and deviate from these themes if desired.

Introduction:

- General purpose and overview of the study
- Aims of interview
- Why the participant's cooperation is important
- Assurance of confidentiality
- What will happen with the collected information
- Any questions?
- Consent

'The aim of this exercise and series of questions is to understand a little about you and to hear your experience as the next-of-kin of someone who was recruited into the AMBITION trial. We are interested to hear your experience of the trial process for your loved one from before they were recruited, the consent process, and throughout the trial itself'

Demographics and Background

- Age
- Gender
- Occupation

'At this point I would like you to consider drawing your experience with the trial as a timeline onto this piece of paper. I would like to know how you experienced each of the parts of the trial, one after the other, from just before you were aware of the trial until today.'

The next-of-kin participant can decline this approach if they wish. If they do want to draw a timeline let them direct the conversation and try to understand their recollection of events. Use prompts to ask follow-up questions as suggested below.

Before the study

- Previous experience with clinical trials, if any
- Previously held perceptions of clinical trials
- Circumstances in which the trial participant became unwell
- How dis/orientated they felt to be at the time
- The admission to the hospital, including experience of diagnostic lumbar puncture
- How and if they were informed of the diagnosis of cryptococcal meningitis and any other illness

Recruitment

Lawrence DS, *et al*. *BMJ Open* 2021; 11:e039191. doi: 10.1136/bmjopen-2020-039191

- Experience of being approached by the team
- First impressions of the clinical trial
- Thoughts on the participant information sheet

Consent (Next-of-kin perspective)

- How did they decide
- What was their motivation and what were their main concerns
- How long did it take to decide
- Did they feel under pressure to consent and if so, by whom
- With whom did they decide
- When completing the form did they feel that they knew what they were signing their loved one up for
- Is there any way this process could have been improved

Consent (Participant perspective)

- Did they think their loved one understood what was happening
- If not, when did they begin to understand what was happening
- Did their confusion resolve all at once or did it come and go
- When they were informed they were in a clinical trial, were they part of the re-consent process
- Have they ever discussed this issue of consent with their loved one and if so would they be willing to share this discussion with the researcher

Within the trial (inpatient)

- Was anything different after the participant entered the trial compared to before
- What did they think about the nature, number and frequency of the procedures their loved one had e.g. blood tests and lumbar punctures
- What did they think about the drugs they were receiving particularly the night time doses
- Are there any specific experiences whilst in hospital they would like to discuss
- Were they confused by what was going on at any point
- How was the communication and care from the trial team
- Did they feel that they were involved in the trial process

For the next-of-kin that accompanied the participant to outpatient appointments, ask these questions at appropriate moments

- How was the outpatient clinic and did you have any concerns (such as confidentiality, security, cleanliness)
- How was your experience of those outpatient visits
- Did your loved one miss any appointments during the trial and if so, why
- At any time did they consider removing their loved one from the trial and if so, why
- At any time did their loved one consider removing themselves from the trial and if so, why
- What did they think about the transport reimbursement, was it enough, did it play a role in encouraging their loved one to attend outpatient visits and for them to accompany them
- Can they summarise the AMBITION trial

LEOPARD Next-of-kin Interview Schedule: Version 1.0 (28th June 2019)

Reflections on the trial

- How do they feel about the trial in general
- What would they like to have seen done differently within the course of the trial
- If they were approached to take part in a clinical trial in the future what would they do and why

Closing:

Is there anything else you think is important that we have not talked about?

- Summarise
- Thank participant
- Provide contacts to participant

Lawrence DS, *et al*. *BMJ Open* 2021; 11:e039191. doi: 10.1136/bmjopen-2020-039191

Appendix 5: Research Paper Three Supplementary Material - Researcher in-depth interview schedule

AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

The Lived Experience Of Participants in an African RandomiseD controlled trial (LEOPARD)

Researcher In-depth Interview Schedule

Note: This is purely a guide for a semi-structured interview and is not a rigid script. The interview should attempt to cover the key themes of enquiry outlined below but the participant should be able to steer the conversation and deviate from these themes if desired.

Introduction:

- General purpose and overview of the study
- Aims of interview
- Why the participant's cooperation is important
- Assurance of confidentiality
- What will happen with the collected information
- Any questions?
- Consent

'The aim of the first series of questions is to contextualise you within the Ambition study and the clinical research community'

Demographics and Background:

- Job title and role
- Institution and number of years there
- Training / qualifications and their locations
- Research posts previously held and their locations

The Ambition study:

- How became involved
- Current role and responsibilities
- Level of engagement with trial participants

Previous research experience:

- Background of working with participants of other trials
- With individuals within Ambition and/or not affiliated
- In other institutions
- In transnational research partnerships

'Drawing predominantly on your current experience within the Ambition study but also from your previous work (if any) please can you share your thoughts on the following:'

Trial participant experience:

- General impressions of how participants experience a trial
- What you and fellow researchers are good at
- What you are not so good at
- Experience of evaluating trial participant experience

LEOPARD Researcher Interview Schedule: Version 1.0 (28th June 2019)

- Suggestions for improvements

Specifically aim to focus on: the consent process, recruiting participants with impaired consciousness and the death of participants, prompting if required. Probing to draw on specific examples to elicit narratives.
'Do you think that the issues you have brought up are specific to your hospital / institution / city / country. Where else can you see they do / may occur?'

Transnational research partnerships:
- Understanding of the EDCTP and how it works
- Perceived benefits of such an approach
- Any shortcomings
- Capacity building
- Ownership
- Impact on the global research agenda
- Any suggestions for improvement

'Do you think that the issues you have brought up are specific to your hospital / institution / city / country. Where else can you see they do / may occur?'

Closing:

Is there anything else you think is important that we have not talked about?

- Summarise
- Thank participant
- Provide contacts to participant

Lawrence DS, *et al*. *BMJ Open* 2021; 11:e039191. doi: 10.1136/bmjopen-2020-039191

Results A total of 26 professionals participated in the interviews. The main facilitator for implementation of the CDSS was considered to be easy access to well-structured patient data, and the resulting reduction of MDTM preparation time and of duration of MDTMs. Less impact of the CDSS was expected on the quality of lung cancer services generated by MDTM decision-making. Main barriers for adoption included incomplete or non-trustworthy output generated by the system and insufficient adaptability of the system to local and contextual needs. Actionable findings for an implementation strategy were a usability test involving key users and a validation study in the organization's real-life setting prior to roll out.
Conclusion Using this CDSS in lung cancer MDTMs was expected to increase efficiency of workflows. Successful implementation is dependent on the reliability and adaptability of the CDSS and involvement of key users in the implementation process.

18 COLLABORATIVE QUALITATIVE RESEARCH ON SUICIDE AND SELF-HARM IN SOUTH ASIA: A REFLECTION ON CHALLENGES AND SOLUTIONS

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10.1136/bmjopen-2021-QHRN.18

Trust is essential to planning and delivering impactful international research that is culturally appropriate and has the potential to change practice and policy on local levels. However, details on how this is can be achieved, and a discussion of challenges encountered are often lacking. A better understanding of building and maintaining of trust in North-South research partnerships is essential, especially when tackling complex and sensitive issues such as self harm and suicide. Suicide is amongst the leading causes of death in South Asia.

This talk will reflect on experiences in the South Asia Self-Harm Initiative (SASHI), a global-challenges funded research project, led by co-investigators from the Global North and South. The research collects empirical evidence to inform the understanding of the nature of self-harm in the context of profound social, political and economic challenges in the global South as well as builds research capacity. We draw on Ben-Ari and Enosh's work (2010), which focuses on identifying incongruities that challenge our knowledge (*discovery*) and examine them in-depth as a source of new knowledge (*construction*) to come to a new understanding. The definition of trust is debated, and our starting point is Luhmann's (1999) approach that trust is expressed through social action in contexts we cannot fully know.

We argue that trust is a building block for fair and equitable international research partnerships and is continually developed and negotiated in relationships and activities. Power inequalities and contextual factors need to be acknowledged. Working on building and maintaining trust is emotionally and cognitively challenging. Our experiences suggest that building and maintaining trust relies on recognising similarities, which can foster respect and equality of status. Acknowledging and exploring differences can provide opportunities for reflection and joint learning. These issues are important to consider as they ultimately shape knowledge production and translation.

19 THE DYNAMICS OF TRUST AND STRUCTURAL COERCION WITHIN A MENINGITIS TRIAL IN SUB-SAHARAN AFRICA

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10.1136/bmjopen-2021-QHRN.19

Background Clinical trials in sub-Saharan Africa typically offer better medical care than is routinely available. This can lead to structural coercion where an individual may consent because of a lack of alternative options and potentially despite being uncertain about the research. An inherent component of this decision making process is an assessment of trust. Trust in the treatment options, the research team, and the process as a whole. This may be polarised in the context of life-threatening illnesses where recruitment (or not) could determine survival.
Aim We sought to understand the dynamics of trust and structural coercion in a multi-site clinical trial for HIV-associated cryptococcal meningitis.
Methods We embedded an ethnographic study within a clinical trial for HIV-associated cryptococcal meningitis. We conducted in-depth interviews with trial participants and their next-of-kin in Uganda and Botswana. We combined these with direct observations and in-depth interviews with researchers working at the African sites and European partner institutions. Interviews were transcribed, translated, and subject to narrative analysis.
Results To date we have recruited 14 trial participants, five next-of-kin and ten researchers. Recruitment is on-going until March 2021. Participants and their relatives often felt they had no choice but to enrol in the clinical trial which was their best chance of survival. Despite the perceived benefits of participation, recruitment came at a cost to participants who agreed to invasive medical procedures such as lumbar punctures despite pre-existing beliefs they could cause death. The severity of the illness contributed to poor comprehension of what the trial entailed and the decision to participate was heavily based on trust in the research team.
Conclusions Structural coercion is a significant factor impacting recruitment into clinical trials in resource-limited settings. In the context of life-threatening illness, trust superseded the need for an in-depth understanding of the research process.

20 TRUST AND RELIANCE WITHIN SPECIALIST CLINICAL SERVICES: COUNTER-PRODUCTIVE OR HELPFUL FOR SELF-MANAGEMENT OF PEOPLE WITH NEUROMUSCULAR CONDITIONS?

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10.1136/bmjopen-2021-QHRN.20

Current approaches to self-management de-emphasise dependency on healthcare services and focus on building confidence and capability. Our qualitative study explores self-management perspectives from individuals with neuromuscular conditions who attend regional specialist clinics, to inform implementation of a self-management intervention.

Cost-effectiveness of the AMBITION regimen for HIV-associated cryptococcal meningitis

00664

Charles Muthoga[1], David S. Lawrence[1,2], David Meya[3], Henry Mwandumba[4], Cecelia Kanyama[5], Graeme Meintjes[6], Conrad Muzoora[3], Mosepele Mosepele[1,7], Chiratidzo E. Ndhlovu[8], Tinevimbo Shiri[9], Shabbar Jaffar[9], Tom Harrison[10], Joseph N. Jarvis[1,2], Louis W. Niessen[9]

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BACKGROUND

- HIV-associated cryptococcal meningitis (CM) remains a key driver of AIDS-related mortality.
- The AMBIsome Therapy Induction Optimisation (AMBITION-cm) trial was a phase-III non-inferiority trial comparing a single, high-dose (10mg/kg) of liposomal amphotericin (AmBisome, L-AmB) dose given alongside 14 days of flucytosine (5FC) and fluconazole versus the WHO recommended standard of care of one week of amphotericin B deoxycholate (AmB) at 1mg/kg/day plus flucytosine (5FC) followed by one week of high-dose fluconazole.
- The trial demonstrated the L-AmB regimen was non-inferior in averting mortality and was associated with significantly fewer adverse events[1].
- Here we present a cost-effectiveness analysis of this approach in five countries.

METHODS

- 814 participants were analysed from eight hospitals across five countries: Botswana, Malawi, South Africa, Uganda and Zimbabwe and randomised 1:1 to either L-AmB (n= 407) or control (n= 407) regimens.
- We developed costing tools for each of the five country settings. Individual resource use per participant was applied to each country costing tool and the health outcome of life years (LY) gained was used.
- The Malawi context was chosen for the primary analysis. Mean costs, cost-differences, and an incremental cost effectiveness ratio were calculated.
- Additional sensitivity analyses were performed based on the potential for the L-AmB regimen to reduce the number of blood tests required and the length of hospital admission under real-world implementation conditions.

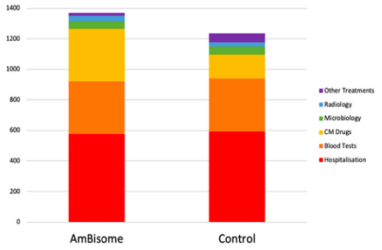

Figure 1: The proportion of the total in-trial per-patient costs attributable to different groups of resource units (US$ 2021) in the Malawi setting.

The single, high-dose L-AmB regimen results in similar efficacy to the current WHO recommended standard of care with fewer side effects at a low incremental cost ($132/patient).

The Incremental Cost Effectiveness Ratio (ICER) was $128/LY saved in trial conditions, falling to $80/LY saved in a potential real-world implementation scenario, indicating increasing cost-effectiveness.

Table 1: Cost-effectiveness analyses for the AMBITION trial for each site based on in-trial resource use and probable real-world resource use

Treatment arm	Mean (95% CI) in-trial treatment costs per patient (2021 US$)	Mean (95% CI) probable real-world resource use costs per patient (2021 US$)	Incremental Cost-Effectiveness Ratio of L-AmB treatment (US$/LY saved)	
			In-trial resource use	Probable real-world resource use
Malawi				
Control	1237 (1180 - 1293)	1125 (1070 - 1179)	Reference	Reference
L-AmB	1369 (1314 - 1424)	1208 (1155 - 1260)	128 (53 - 257)	80 (15 - 275)
Botswana				
Control	2048 (1939 - 2158)	1993 (1884 - 2101)	Reference	Reference
L-AmB	2164 (2048 - 2279)	2083 (1969 - 2198)	92 (53 -221)	71 (40 - 182)
South Africa				
Control	1858 (1761 - 1955)	1799 (1703 - 1896)	Reference	Reference
L-AmB	1993 (1890 - 2097)	1905 (1803 - 2007)	130 (65 - 251)	101 (80 -140)
Uganda				
Control	669 (644 - 693)	628 (604 - 651)	Reference	Reference
L-AmB	810 (783 - 836)	747 (722 - 772)	143 (85 - 217)	121 (55 - 231)
Zimbabwe				
Control	850 (819 - 881)	759 (731 - 787)	Reference	Reference
L-AmB	989 (957 - 1022)	857 (827 - 887)	152 (36 - 381)	106 (17 - 328)

RESULTS

- Mortality risk in the L-AmB group was 24.8% (95% CI; 20.7% - 29.3%) vs 28.7% (95% CI; 24.4% - 33.4%) in the control group giving a risk difference of -3.9% (95 CI; -10.0% - 2.2%).
- Using Malawi as the reference country, the mean per patient total costs were US$1369 (95% CI; $1314 - $1424) and US$1237 (95% CI; $1181 - $1293) in the L-AmB and control arms respectively (Figure 1 and Table 1).
- The mean incremental cost-effectiveness ratio (ICER) was US$128 (95% CI $53 - $257) per LY saved. The results were similar across countries. Using a real-world laboratory monitoring schedule, the mean ICER cost per LY saved fell to US$80 (95% CI $15 - $275).
- Hospital 'hotel' costs were and $13.85 in Uganda, $15.90 in Zimbabwe, $18.36 in Malawi, $80.66 in South Africa and $88.80 in Botswana, (Figure 2). In Botswana and South Africa where hospital admission costs were high, the L-AmB regimen was cost-saving compared to the control arm if patients could be discharged one or two days earlier, respectively.

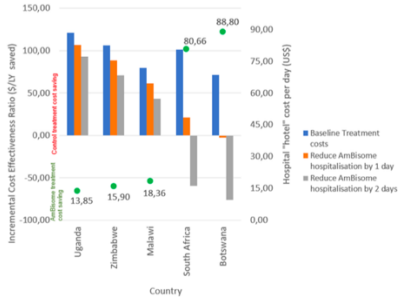

Figure 2: Tipping Point' Scenario analysis using probable real-world scenario, demonstrating change in ICER if the admission duration in AmBisome arm was to reduced by one or two days.

CONCLUSIONS

- The L-AmB regimen was cost-effective when compared to the current WHO at $128 per LY saved, and results were similar across five country settings in southern and east Africa.
- There is an urgent need to increase access to L-AmB and 5FC to ensure improvements in CM patient outcomes made possible by novel treatments are realized globally.

REFERENCE

1. Lawrence DS et al. Single high-dose liposomal amphotericin based regimen for treatment of HIV-associated Cryptococcal Meningitis: results of the phase-3 Ambition-cm Randomised Trial. 11th IAS Conference on HIV Science, Abstract OALB01LB03, 2021.

Appendix 8: Research Paper Six – Excerpts from the World Health Organisation guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV (World Health Organisation, 2022).

Feasibility and acceptability

Qualitative data from a purposively selected group of participants, surrogate decision-makers and researchers working at the AMBITION trial sites in Botswana and Uganda identified a clear preference regarding the administration and tolerability of the single-dose liposomal amphotericin B–containing regimen *(42)*.

There was a general preference for the single-dose liposomal amphotericin B regimen because it was associated with fewer intravenous doses. The single intravenous dose took longer to prepare on the first day of treatment, but the entire regimen was less time-consuming to administer over the course of the induction therapy. In addition, the single dose of liposomal amphotericin B can be infused over two hours, whereas each amphotericin B deoxycholate

infusion must run over four hours. Fewer intravenous doses of liposomal amphotericin B resulted in a reduced need for essential pre- and post-hydration and oral electrolyte supplementation aimed at preventing toxicity. The single high-dose intravenous regimen may enable rapid hospital discharge for people with good clinical status.

The favourable safety profile of the single-dose liposomal amphotericin B–containing regimen with a lower risk of anaemia and hypokalaemia reduced the intensity of monitoring and managing drug-related toxicity (Tables 1 and 2). In the single-dose liposomal amphotericin B–containing regimen, flucytosine is given four times a day for 14 days, but participants broadly accepted this as an important part of their treatment and adhered to it.

Factor	Explanation and evidence	Judgement
Values and preferences	Qualitative data from a purposively selected group of participants, surrogate decision-makers and researchers working at the sites in Gaborone, Botswana and Kampala, Uganda identified a clear preference with regards to the administration and tolerability of the single-dose liposomal amphotericin regimen. The liposomal amphotericin regimen was favoured because it involved a single intravenous dose which, despite taking longer to prepare on the first day of treatment (20–40 minutes versus 5–10 minutes for amphotericin B deoxycholate), was less time consuming over the course of the induction therapy. In addition, liposomal amphotericin can be administered over two hours, whereas amphotericin B deoxycholate must run over four hours. Fewer intravenous doses of amphotericin resulted in a reduced need for essential pre- and post-hydration and oral electrolyte supplementation aimed at preventing toxicity. Liposomal amphotericin was subjectively observed to result in fewer and less severe infusion-related rigours, but this was not objectively measured within the trial.	No important uncertainty or variability of preferences.
Acceptability	Qualitative data from a purposively selected group of participants, surrogate decision-makers and researchers working at the AMBITION trial sites in Gaborone, Botswana and Kampala, Uganda (LEOPARD study) identified a clear preference regarding the administration and tolerability of the single-dose liposomal amphotericin B–containing regimen. There was a general preference for the single-dose liposomal amphotericin B regimen because it was associated with fewer intravenous doses. The single intravenous dose took longer to prepare on the first day of treatment, but the entire regimen was less time-consuming to administer over the course of the induction therapy.	Acceptable to all stakeholders.
Feasibility	The short-course high-dose liposomal amphotericin regimen requires just a single intravenous infusion versus seven with the current WHO-recommended regimen and has significantly fewer side-effects. As a result, it may be feasible to reduce the duration of hospital admission in some cases, and the need for toxicity monitoring is reduced. Unlike amphotericin B deoxycholate, liposomal amphotericin B does not require refrigeration. The short-course treatment would be feasible to implement in all settings in which amphotericin B deoxycholate treatment is currently being used and could be implemented in some settings that are currently unable to implement seven-day courses of amphotericin B deoxycholate. Further, the intervention does not require refrigeration. The Guideline Development Group noted limited access to flucytosine, which is part of the induction therapy for cryptococcal disease and expects feasibility to improve with this recommendation.	Probably feasible

The acceptability of the AMBITION treatment regimen for HIV-associated cryptococcal meningitis: Findings from a qualitative study of patients and providers in Botswana and Uganda

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Background

- HIV-associated cryptococcal meningitis remains a significant contributor to AIDS-related mortality.
- The AMBITION trial found a single, high-dose liposomal amphotericin (AmBisome, Gilead Sciences Inc.) based regimen was non-inferior to the WHO recommended standard of care[1].
- The AMBITION regimen was associated with significantly fewer adverse events.
- We explored the acceptability of the AMBITION regimen from the patient and provider perspectives.

Methods

- We embedded a qualitative methods study within the AMBITION sites in Gaborone, Botswana and Kampala, Uganda.
- We conducted in-depth interviews with trial participants, surrogate decision makers, and researchers and combined these with direct observations.
- Interviews were transcribed and translated, and data underwent thematic analysis.

Figure 1: The difference between the two regimens in terms of antifungals, administration, and management

	AMBITION REGIMEN	CONTROL REGIMEN
ANTIFUNGALS	AMBISOME 10MG/KG DAY 1 + FLUCYTOSINE 100MG/KG FOR 14 DAYS + FLUCONAZOLE 1200MG FOR 14 DAYS	AMPHOTERICIN B DEOXYCHOLATE 1MG/KG FOR 7 DAYS + FLUCYTOSINE 100MG/KG FOR 7 DAYS THEN FLUCONAZOLE 1200MG FOR 7 DAYS
ADMINISTRATION	20-40 MINUTES TO RECONSTITUTE AMBISOME 2 HOUR INFUSION PRE- AND POST-HYDRATION FOR 1 DAY ELECTROLYTE SUPPLEMENTATION FOR 3 DAYS	5-10 MINUTES TO RECONSTITUTE AMPHO B 4 HOUR INFUSION PRE- AND POST-HYDRATION FOR 7 DAYS ELECTROLYTE SUPPLEMENTATION FOR 9 DAYS
MANAGEMENT	CLEAR PREFERENCE 'WORTH THE INVESTMENT' FEWER CANNULAE ISSUES RIGORS LESS COMMON LESS TOXICITY EASIER TO MONITOR AND MANAGE	OVERALL A LOT MORE WORK SHORTER COURSE OF FLUCYTOSINE IS GOOD THROMBOPHLEBITIS COMMON MORE TIME CONSUMING DIFFICULT TO ACCESS BLOOD TRANSFUSIONS

"AmBisome will always be successful in the real world … I think the only challenging thing with AmBisome is the mixing, cause you mix a lot of ampoules at the same time. If we have a heavier patient you need to mix a lot, I think there was a point when I was enrolling somebody who was 110kg, that was a nightmare mixing the AmBisome, but apart from that, giving it is just a smooth ride, two hours and then you are done." *Research Nurse*

"Less admin, less side-effects, because the patients would be having rigors, then I will have to deal with … the toxicities, write lots of adverse events, so, it's less work for me if it's AmBisome. It's nicer for the patient also. I don't have to be changing cannulas on the patient every other day so it's really nice for everyone. The nurses don't have to stay here long, waiting for the 4 hours of amphotericin. We love AmBisome." *Research Doctor*

Figure 2: Quotes from healthcare providers

Results

- We interviewed 38 trial participants, 20 surrogate decision makers and 31 researchers.
- A summary of our key findings is displayed in Figure 1.
- Participant understanding of the intricacies of the treatment regimens was limited, however there was a broad preference for the AMBITION regimen due to the single intravenous dose and fewer side effects, with some in the control arm stating that they would have preferred the single dose.
- The AMBITION regimen was associated with fewer episodes of amphotericin related rigors, a reduced need for intravenous hydration, fewer cases of thrombophlebitis, and a reduction in the number of intravenous cannulae required.
- The reduced toxicity profile resulted in less intensive monitoring and management of participants in the AMBITION arm (Figure 2).
- A particular challenge was accessing blood transfusions which were needed more often in control arm participants who had significantly higher rates of anaemia.
- A challenge of the AMBITION arm was the extended duration of oral flucytosine which was given six hourly and involved participants taking a dose in the night.

Participants, surrogate decision makers, and researchers found the AMBITION regimen to be highly acceptable and it was simpler to administer despite the initial time investment required.

The single dose was well tolerated and associated with less toxicity which required less time and fewer resources to manage and monitor.

Widespread implementation of this regimen would reduce the clinical workload of those caring for patients with HIV-associated cryptococcal meningitis.

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[1]Jarvis JN, Lawrence DS, Meya DB, et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. *New England Journal of Medicine* 2022; **386**(12): 1109-20.

AMBITION-*cm* AMBisome Therapy Induction OptimizatioN

Presented at AIDS 2022 – The 24th International AIDS Conference

AIDS 2022 29 July – 2 August

Lawrence *et al. Trials* (2018) 19:649
https://doi.org/10.1186/s13063-018-3026-4

Trials

STUDY PROTOCOL Open Access

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

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Abstract

Background: Cryptococcal meningitis (CM) is a major cause of mortality in HIV programmes in Africa despite increasing access to antiretroviral therapy (ART). Mortality is driven in part by limited availability of amphotericin-based treatment, drug-induced toxicities of amphotericin B deoxycholate and prolonged hospital admissions. A single, high-dose of liposomal amphotericin (L-AmB, Ambisome) on a fluconazole backbone has been reported as non-inferior to 14 days of standard dose L-AmB in reducing fungal burden. This trial examines whether single, high-dose L-AmB given with high-dose fluconazole and flucytosine is non-inferior to a seven-day course of amphotericin B deoxycholate plus flucytosine (the current World Health Organization [WHO] recommended treatment regimen).

(Continued on next page)

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(Continued from previous page)
Methods: An open-label phase III randomised controlled non-inferiority trial conducted in five countries in sub-Saharan Africa: Botswana, Malawi, South Africa, Uganda and Zimbabwe. The trial will compare CM induction therapy with (1) a single dose (10 mg/kg) of L-AmB given with 14 days of fluconazole (1200 mg/day) and flucytosine (100 mg/kg/day) to (2) seven days amphotericin B deoxycholate (1 mg/kg/day) given alongside seven days of flucytosine (100 mg/kg/day) followed by seven days of fluconazole (1200 mg/day). The primary endpoint is all-cause mortality at ten weeks with a non-inferiority margin of 10% and 90% power. Secondary endpoints are early fungicidal activity, proportion of grade III/IV adverse events, pharmacokinetic parameters and pharmacokinetic/pharmacodynamic associations, health service costs, all-cause mortality within the first two and four weeks, all-cause mortality within the first ten weeks (superiority analysis) and rates of CM relapse, immune reconstitution inflammatory syndrome and disability at ten weeks. A total of 850 patients aged ≥ 18 years with a first episode of HIV-associated CM will be enrolled (425 randomised to each arm). All patients will be followed for 16 weeks. All patients will receive consolidation therapy with fluconazole 800 mg/day to complete ten weeks of treatment, followed by fluconazole maintenance and ART as per local guidance.

Discussion: A safe, sustainable and easy to administer regimen of L-AmB that is non-inferior to seven days of daily amphotericin B deoxycholate therapy may reduce the number of adverse events seen in patients treated with amphotericin B deoxycholate and shorten hospital admissions, providing a highly favourable and implementable alternative to the current WHO recommended first-line treatment.

Trial registration: ISRCTN, ISRCTN72509687. Registered on 13 July 2017.

Keywords: Cryptococcal meningitis, HIV, AmBisome, Amphotericin B, Fluconazole, Flucytosine, Clinical trial

Background

Early mortality among people initiating HIV treatment in Africa is considerably higher than in high-income countries [1–4]. Despite antiretroviral therapy (ART) roll-out, approximately half of HIV-infected individuals in sub-Saharan Africa are not on ART and about one-third still present for care with very low CD4 counts. The incidence of opportunistic co-infections such as CM in this group is high [5] and CM remains the most common cause of adult meningitis in much of Africa [6]. As a result, cryptococcal meningitis (CM) is a major cause of mortality in HIV-infected patients in Africa and is associated with 10–20% of all HIV-related deaths [7]. Furthermore, the number of CM cases remains high despite increased ART access; they now include both ART-naïve and ART-experienced patients, with half of patients diagnosed with CM having had prior exposure to ART but with persisting low CD4 counts due to non-adherence and/or ART failure [8–10]. The poor outcomes reported using currently available antifungal therapy in African centres are a critical driver of this high mortality. Mortality using amphotericin B deoxycholate-based therapy in Africa, even in clinical trial settings, remains in the region of 35–45% [10–13]. Amphotericin B deoxycholate therapy requires hospitalisation for at least seven days and its toxicity profile requires costly laboratory monitoring. The average hospitalisation cost for CM treated with amphotericin B deoxycholate is USD 800–1000 in Zimbabwe where the annual per capita gross domestic product is < USD 1000. Many clinical centres in sub-Saharan Africa lack access to reliable laboratory monitoring and have limited nursing capacity making safe administration of conventional amphotericin B deoxycholate difficult or impossible. Consequently, amphotericin B deoxycholate therapy is often not available in Africa. Fluconazole, the oral alternative widely used in Africa, is much less rapidly fungicidal than amphotericin-B, even at a dosage of up to 1200 mg/day, and mortality at ten weeks is 50–60% [14, 15]. Given the HIV prevalence and incidence in Southern and East Africa, inadequate ART coverage, suboptimal monitoring of individuals on ART leading to treatment failure and limited access to screening and pre-emptive treatment for CM, CM will remain a major cause of morbidity and mortality in the region for the foreseeable future. New treatment strategies are urgently needed.

Until recently, World Health Organization (WHO) treatment guidelines recommended a 14-day course of amphotericin B deoxycholate-based treatment for CM induction therapy. The recently completed phase III ACTA trial showed that patients receiving a short, seven-day course of amphotericin B deoxycholate plus flucytosine had lower mortality at ten weeks (24%, 95% confidence interval [CI]: 16–32) compared to patients receiving 14-day course of amphotericin B plus flucytosine (38%, 95% CI: 29–47, unadjusted hazard ratio [HR] 0.56, 95% CI: 0.35–0.91) [10]. The trial also confirmed that flucytosine (5FC) is a significantly superior partner drug for amphotericin B-based treatments compared with fluconazole, leading to a substantial mortality reduction of 38% (95% CI: 16–55, $p = 0.002$). As a consequence, the WHO guidelines were revised and now recommend first-line treatment with seven days of amphotericin B deoxycholate and flucytosine 100 mg/kg/day followed by seven days of fluconazole 1200 mg/

day. In settings where flucytosine is unavailable, which reflects most settings in Africa, the guidelines continue to recommend 14 days of amphotericin B deoxycholate with fluconazole [16].

A newer lipid-based formulation of amphotericin B deoxycholate (L-AmB or AmBisome©) is particularly suited for use in short-course yet highly effective induction treatment for HIV-associated CM, due to: (1) the potential for high dosing made possible by the lower rates of drug-induced toxicity; and (2) the long tissue half-life. In the context of HIV-associated CM, 14-day courses of conventional amphotericin B deoxycholate are associated with an average drop in haemoglobin of 2.3 g/dL and a mean increase in creatinine of 73% [17]. Even at high doses, L-AmB is associated with significantly less nephrotoxicity and anaemia as well as lower rates of infusion reactions than conventional amphotericin B deoxycholate [18]. The long tissue half-life of L-AmB following high-dose administration in patients is well-established [19–22], as is its effective penetration into brain tissue [23]. The concept of single or intermittent dosing with very high doses is also established in both prophylaxis in haematology patients and treatment of visceral leishmaniasis in lower- and middle-income countries [24]. Single doses of up to 15 mg/kg have been safely given; doses of 10 mg/kg are routinely given with demonstration of efficacy for treatment of visceral leishmaniasis and invasive fungal infections [24, 25]. Pharmacokinetic data from animal models [20] and humans [19] suggest that increasing L-AmB dosing from the currently recommended 3–4 mg/kg may lead to improved outcomes and, as with standard amphotericin B, that intermittent dosing regimens may be as effective as daily therapy [20]. Although L-AmB is recommended as treatment for HIV-associated CM in several national guidelines, optimal dosing is unknown and the strategy of short-course high dosing of L-AmB has not yet been tested in a phase III clinical trial [18].

A randomised controlled trial comparing L-AmB 3 mg/kg/day, L-AmB 6 mg/kg/day and amphotericin B deoxycholate 0.7 mg/kg/day, all given for 14 days, showed no difference in mortality outcome between any of these regimens [18]; 3 mg/kg/day is widely used as the standard dose. However, murine models suggest dosing of 3 mg/kg/day may be sub-optimal [20]. Further evidence to support this comes from the recently completed phase II AMBITION trial which was performed with the primary objective of determining the rate of cryptococcal clearance from cerebrospinal fluid (CSF), presented as Early Fungicidal Activity (EFA), of three alternative schedules of intermittent high-dose L-AmB in comparison with 14 days of standard daily L-AmB for induction therapy for HIV-associated CM [26]. Eighty participants were recruited at sites in Botswana and Tanzania and randomised to one of four treatment arms: (1) L-AmB 10 mg/kg day 1 (single dose); (2) L-AmB 10 mg/kg day 1, L-AmB 5 mg/kg day 3 (two doses); (3) L-AmB 10 mg/kg day 1, L-AmB 5 mg/kg days 3 and 7 (three doses); or (4) the control arm, being standard 14-day L-AmB (3 mg/kg/day). All treatment arms received high-dose fluconazole (1200 mg/day) for 14 days. This phase II trial was stopped by the Data Monitoring Committee (DMC) at the pre-planned interim analysis stage of 80 patients as the primary endpoint had been reached with the recommendation that the trial proceed onto the current clinical endpoint phase III trial using single dose L-AmB. The primary analysis showed that the EFA in all three short-course high-dose arms was comparable to, or greater than, the control arm, with statistical non-inferiority between all short-course arms and control at the pre-defined non-inferiority (NI) of 0.2 $\log_{10}$ colony forming units (CFU)/mL/day difference (Fig. 1). There was no evidence for any dose response effect with additional L-AmB doses, suggesting maximal fungicidal activity was achieved with a single 10 mg/kg dose. All three high-dose short-course L-AmB regimens were well tolerated, with only one Division of AIDS (DAIDS) grade IV laboratory toxicity event occurring during induction therapy, and a total of seven grade III and no grade IV clinical adverse events (AEs) associated with high-dose L-AmB. This toxicity profile compared to 33% of patients reporting grade III or IV anaemia in a combined cohort of 368 patients treated in Africa with conventional amphotericin B for 14 days [27]. There were no safety concerns with short-course treatment and no patients receiving short-course L-AmB required additional 'rescue' L-AmB therapy. Overall mortality in the trial was 29% at ten weeks, comparing very favourably with recent trials of amphotericin B deoxycholate-based treatments, with no significant difference between arms [17].

However, although EFA is an extremely valuable tool to rapidly screen novel antifungal treatment regimens and is associated with mortality [28], it has not been validated as a true 'surrogate' marker of outcome. Large phase III trials with a mortality endpoint are critical to define the optimal treatment regimens for HIV-associated CM and are essential to influence policy.

Method/design

Study design

The AMBITION trial is an open label, phase III, randomised controlled non-inferiority, multi-centre trial to compare single, high-dose L-AmB treatment to seven-day amphotericin B deoxycholate-based treatment for HIV-associated CM (Additional files 1 and 2).

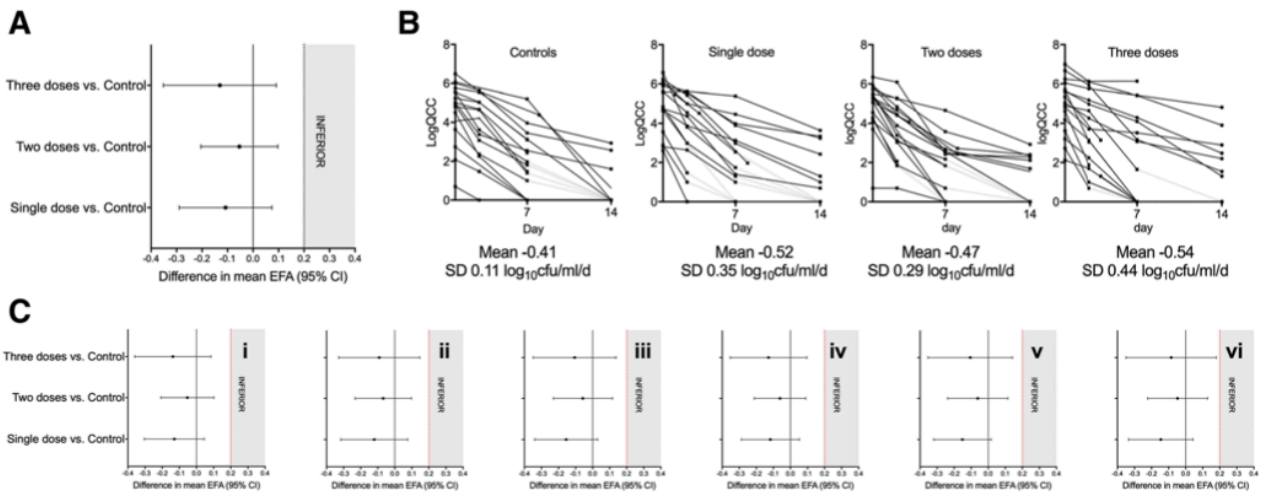

Fig. 1 Primary and key secondary outcomes of the AMBITION Step I phase-II randomised controlled trial. The figure shows: (**a**) all three short-course treatment arms were non-inferior to control; (**b**) EFA and the individual patient slopes over the initial 14 days of treatment; and (**c**) all three short-course treatment arms remained non-inferior to control when controlling for baseline fungal burden (QCC), baseline CD4 count, baseline mental status, QCC and CD4 count, QCC count, CD4 count, mental status and QCC, CD4 count, mental status, sex, age and ART status [26]

Hypothesis

Short-course, high-dose L-AmB given with 14 days of high-dose fluconazole and flucytosine will be non-inferior to seven days of daily-dosed amphotericin B deoxycholate given with seven days of flucytosine, followed by seven days of high-dose fluconazole, for the treatment of HIV-associated CM with all-cause mortality as the primary efficacy endpoint.

Objectives

The primary objective is to determine whether single, high-dose L-AmB given with 14 days of high-dose fluconazole and flucytosine is non-inferior to seven days of daily-dosed amphotericin B deoxycholate given with seven days of flucytosine, followed by seven days of high-dose fluconazole in terms of all-cause mortality in HIV-associated CM patients.

Setting

The trial will be conducted in six large referral hospitals across five countries in sub-Saharan Africa. The sites include: Princess Marina Hospital, Gaborone, Botswana; Mitchells Plain District Hospital, Cape Town, South Africa; Parirenyatwa Central Hospital, Harare, Zimbabwe; Queen Elizabeth Central Hospital, Blantyre, Malawi; Kamuzu Central Hospital, Lilongwe, Malawi; and the Infectious Diseases Institute, Kampala and Mbarara, Uganda.

Outcome measures

The primary outcome measure is all-cause mortality within the first ten weeks after randomisation (non-inferiority). Secondary outcome measures include: EFA derived from serial lumbar punctures (LPs) on days 1, 7 and 14; proportions of patients in each arm developing clinical and DAIDS laboratory-defined grade III/IV AEs; median % change from baseline in laboratory defined parameters; PK parameters and PK/PD associations of single high-dose L-AmB; health service costs; all-cause mortality within the first two and four weeks; all-cause mortality within the first ten weeks (superiority analysis); rates of cryptococcal relapse / IRIS within the first ten weeks; and disability at ten weeks.

Sample size

The WHO now recommends seven days amphotericin B deoxycholate-based regimens for the treatment of CM if flucytosine is available as an adjunctive antifungal. A non-inferiority design has been chosen as the primary aim of this trial is to identify an alternative safe and easy to administer short-course L-AmB treatment regimen that can be implemented in settings where giving amphotericin B deoxycholate-based treatment is difficult or impossible. An efficacious single dose L-AmB treatment would also markedly facilitate CM therapy in settings currently using amphotericin B deoxycholate-based treatment, reducing the duration of hospitalisation and the associated risks (e.g. nosocomial sepsis) and costs. Ten-week mortality in our previous trials using amphotericin B deoxycholate-based regimens at the study sites has been in the range of 28–41% [13, 29]; it was 30% with short-course high-dose L-AmB treatments in the recent phase II study. Assuming 35% ten-week mortality in both the control and test groups and using a 10% non-inferiority margin (i.e. the upper margin of the one-sided 95% CI of the difference in ten-week

mortality between the two arms does not exceed 10%) and one-sided 5% type one error, 390 participants would be required per arm to achieve 90% power. This sample size will also have 83.25% power at a one-sided $\alpha = 0.025$ or two-sided $\alpha = 0.05$. The 10% non-inferiority margin has been chosen to ensure that only clinically unimportant differences are deemed non-inferior and is in keeping with conventional practice. If the ten-week mortality is increased to 40% the equivalent sample size is 412 per arm. Making a conservative allowance for withdrawals and losses to follow-up of up to 8% (losses are in the range of 2–4% in similar trials [10]), or a higher than anticipated mortality rate, we plan to enrol 425 participants per arm. Thus, we will randomise a total of 850 participants. This will be the largest CM treatment trial conducted in Africa.

Inclusion and exclusion criteria

Consecutive patients aged ≥ 18 years with a first episode of CM (confirmed by either India ink or cryptococcal antigen [CrAg] test in the CSF) will be enrolled. Participants must be HIV-infected or willing to undertake an HIV test if their status is unknown. Participants must provide written informed consent or, if unable to consent, have a next of kin who agrees to the patient participating in the study, providing written consent. Pregnant (confirmed by urinary or serum pregnancy test) or lactating women, patients with a previous serious reaction to study drugs, or patients on antifungal treatment at CM treatment doses (amphotericin B deoxycholate ≥ 0.7 mg/kg or fluconazole ≥ 800 mg/day) for > 48 h or concomitant medication that is contraindicated with the study drugs at the time of assessment will be excluded.

Consent

Written informed consent to enter the trial and be randomised will be obtained from participants or, in the case of those lacking capacity to consent, from next of kin with legal responsibility (if appropriate and in keeping with national guidance and regulations). Consent will be obtained after explanation of the aims, methods, benefits and potential hazards of the trial, and before any trial-specific procedures are performed or any blood is taken for the trial. Once the patient's mental status improves and they regain the capacity to consent, persons enrolled via surrogate consent will be re-consented, with care taken to ensure they understand that they are: (1) free to withdraw from the research study; and (2) if they do withdraw, this will not jeopardise their future care. Patients who withdraw will revert to the standard of care at the treatment site (usually amphotericin B deoxycholate and fluconazole daily for two weeks or fluconazole monotherapy for two weeks). It will be made unambiguously clear that the participant (or guardian) is free to refuse to participate in all or any aspect of the research trial, at any time and for any reason, without incurring any penalty or affecting their access to the standard treatment available at the recruiting site (or that of their relative). Separate consent forms will be completed for the storage and/or genetic analysis of samples as determined by local guidelines. Original signed consent forms will be kept by the investigator and documented in the electronic case report form (eCRF), a copy given to the participant or family and a copy placed in the participant's medical notes.

Allocation

Patients will be randomised individually using a computer-generated programme. Randomisation codes will be generated via a permuted-block randomisation method and stratified by site. Block sizes will vary at four and six. Randomisation lists will be created for each site by an independent statistician and each list will be housed on the electronic data capture system (EDC) for that particular site. The full lists will be inaccessible to trial staff. Randomised allocation for each trial participant will be provided to trial staff from the randomisation list for that site. Internally, the EDC selects against the electronic randomisation and guarantees to make the selection in the natural order of the list. Once a selection is made, the randomisation record is tagged with the participant study allocated identifier, date and time of randomisation, and other EDC system audit values (username, machine name, etc).

Interventions

Participants will be randomised to receive either intravenous L-AmB 10 mg/kg on day 1 given with 14 days of oral fluconazole 1200 mg/day and oral flucytosine 100 mg/kg/day (intervention) or intravenous amphotericin B deoxycholate 1 mg/kg/d for seven days given with seven days of oral flucytosine 100 mg/kg/day followed by seven days of oral fluconazole 1200 mg/day (control) (Fig. 2). After the two-week induction phase, all participants will then receive oral fluconazole 800 mg/day to complete ten weeks therapy and 200 mg/day thereafter. ART will be commenced four to six weeks after initiation of antifungal therapy, in line with national guidelines. Given the combination of oral and intravenous therapies, the differing duration in days of intravenous therapy and the known drug-induced toxicities that require monitoring and managing, blinding of treatment allocation was deemed to be impractical. To counter this, an objective endpoint of all-cause mortality has been chosen. In addition, all staff performing quantitative cell cultures are blind to treatment, as are coordinating investigators, including the Trial Management Group (TMG) members.

Rescue medication

Although the results from our phase II trial demonstrate that it is unlikely that CSF fungal burden will increase

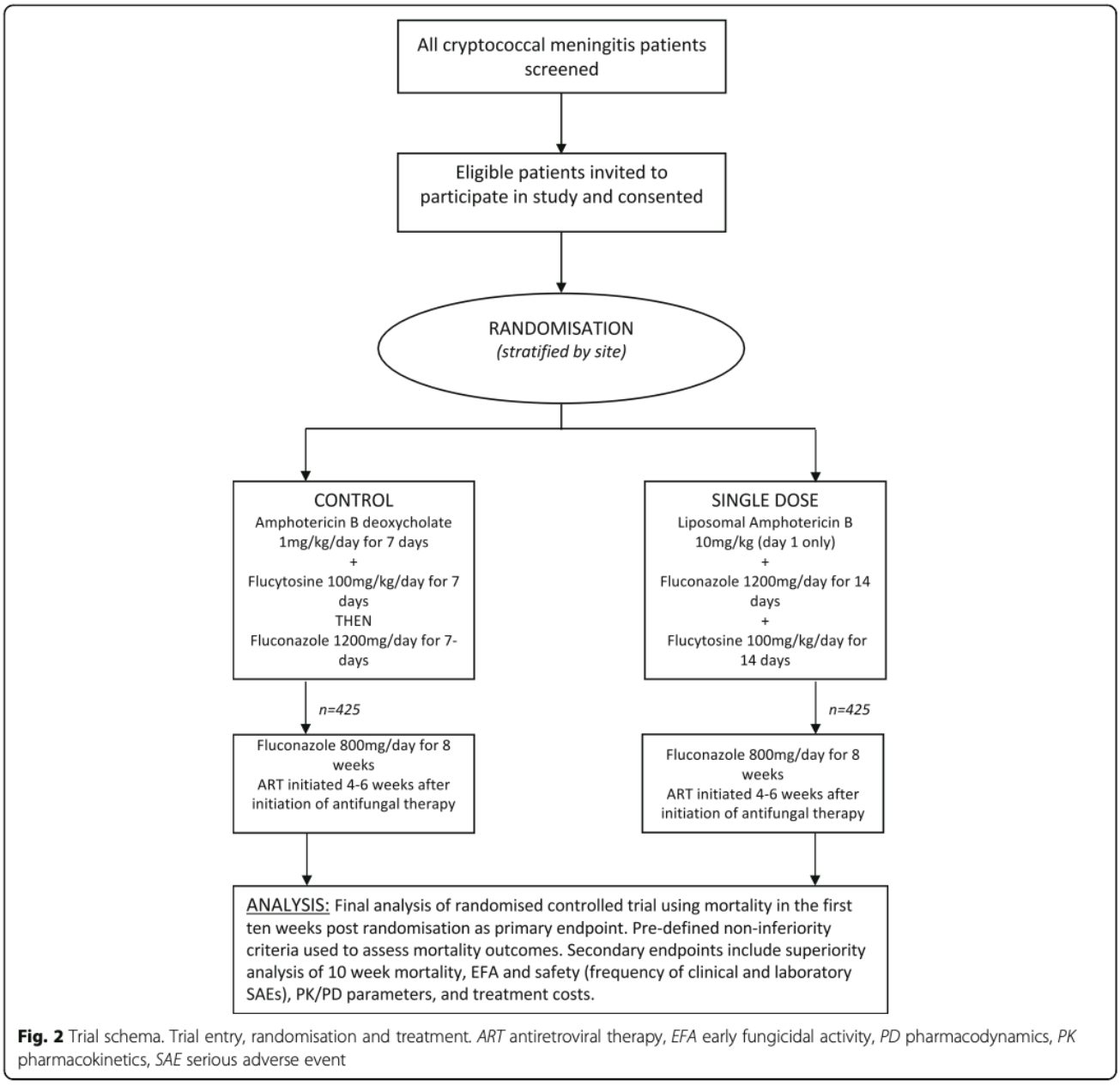

Fig. 2 Trial schema. Trial entry, randomisation and treatment. *ART* antiretroviral therapy, *EFA* early fungicidal activity, *PD* pharmacodynamics, *PK* pharmacokinetics, *SAE* serious adverse event

after initiation of treatment, if the day 7 LP identifies an increase in CFU from baseline this will be reported as a serious adverse event (SAE) and experienced, senior clinicians at the coordinating centre will be responsible for managing this situation on a case-by-case basis to ensure all participants receive effective induction therapy.

Schedule

All participants will be admitted to hospital for a minimum of one week. As the induction phase occurs over two weeks if participants are well enough to be discharged after day 7 and before day 14, treatment will be given under close outpatient supervision during the second week, ensuring compliance to the trial intervention and facilitating close clinical and laboratory monitoring. After the intensive phase, participants will be seen in clinic at four, six, eight and ten weeks and a single telephone follow-up to ascertain vital status and level of disability will be made at week 16. Every effort will be made (e.g. with mobile telephone calls, home visits and financial help with travelling expenses) to obtain accurate and complete follow-up data for ten weeks after the start of treatment. Particular attention will be paid to the possibility, in ART-naïve participants, of developing IRIS after starting ART [30].

Participants will have a full history and examination at baseline (Table 1). Blood will be drawn for full blood count (FBC), urea, creatinine, electrolytes and alanine transaminase (ALT). If unknown, HIV serology will be

Table 1 Schedule of enrolment, interventions and assessments adapted from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure

	Screening	Week 1							Week 2							Week 4	Week 6	Week 8	Week 10	Week 16
Study day	≤D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14					
Consent and randomisation																				
Eligibility criteria	X	X																		
PIS and signed consent	X	X																		
Randomisation	X	X																		
Treatment																				
Intervention: Ambisome 10 mg/kg		X																		
Intervention: Fluconazole 1200 mg/day		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Intervention: Flucytosine 100 mg/kg/day		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Control: Amphotericin B deoxycholate 1 mg/kg		X	X	X	X	X	X	X												
Control: Flucytosine 100 mg/kg/day		X	X	X	X	X	X	X												
Control: Fluconazole 1200 mg/day									X	X	X	X	X	X	X					
All participants: Fluconazole 800 mg/day															X	X	X	X	X	
All participants: 200 mg/day																			X	X
Clinical, safety and compliance assessment																				
Inpatient clinical review		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Outpatient follow-up																X	X	X	X	
Week 16 telephone																				X
Clinical labs																				
HIV testing		X																		
Pregnancy test (urine/serum)[a]		X																		
Full blood count		X						X							X	X				
CD4 count		X																		
ALT		X						X							X	X				
Urea, creatinine and electrolytes		X		X		X		X			X		X		X	X				
Drug levels		X						X												
Quantitative PCR sub-study		X		X				X							X					
Semi-quantitative cryptococcal antigen		X																		
CSF																				
Opening pressure		X						X							X					
Cell count and differential[b]		X																		
Protein, glucose[b]		X																		

Table 1 Schedule of enrolment, interventions and assessments adapted from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure *(Continued)*

	Screening	Week 1							Week 2							Week 4	Week 6	Week 8	Week 10	Week 16
Study day	≤D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14					
Routine culture[b]		X																		
India ink examination[b,c]		X																		
Cryptococcal antigen[b,c]		X																		
Quantitative fungal culture		X						X							X					
CSF drug levels		X						X							X					
Immune parameters		X						X							X					
Semi-quantitative cryptococcal antigen		X																		

[a]For women of childbearing age; [b]Part of routine care; [c]India ink or cryptococcal antigen required for inclusion

performed in addition to CD4 and viral load samples, as clinically indicated. Women of reproductive age will have a pregnancy test (urine or serum). All participants will have an LP for opening pressure, total and differential white cell count, protein, glucose, India ink, CrAg, routine culture, quantitative fungal culture and immune parameters. Further blood samples will be collected on days 3, 5, 7, 10, 12, 14 and 28 for urea and creatinine. FBC and ALT will be repeated on days 7, 14 and 28. Additional samples will be taken alongside monitoring blood tests for sub-studies, including PK/PD studies. LPs will be repeated on days 7 and 14 for opening pressure, quantitative fungal culture, CSF drug levels and immune parameters. Raised intracranial pressure will be managed with LPs as per a standard operating procedure. Cryptococcal clearance rates will be calculated using summary statistics for each patient: the rate of decrease in $\log_{10}$ CFU per mL CSF per day derived from the slope of the linear regression of $\log_{10}$ CFU against time for each patient. A linear regression model will be used to compare mean rates of decline EFA for each arm, giving summary differences with 95% CI and significance levels [31, 32]. We will adjust analyses for potential confounding factors, including baseline fungal burden. Disability at ten weeks will be assessed using two simple questions and a modified Rankin scale.

Statistical methods

The primary endpoint (all-cause mortality at ten weeks) will be analysed using a generalised linear model (GLM). The model will have treatment group as the sole predictor, a binomial distribution and an identity-link function, from which the (unadjusted) risk difference between the treatment groups and its one-sided 95% CI will be estimated. If the upper limit of the one-sided 95% CI falls below the non-inferiority margin of 10%, non-inferiority will be declared. Sensitivity analyses of the primary endpoint making different assumptions for the losses to follow-up will be conducted. Covariate-adjusted analyses for the primary endpoint will be conducted by adding pre-specified covariates into the GLM model to derive the adjusted risk difference and the upper limit of one-sided 95% CI. Imputation for baseline missing covariates will be made for the covariate-adjusted analysis. Subgroup analysis of the primary endpoint will also be performed on prespecified covariates.

The analyses of the secondary endpoints will be based on superiority test using a 5% two-sided significance level. Analyses of survival data will be conducted using unadjusted Cox regression analysis to calculate the HR and 95% CI between the treatment groups. Kaplan–Meier survival curves by treatment group will be calculated and displayed. A log-rank test will be conducted to compare the survival curves between the treatment groups. Analyses of binary secondary outcomes will be performed in a similar way as the primary endpoint analysis using GLMs with treatment group as the sole predictor. The point estimate of the treatment effect with two-sided 95% CI will be derived. The safety analysis will be descriptive and the frequency and proportions of participants suffering clinical and laboratory-defined side effects will be generated by treatment arms. Other statistical analyses may be performed if deemed necessary.

Data will be analysed using SAS 9.4 and Stata 13. Findings will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomised controlled trials. Primary analyses will be based on the intention-to-treat population and secondary analyses will be based on the per-protocol population. All analyses will be described in detail in the finalised and signed statistical analysis plan before data are locked and unblinding occurs.

Dissemination of results

The results of the trial will be analysed, presented and published as soon as possible. The TMG will form the basis of the Writing Committee and will advise on the nature of the publication. The names of all investigators will be included in the authorship of any publication. An authorship policy will be agreed by all investigators before the commencement of the trial. The independent members of the Trial Steering Committee (TSC) and DMC will be listed with their affiliations in the acknowledgements or appendix sections of the main publication. The funders will have no role in the decision to publish or the content of the publication.

Ethical approval

The Research Ethics Committee of the London School of Hygiene and Tropical Medicine have approved the protocol v2.1 07.11.17 (ref. 14,355). Approval has also been granted by the following: University of Botswana Office of Research and Development (UBR/RES/IRB/BIO/042); Botswana Ministry of Health and Wellness Health Research and Development Division (HPDME:13/18/1); Princess Marina Hospital Research and Ethics Committee (PMH 5/79(407-1-2017); University of Cape Town Human Research Ethics Committee (642/2017); Malawi National Health Sciences Research Committee (1907); Mulago Hospital Research and Ethics Committee (MHREC 1297); and the Medical Research Council of Zimbabwe (MRCZ/A/2263). Any amendments will be submitted and approved by each ethics committee.

Timeline

In total, 850 participants will be recruited over a three-year period with a planned trial completion date of

31 December 2020. This is feasible based upon previous experience and rates of CM at the hospital sites.

Ancillary studies

PK/PD

The PK/PD of L-AmB, fluconazole and flucytosine and the impact of PK variability on outcome will be described. Plasma samples will be collected at the end of the L-AmB infusion and then at 2, 4, 8, 12 and 24 h in a sub-study of participants at the Blantyre study site. A portion (0.5 mL) of the CSF sample obtained for quantitative counts will be reserved to measure fluconazole and flucytosine concentrations and thereby estimate the extent of penetration of these drugs into the CSF. Amphotericin levels will not be measured in CSF since they are known to be negligible. A PK-PD model will be constructed to explore the persistence of amphotericin B within the central nervous system and the resultant antifungal effect. Amphotericin penetration into the CNS will be estimated using compartmental modelling techniques. Monte Carlo simulation will enable further insights into the regimen(s) that may be associated with maximal antifungal activity.

Economic analysis

An economic analysis will be conducted to provide evidence for the cost-effectiveness of short-course L-AmB treatment. The objective of the economic analysis is to estimate the cost consequences and the cost-effectiveness of short-course L-AmB treatment compared to current care. Both societal and healthcare perspectives are chosen and health service patient costs including household costs, treatment cost and hospitalisations in both arms will be compared over the trial period in a probabilistic approach, using Monte Carlo bootstrapping methods in STATA, @Risk software and TreeAge. In the country-specific cost-consequence analyses, the societal and health service costs will be compared and used along with the trial-wide primary endpoint data to perform cost-effectiveness modelling using a decision-tree model for each country with historical data as comparison.

Semi-quantitative CrAg testing and diagnostic quantitative polymerase chain reaction (PCR)

A newly developed point of care, lateral flow, semi-quantitative CrAg test is now available from Institut Pasteur and Biosynex. We will use this semi-quantitative test in real time to determine antigen titre at baseline, in blood and CSF, and compare results to the currently established point of care test. Secondary trial analyses will include the association of baseline titre with outcome and exploration of the possibility of a differential treatment response between arms according to baseline titre. If such a differential response was observed, this sub-study could provide the rationale for and demonstrate the means for individualised treatment, based on a rapid assessment of antigen load. A novel diagnostic quantitative PCR (DNA and RNA) tool will be also be used in each treatment arm and correlated with quantitative culture counts. We aim to estimate the fungal load and fungal viability in blood and CSF at baseline using the PCR in addition to fungal load kinetics on treatment. The objective will be to develop a practical alternative to time-consuming quantitative cultures in order to improve detection of fungaemia and measurement of fungal burden and develop a novel biomarker for assessing the best fungicidal treatments in this and subsequent research studies.

Quality control and assurance

Trial oversight will be provided by the TMG, TSC and Independent DMC. The study sponsor is the London School of Hygiene and Tropical Medicine. The sites will be monitored at regular intervals with visits by the trial manager/monitor in order to monitor the conduct of the trial and ensure that the principles of International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) are being adhered to. Sites will be visited by an internal monitor for initiation visits before starting recruitment, after the first 10–15 participants, at 40% and 70% of recruitment targets and at trial closure, with additional visits made if required. Visits will ensure that all training has been completed, that drug supply and equipment are in place and that all staff are up to date on the protocol and procedures. A monitor from the Sponsor will visit at least three of the six sites. Central monitoring will be performed in addition to the on-site monitoring procedures. Bimonthly reports on the progress of the trial as well as the frequency of DAIDS laboratory-defined grade III/IV AEs/SAEs/suspected unexpected serious adverse events (SUSARs) will be compiled by the trial manager/statistician and reviewed by the Sponsor. All Grade IV AEs, all SAEs and all SUSARs will be reported to the TMG within 24 h [27].

Data collection and data management

eCRF data collected and validated using the EDC will be stored in an electronic database that is protected using a scheme of authentication and encryption. Paper documents, such as clinical notes and administrative documentation, will be kept in a secure location and held for at least five years after the end of the trial. During this period, all data should be accessible to the competent or equivalent authorities, the sponsor and other relevant parties with suitable notice. Security of electronic records and data is a significant concern. All components of the distributed data systems will use authentication and encryption to render subject identity and personal health information unusable, unreadable or indecipherable to

unauthorised individuals. Full drive encryption will be implemented at the hardware layer of all devices storing protected health information. A three-factor scheme will be used to authenticate users through the hardware layer to the application layer where personal health information is available. The applications will have user profiles to control access to certain data and reports. The application and database layers will use a combination of hashing and encryption for sensitive and personal data. Mobile devices and the staff operating them will not be equipped with the encryption keys to decrypt selected sensitive data fields.

Confidentiality

We will follow the principles of the UK Data Protection Act (DPA) regardless of the countries where the trial is being conducted. Consent forms will be stored under the supervision of each local primary investigator (PI) in a secured office and accessible to trial staff only. Participants' personal details are stored in an encrypted, separate server to the main database and participants are identified by their study number throughout the trial.

Termination of the study

The trial will be considered closed when the last patient has completed ten weeks of active follow-up in the study, the 16-week telephonic follow-up call, and all follow-up and laboratory reports, including repeat plasma HIV viral load testing in ART failure cases, have been received. Early termination could occur if the DMC decides there is an unacceptable level of AEs in either test arm or if the intervention arm is shown to be inferior with stringent p value testing.

Indemnity

The sponsor of the trial is the London School of Hygiene and Tropical Medicine and as such provides indemnity for the trial. All personnel involved in the trial will be expected to be indemnified by their employing authority. Local insurance will be taken out where local regulations require this.

Discussion

The potential impact of a safe, sustainable regimen of high-dose L-AmB with non-inferior efficacy when compared to one week of daily-dosed amphotericin B deoxycholate would be to reduce the number of AEs seen in patients treated with amphotericin and shorten the length of hospital admissions. It is hoped that our economic analysis will demonstrate the cost-effectiveness of this intervention across all our sites in southern Africa and provide a highly favourable alternative to the current WHO-recommended first-line treatment.

Trial status

The study is jointly funded through the European and Developing Countries Clinical Trials Partnership (EDCTP), Swedish International Development Cooperation Agency (SIDA) and Wellcome Trust / Medical Research Council (UK) / UKAID Joint Global Health Trials. Recruitment commenced in Botswana in January 2018 and in South Africa in July 2018; recruitment will commence at the other sites pending the requisite ethical and regulatory approvals.

Additional files

Additional file 1: AMBITION Study Protocol v2.1 date: 7th November 2017. (PDF 1954 kb)

Additional file 2: AMBITION Study SPIRIT Checklist. (DOC 121 kb)

Abbreviations

5FC: Flucytosine; ACTA: Advancing Cryptococcal Meningitis Treatment for Africa; AE: Adverse event; ALT: Alanine transaminase; AMBITION: AMBIsome Therapy Induction OptimisatioN; ART: Antiretroviral therapy; CFU: Colony-forming units; CI: Confidence interval; CM: Cryptococcal meningitis; CrAg: Cryptococcal antigen; CSF: Cerebrospinal fluid; DAIDS: Division of AIDS; DMC: Data Monitoring Committee; DPA: Data Protection Act; eCRF: Electronic case record form; EDC: Electronic data capture; EDCTP: European and Developing Countries Clinical Trials Partnership; EFA: Early fungicidal activity; FBC: Full blood count; GCP: Good Clinical Practice; GLM: Generalised linear model; HR: Hazard ratio; ICH: International Conference of Harmonisation; IRIS: Immune reconstitution inflammatory syndrome; L-AmB: Liposomal amphotericin B deoxycholate; LP: Lumbar puncture; LSHTM: London School of Hygiene and Tropical Medicine; NI: Non-inferiority; PD: Pharmacodynamics; PI: Primary investigator; PK: Pharmacokinetics; SAE: Serious adverse event; SAR: Serious adverse reaction; SUSAR: Suspected unexpected serious adverse reaction; TMG: Trial Management Group; TSC: Trial Steering Committee; USD: United States Dollar; WHO: World Health Organization

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Funding

The study is jointly funded through the European and Developing Countries Clinical Trials Partnership (EDCTP), Swedish International Development Cooperation Agency (SIDA) and Wellcome Trust / Medical Research Council (UK) / UKAID Joint Global Health Trials. The AmBisome for the trial has been donated by Gilead. The funders had no role in the design of the trial, nor will they be involved in the collection, analysis and interpretation of data or the preparation of manuscripts. Katharine Stott is a Wellcome Trust Clinical PhD Fellow (203919/Z/16/Z).

Availability of data and materials

Not applicable.

Authors' contributions

DSL wrote the initial manuscript and is the International Lead Clinician for the AMBITION study. NY and SM helped write the manuscript and are the International Trial Manager and Trial Epidemiologist, respectively. DRB, AH, MH, CK, DBM, MM, CM, HCM, CEN and CS are site investigators. TC and DW are statisticians for the study. LN leads the Health Economics sub-study. KES and WH oversee the PK/PD sub-study. AA, OL, FD and TBC coordinate the

semi-quantitative CrAg and qPCR sub-studies. TBC is international clinical adviser to the study. AL is an expert adviser within the TMG. SJ, DGL and GM provided expert input into the conceptualisation and design of the study. TSH conceived and designed the trial and is the co-principal investigator. JNJ conceived and designed the trial and is the co-principal investigator. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Research Ethics Committee of the London School of Hygiene and Tropical Medicine (ref. 14,355) have approved the protocol. We will not begin recruitment at any of the African sites until local ethical approval has been obtained. Any further amendments will be submitted and approved by each ethics committee.

Written informed consent to enter the trial and be randomised will be obtained from participants or, in the case of those lacking capacity to consent, from family/guardians/persons with legal responsibility (if appropriate and in keeping with national guidance and regulations). Consent will be obtained after explanation of the aims, methods, benefits and potential hazards of the trial, and before any trial-specific procedures are performed or any blood is taken for the trial. Patients with altered mental status who are unable to consent will be enrolled into the study if their next of kin gives informed consent or assent (in keeping with appropriate national guidance and regulations) on their behalf. As soon as the patient's mental status improves consent will be obtained as above, with care taken to ensure they understand that they are free to withdraw from the study and if they do so this will not jeopardise their future care. Participants who withdraw will revert to the standard of care at the treatment site (usually amphotericin B deoxycholate and fluconazole daily for two weeks or fluconazole monotherapy for two weeks). It must be made completely and unambiguously clear that the participant (or guardian) is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their access to the standard treatment available at the recruiting site (or that of their relative). Separate consent forms will be completed for the storage and/or genetic analysis of samples as determined by local guidelines. Original signed consent forms will be kept by the investigator and documented in the eCRF, a copy given to the participant or family and a copy placed in the participant's medical notes.

Consent for publication

Not applicable.

Competing interests

JNJ and TSH were the recipients of a Gilead Investigator Initiated Award (completed). TSH has received speaker fees from Gilead Sciences and Pfizer.

Publisher's Note

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Appendix 11: Additional Publication - AMBITION-cm Trial Results. New England Journal of Medicine.

The NEW ENGLAND JOURNAL of MEDICINE

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Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

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ABSTRACT

BACKGROUND

Cryptococcal meningitis is a leading cause of human immunodeficiency virus (HIV)–related death in sub-Saharan Africa. Whether a treatment regimen that includes a single high dose of liposomal amphotericin B would be efficacious is not known.

METHODS

In this phase 3 randomized, controlled, noninferiority trial conducted in five African countries, we assigned HIV-positive adults with cryptococcal meningitis in a 1:1 ratio to receive either a single high dose of liposomal amphotericin B (10 mg per kilogram of body weight) on day 1 plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) or the current World Health Organization–recommended treatment, which includes amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) for 7 days (control). The primary end point was death from any cause at 10 weeks; the trial was powered to show noninferiority at a 10-percentage-point margin.

RESULTS

A total of 844 participants underwent randomization; 814 were included in the intention-to-treat population. At 10 weeks, deaths were reported in 101 participants (24.8%; 95% confidence interval [CI], 20.7 to 29.3) in the liposomal amphotericin B group and 117 (28.7%; 95% CI, 24.4 to 33.4) in the control group (difference, −3.9 percentage points); the upper boundary of the one-sided 95% confidence interval was 1.2 percentage points (within the noninferiority margin; P<0.001 for noninferiority). Fungal clearance from cerebrospinal fluid was −0.40 $\log_{10}$ colony-forming units (CFU) per milliliter per day in the liposomal amphotericin B group and −0.42 $\log_{10}$ CFU per milliliter per day in the control group. Fewer participants had grade 3 or 4 adverse events in the liposomal amphotericin B group than in the control group (50.0% vs. 62.3%).

CONCLUSIONS

Single-dose liposomal amphotericin B combined with flucytosine and fluconazole was noninferior to the WHO-recommended treatment for HIV-associated cryptococcal meningitis and was associated with fewer adverse events. (Funded by the European and Developing Countries Clinical Trials Partnership and others; Ambition ISRCTN number, ISRCTN72509687.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Jarvis can be contacted at joseph.jarvis@lshtm.ac.uk or at the Botswana–Harvard AIDS Institute Partnership, Private Bag BO320, Gaborone, Botswana.

*A list of the Ambition Study Group members is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Jarvis and Lawrence contributed equally to this article.

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Cryptococcal meningitis is the most frequent cause of adult meningitis in areas with a high prevalence of human immunodeficiency virus (HIV)[1,2] and is the second leading cause of HIV-related death worldwide, with the majority of deaths occurring in sub-Saharan Africa.[3] Despite widened access to antiretroviral therapy, there is a persistent burden of advanced HIV disease in the sub-Saharan African region,[4-6] and the number of cryptococcal meningitis cases remains high.[6,7]

Poor outcomes with conventional antifungal treatment regimens are a key driver of the high mortality from cryptococcal meningitis, with a high incidence of toxic effects with the commonly used 2-week amphotericin B deoxycholate–based regimens and poor efficacy with fluconazole monotherapy, which has been associated with a 10-week mortality in excess of 50%.[8,9] In 2018, after the publication of the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial,[10] the World Health Organization (WHO) updated international guidelines to recommend induction therapy with the less toxic and more efficacious 1-week regimen of amphotericin B deoxycholate and flucytosine in resource-limited settings.[11] However, even 1 week of treatment with amphotericin B deoxycholate is associated with anemia, kidney impairment, and electrolyte abnormalities,[8] and administering and monitoring intravenous amphotericin for 7 days poses logistic challenges in many clinical settings.

Liposomal amphotericin B is potentially well suited for use in short-course induction treatments of cryptococcal meningitis because it can be given at higher doses owing to a lower incidence of drug-induced toxic effects,[12-14] has a long tissue half-life,[12,13,15-17] and effectively penetrates into brain tissue.[12,18,19] The concept of a single high-dose intravenous infusion of liposomal amphotericin B has been established in the treatment of visceral leishmaniasis,[20] and pharmacokinetic data from animal models and humans indicate that increasing the dose of liposomal amphotericin B from the currently recommended dose of 3 to 4 mg per kilogram of body weight may lead to improved outcomes in patients with cryptococcal meningitis and that short-course regimens may be as effective as daily therapy.[15,16,21,22] In a phase 2 clinical trial, investigators assessed the efficacy of a short-course regimen with a single high dose of liposomal amphotericin B, two high doses of liposomal amphotericin B given on days 1 and 3, or three high doses of liposomal amphotericin B given on days 1, 3, and 7, as compared with the control regimen of 14 daily doses of 3 mg per kilogram of liposomal amphotericin B (all four regimens included 14 days of high-dose fluconazole); they showed that the rate of fungal clearance from the cerebrospinal fluid with any of the three short-course, high-dose regimens was noninferior to that in the control group.[23] Maximal fungicidal activity was attained with a single 10-mg-per-kilogram dose of liposomal amphotericin B, and there was no evidence that additional doses led to greater benefit — findings that are in keeping with the data obtained from animal models.[22,24] No safety concerns have been identified with the use of high-dose liposomal amphotericin B, which has a better adverse-effect profile than that observed with amphotericin B deoxycholate in previous trials.[8,23]

On the basis of the findings of the phase 2 trial[23] and the data from a phase 3 trial that showed a role for flucytosine in the induction treatment of cryptococcal meningitis,[10] we conducted an open-label, phase 3, randomized, controlled, noninferiority trial (the Ambition trial) to test a single high dose (10 mg per kilogram) of liposomal amphotericin B given with oral flucytosine and fluconazole for 2 weeks[10] against the WHO-recommended first-line induction treatment with 1 week of amphotericin B deoxycholate plus flucytosine followed by 1 week of high-dose fluconazole.

METHODS

TRIAL DESIGN AND OVERSIGHT

The trial design has been described previously,[25] and the details are provided in the trial protocol, available with the full text of this article at NEJM.org. The protocol was approved by the London School of Hygiene and Tropical Medicine Research Ethics Committee and by the relevant ethics committees and national regulatory agencies overseeing the trial sites. All the participants provided written informed consent. If a participant had abnormal mental status, written informed consent was obtained from the next of kin; if a participant recovered the capacity to provide consent, written informed consent was obtained from that participant. An independent data-monitoring committee oversaw the trial and reviewed the trial data regularly. The trial funders,

suppliers, and drug manufacturers had no role in the design of the trial; in the collection, analysis, or interpretation of the data; or in the preparation of the manuscript or the decision to submit it for publication. Liposomal amphotericin B was donated by Gilead Sciences; amphotericin B deoxycholate was purchased from Bristol Myers Squibb; flucytosine was purchased from Mylan; and fluconazole was purchased from Cipla–Medopharm. At sites where the Pfizer Diflucan Partnership Program was operational, fluconazole donated by Pfizer was used if available. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol.

TRIAL PARTICIPANTS

HIV-positive adults (≥18 years of age) who had a first episode of cryptococcal meningitis, as diagnosed on the basis of a positive India ink stain or cryptococcal antigen test (CrAg lateral flow assay, IMMY) of a cerebrospinal fluid sample, were recruited from eight hospitals: Princess Marina Hospital, Gaborone, Botswana; Queen Elizabeth Central Hospital, Blantyre, and Kamuzu Central Hospital, Lilongwe, Malawi; Mitchells Plain Hospital and Khayelitsha Hospital, Cape Town, South Africa; Kiruddu National Referral Hospital, Kampala, and Mbarara Regional Referral Hospital, Mbarara, Uganda; and Parirenyatwa Central Hospital, Harare, Zimbabwe. Participants were excluded if they had received more than two doses of either amphotericin (at any dose) or fluconazole (at a dose of ≥800 mg) before screening; declined to consent or, if they had impaired capacity to consent, had no legal representative to consent on their behalf; were pregnant or breast-feeding; were taking contraindicated concomitant drugs; or had had any previous adverse reaction to a trial drug. Late-exclusion criteria, which were put in place to enable the rapid enrollment of critically ill participants pending baseline blood test results, were an alanine aminotransferase level greater than 5 times the upper limit of the normal range (>200 IU per liter), a polymorphonuclear leukocyte count of less than 500 per cubic millimeter, or a platelet count of less than 50,000 per cubic millimeter.

INTERVENTIONS AND RANDOMIZATION

Participants underwent randomization individually and were assigned in a 1:1 ratio to receive the experimental regimen that included a single dose (10 mg per kilogram of body weight) of liposomal amphotericin B (AmBisome, Gilead Sciences) plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day)[26] or the current WHO-recommended regimen, which includes amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) on days 8 through 14 (the control group). Randomization was performed with the use of a computer-generated randomization list with block sizes of four and six, stratified according to site. Randomization was performed electronically with a bespoke electronic data-capture tool in which the random-assignment sequence was concealed from all trial investigators involved in participant recruitment. The treatment-group assignments were provided to the recruiting teams after consent had been obtained and the participant enrolled. The trial medications were administered on an open-label basis.

All the participants were treated in-hospital for a minimum of 7 days. The single 10-mg-per-kilogram dose of liposomal amphotericin B was suspended in 1 liter of 5% dextrose and administered over the course of 2 hours, and the 1-mg-per-kilogram doses of amphotericin B deoxycholate were dissolved in 1 liter of 5% dextrose and administered over the course of 4 hours. Participants received 1 liter of intravenous normal saline before any amphotericin dose, plus at least 1 additional liter of intravenous fluid (5% dextrose or normal saline) on each day of amphotericin therapy. Potassium and magnesium supplements were given on each day that the participants received amphotericin and then for 2 additional days. Oral medications were administered through a nasogastric tube if participants were unable to swallow.

The results of laboratory blood tests were monitored regularly during the first 2 weeks and again at week 4. The monitoring schedule is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. Lumbar punctures for quantitative cryptococcal cultures were performed at the time of diagnosis and on days 7 and 14. Participants with increased intracranial pressure received additional daily therapeutic lumbar punctures until the pressure was controlled at less than 20 cm of water.

Participants were followed at outpatient clinics for 10 weeks and were contacted by telephone

at week 16. If a participant missed a clinic appointment, follow-up was performed by the trial teams either by telephone or in person. After the 2-week induction period, all the participants received fluconazole at a dose of 800 mg per day for 8 weeks and then at a dose of 200 mg per day thereafter. Antiretroviral therapy was initiated, reinitiated, or switched to a new antiretroviral therapy with a different agent during weeks 4 to 6 and was chosen in accordance with national guidelines.

END POINTS

The primary end point was death from any cause at 10 weeks after randomization. As prespecified in the statistical analysis plan, the primary end point was tested for superiority after noninferiority was established. Secondary end points were death from any cause at 2 weeks, 4 weeks, and 16 weeks; overall mortality in a time-to-event analysis; the rate of fungal clearance from the cerebrospinal fluid per day over the course of 14 days of induction therapy; the percentage of participants in each trial group with clinical or laboratory-defined adverse events of grade 3 or 4, as determined according to the criteria of the Division of AIDS[27]; and the median absolute or percentage change from baseline in laboratory values.

STATISTICAL ANALYSIS

Assuming 35% mortality at 10 weeks in both treatment groups, we calculated that a sample size of 390 per group (780 in total) would provide the trial with 90% power to show noninferiority of a single high dose of liposomal amphotericin B given with flucytosine and fluconazole to the current WHO recommended standard of care, with a specified noninferiority margin of 10 percentage points (the upper boundary of the one-sided 95% confidence interval of the absolute difference in mortality). The primary analysis was performed in the intention-to-treat population, which included all the participants who had undergone randomization and had not met any late-exclusion criteria. A generalized linear model with a binomial distribution was used to calculate the differences in mortality.

We performed two sensitivity analyses. First, a per-protocol analysis was performed in which participants were excluded if they had missed more than 1 day of any single treatment in the first 2 weeks or had missed more than 2 weeks of fluconazole consolidation treatment between weeks 2 and 10. Second, we performed analyses that adjusted for the prespecified covariates of trial site, age, sex, baseline Glasgow Coma Scale score, CD4+ cell count, cryptococcal colony-forming units (CFU) per milliliter of cerebrospinal fluid, antiretroviral therapy status, hemoglobin level, and cerebrospinal fluid opening pressure. In the superiority, secondary end-point, and sensitivity analyses, no adjustments were made for multiple comparisons. Analysis of log-transformed longitudinal fungal counts in the cerebrospinal fluid was performed with the use of a linear mixed-effects model, in which undetectable measurements were left-censored (i.e., sterile cultures from day 7 onward were excluded if the values lessened the slope, because sterility would have been achieved before lumbar puncture on that day and use of these values would have therefore led to an underestimation of the true slope).[28] Adverse events were evaluated in the safety population, which included all the participants who had received one or more doses of a trial medication. Analyses were conducted with the use of SAS statistical software, version 9.4 (SAS Institute). The full statistical analysis plan is provided in the protocol.

RESULTS

TRIAL POPULATION

From January 2018 through February 2021, a total of 844 participants underwent randomization (Fig. 1). Of these participants, 30 were excluded — 24 met the prespecified late-exclusion criteria (13 had a low platelet count, 5 had a low neutrophil count, 2 had an increased alanine aminotransferase level, 3 had a low platelet count and a low neutrophil count, and 1 had a low platelet count and an increased alanine aminotransferase level [Table S2]), 5 did not have cryptococcal meningitis, and 1 was HIV-negative, which left 814 participants (407 in each treatment group) in the intention-to-treat population. None were lost to follow-up. An additional 30 participants were excluded from the per-protocol population (20 had missed more than 1 day of treatment in the first 2 weeks, 6 had received incorrect treatment, and 4 had missed more than 2 weeks of fluconazole consolidation treatment between weeks 2 and 10). The baseline characteristics of the participants were similar in the trial groups (Table 1).

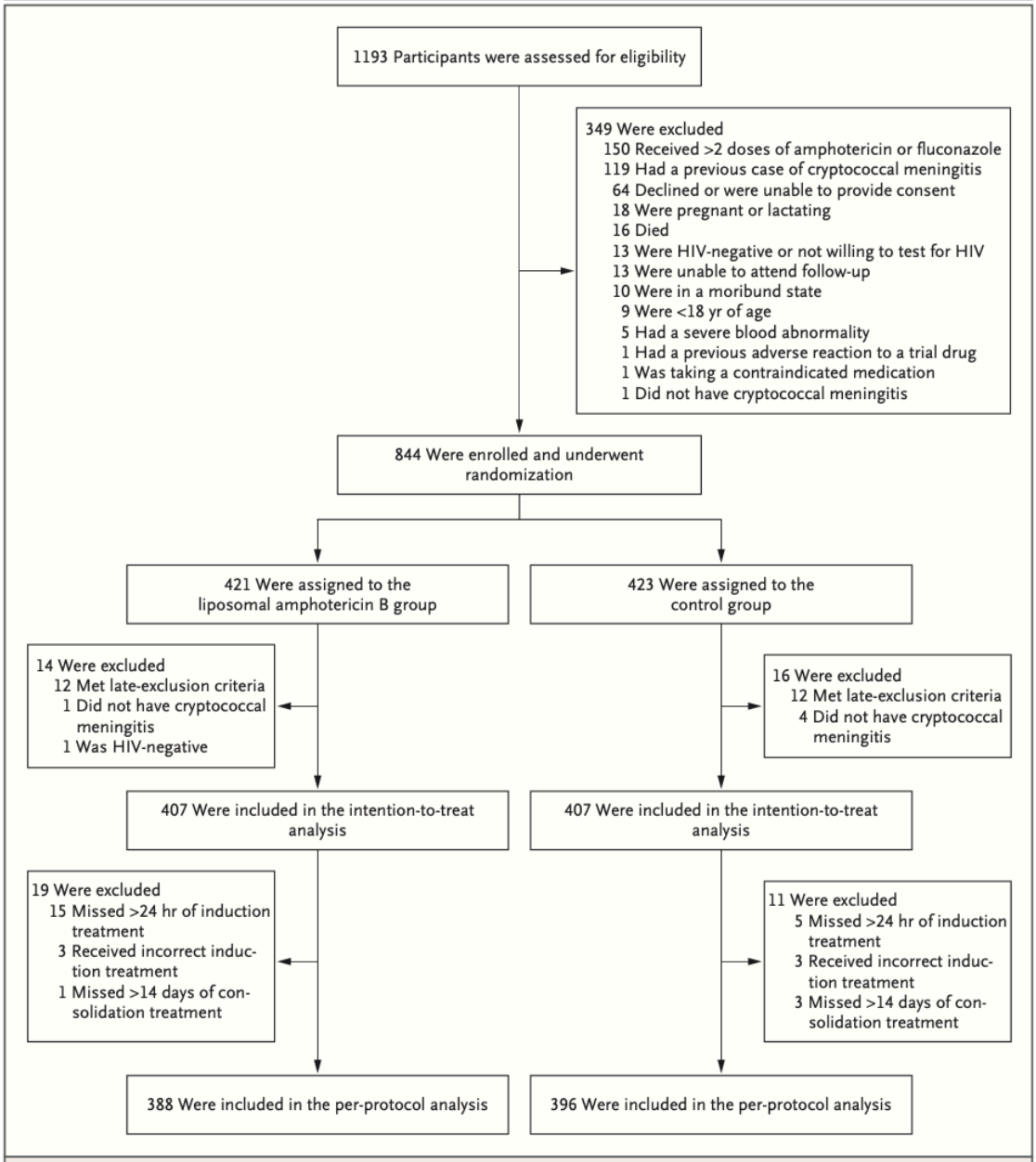

Figure 1. Screening, Randomization, and Analysis Populations.

The participants who were assigned to the liposomal amphotericin B group received a single dose of liposomal amphotericin B (10 mg per kilogram of body weight) plus 14 days of oral therapy with flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day), and the participants assigned the control group received 7 days of amphotericin B deoxycholate (1 mg per kilogram) plus flucytosine (100 mg per kilogram per day) followed by 7 days of oral therapy with fluconazole (1200 mg per day). During the first week of induction therapy, two participants in the liposomal amphotericin B group received at least one dose of amphotericin B deoxycholate, and three participants in the control group received high-dose fluconazole. Participants may have had more than one reason for exclusion. HIV denotes human immunodeficiency virus.

PRIMARY END POINT

In the intention-to-treat analysis, 10-week mortality was 24.8% (95% confidence interval [CI], 20.7 to 29.3) in the liposomal amphotericin B group (101 of 407 participants had died) and 28.7% (95% CI, 24.4 to 33.4) in the control group (117 of 407 participants had died) (Table 2 and Fig. 2A). The absolute difference in mortality at 10 weeks between the liposomal amphotericin B group and control group was −3.9 percentage

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Liposomal Amphtericin B (N=407)	Control (N=407)
Median age (IQR) — yr	37 (32–44)	37 (32–43)
Male sex — no. (%)	246 (60.4)	245 (60.2)
New diagnosis of HIV — no. (%)	127 (31.2)	118 (29.0)
Report of previous antiretroviral therapy — no. (%)†	256 (62.9)	266 (65.4)
Median weight (IQR) — kg	53 (47–60)	53 (48–60)
Headache		
Current symptom — no. (%)	390 (95.8)	394 (96.8)
Median duration (IQR) — days	14 (7–21)	14 (7–21)
Seizures within 72 hr before enrollment — no. (%)	45 (11.1)	42 (10.3)
Glasgow Coma Scale score <15 — no. (%)‡	115 (28.3)	117 (28.7)
Median values from CSF sample analysis (IQR)		
Cryptococcal quantitative value — CFU/ml	48,500 (300–420,000)	42,000 (585–365,000)
CSF opening pressure) — cm of water	21 (14–32)	21 (13–31)
CSF opening pressure >25 cm of water — no./total no. (%)	165/399 (41.4)	158/400 (39.5)
White-cell count — cells/mm^3	6 (4–75)	5 (3–52)
Glucose level — mg/dl	45 (29–61)	43 (27–58)
Protein level — g/l	0.90 (0.46–1.48)	0.84 (0.44–1.38)
Median blood hemoglobin level (IQR) — g/dl	11.2 (9.7–12.7)	11.2 (9.6–12.9)
Median serum creatinine level (IQR) — mg/dl	0.7 (0.6–0.9)	0.8 (0.6–1.0)
Median blood CD4+ cell count (IQR) — cells/mm^3	26 (9–56)	28 (11–59)

* Baseline data were missing for the following characteristics: cerebrospinal fluid (CSF) cryptococcal quantitative value (missing for 1 participant in the liposomal amphotericin B group), CSF opening pressure (missing for 8 participants in the liposomal amphotericin B group and for 7 participants in the control group), CSF white-cell count (missing for 11 and 9 participants, respectively), CSF glucose level (missing for 11 and 15 participants, respectively), CSF protein level (missing for 14 and 16 participants, respectively), hemoglobin level (missing for 2 and 1 participant, respectively), CD4+ cell count (missing for 18 and 11 participants, respectively), and creatinine level (missing for 1 participant in the liposomal amphotericin B group). To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. CFU denotes colony-forming units, HIV human immunodeficiency virus, and IQR interquartile range.

† The median interval from randomization to the reinitiation of antiretroviral therapy or switch to another therapy (for those with previous exposure to antiretroviral therapy) was 30 days in the liposomal amphotericin B group and 29 days in the control group.

‡ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating worse mental status.

points, and the upper boundary of the one-sided 95% confidence interval was 1.2 percentage points, which was within the prespecified 10-percentage-point noninferiority margin (P<0.001 for noninferiority) (Fig. 2B). In the per-protocol analysis, 10-week mortality at 10 weeks was 24.5% (95% CI, 20.3 to 29.1) in the liposomal amphotericin B group (95 of 388 participants had died) and 28.5% (95% CI, 24.1 to 33.3) in the control group (113 of 396 participants had died), for a between-group difference of –4.1 percentage points and an upper boundary of the one-sided 95% confidence interval of 1.1 percentage points.

The results of the prespecified adjusted analyses (Table 2 and Fig. 2B) and key subgroup analyses (Table S3B) were consistent with those of the primary end-point analysis. In prespecified superiority analyses performed at the 10-week time point, the between-group difference in mortality was –3.9 percentage points with the 95% confidence interval crossing zero (95% CI, –10.0 to 2.2) in the unadjusted analysis and –5.7 percentage points with the 95% confidence in-

Table 2. Primary and Key Secondary End Points.*

Outcome	Unadjusted Analysis				Adjusted Analysis†	
	Liposomal Amphtericin B	Control	Difference (95% CI)‡	Upper Boundary of One-Sided 95% CI	Difference (95% CI)	Upper Boundary of One-Sided 95% CI
				percentage points	*percentage points*	
Death from any cause at 10 wk (primary end point)						
Intention-to-treat population						
Deaths — no./total no.	101/407	117/407				
Mortality (95% CI) — %	24.8 (20.7 to 29.3)	28.7 (24.4 to 33.4)	−3.93 (−10.0 to 2.2)	1.2§	−5.71 (−11.4 to −0.04)	−1.0
Per-protocol population						
Deaths — no./total no.	95/388	113/396				
Mortality (95% CI) — %	24.5 (20.3 to 29.1)	28.5 (24.1 to 33.3)	−4.05 (−10.2 to 2.1)	1.1	−5.04 (−10.8 to 0.8)	−0.2
Early fungicidal activity (key secondary end point)						
Participants with available data in the intention-to-treat population — no.¶	363	381				
Rate of fungal clearance over the course of 14 days — $\log_{10}$ CFU/ml/day						
Mixed-effects model	−0.40±0.13	−0.42±0.13	0.017 (−0.001 to 0.036)			
Linear-regression model‖	−0.41±0.19	−0.44±0.21	0.0270 (−0.004 to 0.058)			

* Plus–minus values are means ±SD.
† The analysis was adjusted for the prespecified baseline covariates of site, age, sex, Glasgow Coma Scale score, CD4+ cell count, CSF cryptococcal quantitative culture, antiretroviral therapy status, hemoglobin level, and CSF opening pressure.
‡ The between-group difference is reported as the percentage-point difference for mortality and as absolute difference in the mean rate of fungal clearance for early fungicidal activity; the 95% confidence intervals are two-sided.
§ P<0.001 for noninferiority.
¶ Participants needed a nonsterile CSF culture at baseline to be included in this analysis.
‖ To enable comparison with previously published data regarding early fungicidal activity that were derived from individual-patient linear-regression models, data were also analyzed by means of linear regression.

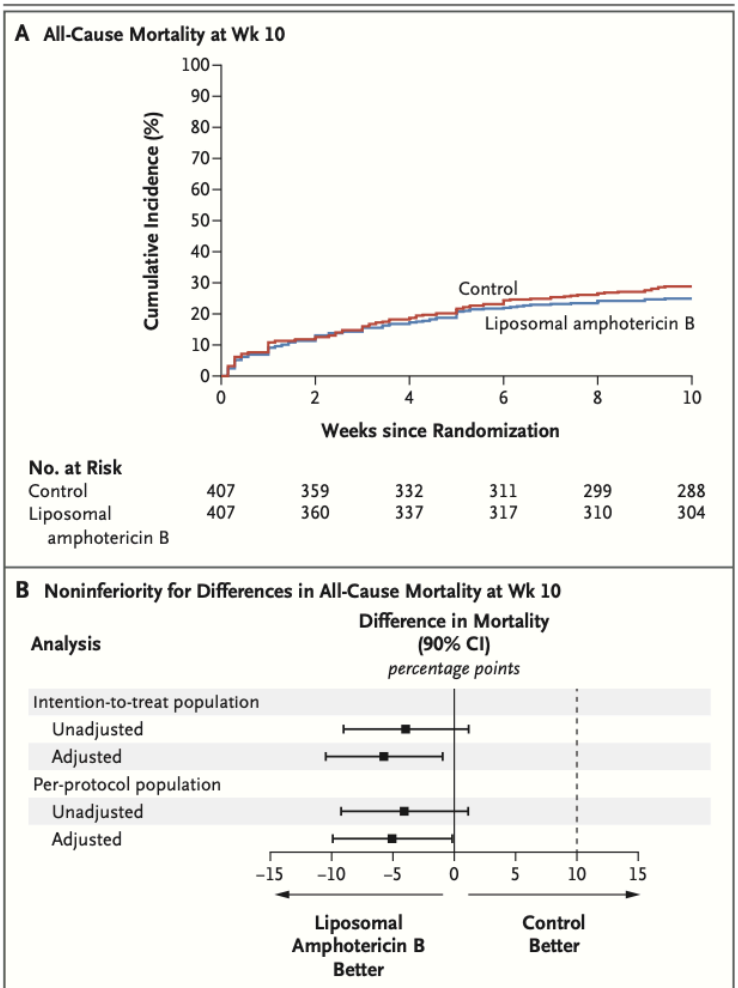

Figure 2. Cumulative All-Cause Mortality Up to Week 10 and Noninferiority Analyses.

Panel A shows the cumulative all-cause mortality up to week 10 according to treatment strategy in the intention-to-treat population. Panel B shows a noninferiority graph for the differences in all-cause mortality at 10 weeks (calculated as the value in the liposomal amphotericin B group minus the value in the control group). The mean absolute difference in 10-week mortality between the liposomal amphotericin B group and the control group and the two-sided 90% confidence intervals in both unadjusted and adjusted intention-to-treat and per-protocol analyses are shown. The dashed line indicates the prespecified 10-percentage-point noninferiority margin. The analysis was adjusted for prespecified baseline covariates of trial site, age, sex, Glasgow Coma Scale score, CD4+ cell count, cryptococcal colony-forming units per milliliter of cerebrospinal fluid, HIV therapy status, hemoglobin level, and cerebrospinal fluid opening pressure.

terval not crossing zero (95% CI, −11.4 to −0.04) in the analysis that was adjusted for the covariates associated with cryptococcal mortality.

SECONDARY END POINTS

Mortality at 2 weeks, 4 weeks, and 16 weeks is shown in Table S3. The results were consistent with the result of the primary end-point analysis of 10-week mortality, with upper boundaries of the one-sided 95% confidence intervals of less than 10 percentage points. The results of time-to-event analyses of mortality that were performed with the use of Cox regression are shown in Table S4 and Figure 2A.

The mean rate of fungal clearance from the cerebrospinal fluid over the course of 14 days was −0.40 $\log_{10}$ CFU per milliliter per day in the liposomal amphotericin B group and −0.42 $\log_{10}$ CFU per milliliter per day in the control group, for a difference of 0.017 $\log_{10}$ CFU per milliliter per day (95% CI, −0.001 to 0.036) (Table 2 and Fig. S2). Paradoxical immune reconstitution inflammatory syndrome was reported in 15 of 407 participants (3.7%) in the liposomal amphotericin B group and in 19 of 407 participants (4.7%) in the control group (Table S6). There were no cases of culture-positive relapse in the liposomal amphotericin B group. One case of relapse occurred in a participant in the control group who had received full induction therapy and had initial clearance of cryptococcus from the cerebrospinal fluid but subsequently had poor adherence to consolidation-phase fluconazole. During the initial 10 weeks of follow-up, 71 of 407 participants (17.4%) in each treatment group were readmitted to the hospital at least once (Table S7).

SAFETY AND ADVERSE EVENTS

During the initial 21 days of treatment in the safety population, there were 382 grade 3 or 4 adverse events in 210 of 420 participants (50.0%) in the liposomal amphotericin B group and 579 grade 3 or 4 adverse events in 263 of 422 participants (62.3%) in the control group (P<0.001). A summary of clinical and laboratory-defined adverse events is provided in Table 3, and a detailed list is provided in Table S8. Potentially life-threatening (grade 4) adverse events occurred in significantly fewer participants in the liposomal amphotericin B group than in the control group (91 of 420 participants [21.7%] vs. 127 of 422 participants [30.1%], P=0.005). Grade 3 or 4 anemia developed in 56 of 420 participants (13.3%) in the liposomal amphotericin B group and in 165 of 422 participants (39.1%) in the control group (P<0.001).

The mean decrease in hemoglobin level during the first week of the induction period was 0.3 g per deciliter in the liposomal amphotericin B group and 1.9 g per deciliter in the control group (P<0.001); blood transfusion was performed

in 32 of 420 participants (7.6%) in the liposomal amphotericin B group and in 76 of 422 participants (18.0%) in the control group. A grade 3 or 4 increase in the creatinine level developed in 22 of 420 participants (5.2%) in the liposomal amphotericin B group and in 25 of 422 participants (5.9%) in the control group. The mean relative increase in the serum creatinine level from baseline to day 7 was 20.2% in the liposomal amphotericin B group and 49.7% in the control group (P<0.001). Thrombophlebitis leading to antibiotic therapy occurred in 8 of 420 participants (1.9%) in the liposomal amphotericin B group and in 28 of 422 participants (6.6%) in the control group (P=0.001). A low incidence of grade 4 thrombocytopenia, neutropenia, and elevated alanine aminotransferase level was observed in both treatment groups.

DISCUSSION

This trial showed that induction therapy with a single 10 mg-per-kilogram dose of liposomal amphotericin B in combination with oral flucytosine and fluconazole was noninferior to the WHO-recommended standard of care that included 1 week of amphotericin B deoxycholate given with flucytosine and was associated with significantly fewer adverse events. Because this clinical trial involving HIV-positive adults with cryptococcal meningitis was conducted in a range of health care settings across five countries in southern and eastern Africa with no loss to follow-up, our results are likely to be generalizable to other African settings with a high prevalence of HIV (Table S9).

The 10-week mortality of 24.8% observed in the liposomal amphotericin B group in our trial is among the lowest reported from a major cryptococcal meningitis trial in Africa, despite more than a quarter of participants presenting with very severe disease and abnormal baseline mental status. Our trial showed that either strategy (a single dose of liposomal amphotericin B plus 14 days of therapy with flucytosine and fluconazole or short-course treatment with 7 days of amphotericin B deoxycholate plus flucytosine followed by 7 days of fluconazole therapy) can reduce 10-week mortality from cryptococcal meningitis to below 30%. This finding represents a notable improvement on the rates of 40 to 45% reported in trials of 2-week amphotericin B deoxycholate–based regimens that were conducted in resource-limited settings[10,29-31] and is consistent with the relatively favorable outcomes with the 1-week regimen of amphotericin B deoxycholate plus flucytosine that were reported in the ACTA trial.[10]

Our trial builds on phase 2 data[23] showing that a single 10-mg-per-kilogram dose of liposomal amphotericin B is effective in clearing cryptococcus from the cerebrospinal fluid. The effect on fungicidal activity with a single high dose of liposomal amphotericin B given with flucytosine and fluconazole matched that of 7 days of treatment with amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine. In addition, the regimen that included a single high dose of liposomal amphotericin B led to fewer adverse effects than the 1-week amphotericin B deoxycholate regimen, with fewer adverse events overall, fewer life-threatening grade 4 events, fewer episodes of grade 3 or 4 anemia, a reduced need for blood transfusion, and less severe thrombophlebitis. These findings reflect the toxicity profile of liposomal amphotericin B that is known to be better than that of amphotericin B deoxycholate.[12,14] In this trial, we administered preemptive fluid and electrolytes to all the participants to reduce the risk of amphotericin B–related toxic effects, adopted an intensive blood-monitoring schedule, and actively managed adverse events when they occurred. The reality of routine care in resource-limited settings is that the necessary resources are often not available to implement measures to reduce toxic effects and an intensive monitoring and management approach.

An additional potential benefit of the liposomal amphotericin B regimen is that it may be possible to shorten the length of hospital stay needed to safely administer effective treatment. For the evaluation of safety in this trial, our protocol required that all participants be hospitalized for a 7-day period of inpatient monitoring. However, when scaled-up in real-world situations, earlier discharge will probably be possible for some patients. A cost-effectiveness comparison is under way. Given our results, a single high dose of liposomal amphotericin B may be worth investigating in the treatment of other systemic fungal infections that are prevalent in resource-limited settings, such as histoplasmosis and talaromycosis.[32,33]

Our trial was open label, and clinical care of the critically ill participants with advanced HIV disease was complex. However, both the primary

Table 3. Laboratory-Defined and Clinical Adverse Events Occurring within 21 Days after Randomization.*

Event	Liposomal Amphtericin B (N=420)	Control (N=422)	P Value†
Grade 3 or 4 adverse events — no. of events	382	579	
Any grade 3 or 4 adverse event — no. of participants (%)			
Grade 3 or 4	210 (50.0)	263 (62.3)	<0.001
Grade 3	173 (41.2)	225 (53.3)	<0.001
Grade 4	91 (21.7)	127 (30.1)	0.005
Anemia — no. of participants (%)‡			
Grade 3	44 (10.5)	108 (25.6)	<0.001
Grade 4	12 (2.9)	62 (14.7)	<0.001
Mean change in hemoglobin level from baseline to day 7 — g/dl§	−0.3±1.39	−1.9±1.8	<0.001
Receipt of blood transfusion — no. of participants (%)	32 (7.6)	76 (18.0)	<0.001
Neutropenia — no. of participants (%)¶			
Grade 3	27 (6.4)	21 (5.0)	0.36
Grade 4	20 (4.8)	16 (3.8)	0.49
Thrombocytopenia — no. of participants (%)‖			
Grade 3	9 (2.1)	17 (4.0)	0.11
Grade 4	4 (1.0)	6 (1.4)	0.75
Creatinine increase — no. of participants (%)**			
Grade 3	17 (4.0)	22 (5.2)	0.42
Grade 4	5 (1.2)	3 (0.7)	0.51
Mean relative increase in creatinine level from baseline to day 7 — %††	20.2±48.1	49.7±70.8	<0.001
Hypokalemia — no. of participants (%)‡‡			
Grade 3	6 (1.4)	27 (6.4)	<0.001
Grade 4	0	3 (0.7)	0.25
Elevated ALT — no. of participants (%)§§			
Grade 3	6 (1.4)	4 (0.9)	0.52
Grade 4	1 (0.2)	1 (0.2)	1.0
Thrombophlebitis requiring antibiotic therapy — no. of participants (%)	8 (1.9)	28 (6.6)	<0.001
Other grade 3 or 4 adverse event — no. of participants (%)¶¶	167 (39.8)	173 (41.0)	0.72

* Plus–minus values are means ±SD. The adverse event data are presented for the safety population, which included all the participants who underwent randomization and received at least one dose of a trial medication. One participant in the liposomal amphotericin B group withdrew consent after randomization but before receiving any trial medication, and one participant in the control group died after randomization but before receiving any trial medication. Both participants were excluded from the safety analysis. ALT denotes alanine aminotransferase.

† P values were derived from chi-square or Student t-tests as appropriate.

‡ Grade 3 anemia was defined as a hemoglobin level of 7.0 to less than 9.0 g per deciliter in men and of 6.5 to less than 8.5 g per deciliter in women, and grade 4 as a hemoglobin level of less than 7.0 g per deciliter in men and of less than 6.5 g per deciliter in women.

§ Data regarding grade 3 events are reported for the participants who had both baseline and day 7 values available. Data were missing for 50 participants in the liposomal amphotericin B group and 61 in the control group.

¶ Grade 3 neutropenia was defined as a neutrophil count of 400 to 599 per cubic millimeter, and grade 4 as a neutrophil count of less than 400 per cubic millimeter.

‖ Grade 3 thrombocytopenia was defined as a thrombocyte count of 25,000 to 49,999 per cubic millimeter, and grade 4 as a thrombocyte count of less than 25,000 per cubic millimeter.

** Grade 3 creatinine increase was defined as creatinine level of 2.47 to 4.42 mg per deciliter (216 to 400 μmol per liter), and grade 4 as a creatinine level of greater than 4.42 mg per deciliter.

†† Data regarding grade 4 events are reported for participants who had both baseline and day 7 values available. Data were missing for 42 participants in the liposomal amphotericin B group and 50 in the control group.

‡‡ Grade 3 hypokalemia was defined as a potassium level of 2.0 to 2.4 mmol per liter, and grade 4 as a potassium level greater than 2.4 mmol per liter.

§§ A grade 3 elevation in ALT level was defined as an ALT level of 200 to 400 IU per liter, and a grade 4 elevation as an ALT level greater than 400 IU per liter.

¶¶ During the course of the trial there were two infusion reactions that met the grade 3 criteria, both of which occurred in the liposomal amphotericin B group. Both cases responded to simple supportive measures. There were no participants in whom the prescribed dose of either liposomal amphotericin B or amphotericin B deoxycholate could not be given owing to infusion-related adverse events. We did not collate data on milder infusion reactions.

end point of death from any cause and the key safety end points of laboratory-confirmed toxic effects were objectively measured, and a consistent approach to HIV management and antiretroviral therapy was agreed on by the investigators and applied throughout the trial (Table S10) in order to avoid differential management strategies or outcome assessments in the treatment groups.

This trial showed that a single high dose of liposomal amphotericin B given with flucytosine and fluconazole was noninferior to the current WHO recommended standard of care for cryptococcal meningitis and offers a practical treatment for the management for HIV-associated cryptococcal meningitis that is easier to administer and associated with fewer drug-related adverse effects. Continued efforts to ensure access to liposomal amphotericin B and flucytosine are needed to enable the implementation of this treatment.

The views expressed in this article are those of the authors and not necessarily those of the funders.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Spotlight on global health research

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Global health research is a discipline in which it is highly possible to cause more harm than good. Universally, the conduct of ethical research is bound by international principles and guidelines and its design and implementation are interrogated by funders and institutional review boards. Research in resource-limited settings is no different in this respect but poses additional ethical considerations due to the nature that the research is conducted alongside or within poorly resourced healthcare systems. The aim of this special issue is to identify work that acknowledges this complexity but demonstrates best practice in the pursuit of fair and equitable approaches to global health research. We were thrilled to receive a total of 27 paper proposals from a broad range of institutions, research teams and geographical locations. After some tough deliberation we are pleased to present the final 12 manuscripts that make up this special issue.

We begin in post-Ebola Sierra Leone, where Pena-Fernandez et al. outline the experience of setting up a transnational research partnership to deliver a parasitology training programme and demonstrate the complexity of forming equitable and ethical research partnerships. Their team highlight that whether something is ethical (or not) cannot be determined simply in an ethics committee meeting. Wright echoes this sentiment in a short communication summarising a recently published Nuffield Council on Bioethics report: 'Research in global health emergencies', arguing that research can only be ethical if it encompasses three core values: equal respect, fairness and helping to reduce suffering, all of which are the responsibility of all the stakeholders or 'duty bearers' involved in research. Transnational research partnerships are then scrutinised more broadly under the lens of the Decolonising Global Health movement by Lawrence and Hirsch, who focus particularly on what researchers from high-income settings can and need to do to make partnerships more equitable.

The design of global health research raises particular ethical issues related to both participant reimbursement and the provision of ancillary care to individuals who may live in resource-limited settings with weak healthcare infrastructure. Reflecting on their ethnographic community-based study of air pollution in Malawi, Saleh et al. demonstrate the complexity of decision-making around participant compensation and encourage researchers to engage with research participants and communities to develop and evolve their approach. Sansom and colleagues from the Oxford University Clinical Research Unit in Vietnam outline the steps their institution took to develop a fair and transparent research participant compensation and reimbursement framework, encouraging others to learn from and adapt their method. In their research with ethics committee members and research investigators in Uganda, Ssali et al. identify shared concerns about the potential for participants to consent to a study as a surrogate for routine healthcare provision, and Nkosi et al. describe the dilemmas faced by HIV prevention research workers in South Africa when trying to meet the ancillary care needs of their vulnerable participants.

What it means to be vulnerable and the importance of including a broad range of communities in clinical trials is the focus of the research conducted by Khirikoekkong et al. on the Thai-Myanmar border. The authors show us how and why the design of clinical trials must be adapted to enable vulnerable communities to participate. We also learn from Ngwenya et al. about how changes in the focus of research in South Africa, in their case from infectious to non-communicable diseases and increasingly towards genetic analyses, should lead to changes in the way we communicate with potential participants to ensure that consent is truly informed and voluntary.

One key message to take home from this special issue is that the social sciences have an immense amount to contribute to global health research. Peay et al. show us how social science and community engagement performed alongside a HIV cure trial in Thailand helped to determine what is truly ethical, particularly in a dynamic research discipline where the standard of care is rapidly changing. Lees and Enria's comparative ethnographies of preventive clinical trials conducted in Sierra Leone and Tanzania highlight the contributions of critical anthropological engagement in research, taking into account global and local power dynamics and demonstrating the true value of anthropology in clinical trials. Finally, Henderson et al. point out that observational studies are also worthy of qualitative

enquiry, outlining the bioethical nuances of a cohort study in Thailand.

Thank you to all those who submitted paper proposals, the authors of the final manuscripts and to our reviewers, who kindly gave up their valuable time and used their expertise to improve the quality of this collection. Each of these individual papers is excellent and worth reading but it is only when read together as a combined whole that their true value emerges. When this special issue was conceived we set out with the aim of stimulating discussion around the ethos of global health research, to deepen our understanding of what constitutes responsible conduct in our discipline and to propose areas for improvement. We are sure that after reading this special issue you will be motivated to reflect on the way in which global health research is conducted. We hope this collection will help us to learn from one another as we strive to improve health worldwide.

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Decolonising global health: transnational research partnerships under the spotlight

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There are increasing calls to decolonise aspects of science, and global health is no exception. The decolonising global health movement acknowledges that global health research perpetuates existing power imbalances and aims to identify concrete ways in which global health teaching and research can overcome its colonial past and present. Using the context of clinical trials implemented through transnational research partnerships (TRPs) as a case study, this narrative review brings together perspectives from clinical research and social science to lay out specific ways in which TRPs build on and perpetuate colonial power relations. We will explore three core components of TRPs: participant experience, expertise and infrastructure, and authorship. By combining a critical perspective with recently published literature we will recommend specific ways in which TRPs can be decolonised. We conclude by discussing decolonising global health as a potential practice and object of research. By doing this we intend to frame the decolonising global health movement as one that is accessible to everyone and within which we can all play an active role.

Keywords: authorship, decolonisation, ethics, global health, transnational research partnerships.

Introduction

There are increasing calls to decolonise aspects of science, and global health is no exception. What it means to decolonise global health is not always well explained or understood and to some the act itself may seem too ill-defined, obscure or daunting for it to be achievable. Using the context of clinical trials conducted through transnational research partnerships (TRPs) as a case study, the purpose of this article is to demonstrate that a multidisciplinary approach, combining the practical experience of a research physician with the critical perspective of a social scientist, can be applied to critique aspects of global health research. We will draw particularly on experience from the continent of Africa, but aspects of this review will apply to broader contexts. We focus particularly on randomised controlled trials, which are, despite criticism,[1,2] regarded as producing the most rigorous data for an intervention and, possibly because of this, where TRPs are commonly found. Specifically, we historicise and contextualise three aspects of TRPs (participant experience, expertise and infrastructure, and authorship) to lay out specific ways in which TRPs build on and perpetuate colonial power relations before suggesting specific ways in which we can work towards more equitable TRPs. By doing this, we intend to frame the decolonising global health movement as one that is accessible to everyone and within which we can and should all play an active role. We refrain here from offering a normative or static definition of what decolonising global health means and accept, following Tuck and Yang,[3] that real decolonisation needs to take place outside academia and needs to be led and abide by the principles of indigenous communities. Although we primarily focus on decolonisation, we also recognise the intersectional vulnerabilities that disproportionately affect women and junior researchers (of colour) within global health.[4]

The decolonising global health movement

When working in the field of global health research one is constantly exposed to, and even complicit in, the power imbalances that exist between researchers in high-income countries (HICs), researchers in low- and middle-income countries (LMICs) and the research participants we work with.[5] These inequalities largely derive from colonialism and are frequently the subject of debate within the field.[6] Indeed, the very notion of global health and

global health research have been subject to the label of 'scientific colonialism'.[6,7] Against this background, various 'decolonising global health' (DGH) movements have emerged at universities in the last few years.[8–10] Importantly, these movements are often student-led and include high proportions of students from LMICs and their diasporas. Where we work, at the London School of Hygiene and Tropical Medicine, the DGH movement has started exploring concrete ways in which global health teaching and research can overcome its colonial past in terms of representation, research and funding processes. These movements, which have emerged predominantly within universities in the Global North, are only one of many manifestations that critiques of our current global health system have taken. As pointed out by DGH movements, we have to be mindful to listen to and learn from the people at the receiving end of global health interventions. In this article we want to draw on the important and innovative work of the DGH movement to think through and provide suggestions for the decolonisation of TRPs.[4]

The importance of global health research

Clinical trials generate important knowledge and there is a need for well-conducted clinical trials to take place in sub-Saharan Africa. In fact, there has been long-standing criticism surrounding the general neglect of the region in terms of clinical research. Roughly 80% of all clinical trials are conducted in HICs[11] and diseases of relevance to HICs are investigated in clinical trials seven to eight times more often than those whose burden lies in LMICs.[12] Criticism continues concerning the representation of different populations in research and this is exemplified by the disproportionately low number of individuals from LMICs who are recruited into clinical trials, despite the often higher burden of disease.[13] For example, one review found that in the context of human immunodeficiency virus (HIV), only 31% of all prevention or treatment trials prior to 2009 were conducted in LMICs despite these countries representing 99% of the mortality associated with HIV infection.[14] The underrepresentation of LMIC populations in medical trials, apart from being seemingly unfair, has important consequences for how we understand and measure health. Biomedical interventions in LMICs have, since the advent of tropical medicine, relied on the assumption that European white bodies are the normative gauge of health.[15] As with women and children, who have historically been excluded from medical trials,[16,17] the exclusion of diverse, non-European bodies impacts who treatments and medications are designed for and is likely to disadvantage the health of non-white European male bodies.[18] Research in LMICs is therefore essential but must be designed to benefit the local population. Foreign characterisations of LMICs as suitable locations for high-risk or ethically dubious research that can benefit individuals in HICs, as was recently proposed by researchers trialling a coronavirus vaccine, must be rejected.[19]

Transnational research partnerships

Clinical trials in LMICs are most commonly conducted through TRPs. These are cooperative pieces of research conducted by a combination of research institutions from different countries. In the context of global health, these partnerships are almost always between institutions in both LMICs and HICs. The premise of these partnerships is that institutions can collectively pool expertise, infrastructure and resources to deliver a high-quality outcome. The number of partners may be as small as two, but can be much larger. In an attempt to quantify the scale of these partnerships, a study from 2005 identified all published HIV treatment and prevention trials conducted in sub-Saharan Africa between 1987 and 2003 and focused on funding, geographical reach and authorship.[20] A total of 77 published trials that recruited patients from across 18 countries were included. The main funders were government agencies outside of Africa in 56% of trials and the pharmaceutical industry provided either full or partial funding to 44%. Funding from African government or non-governmental organisations contributed to 5 of 77 trials but were not the sole funders of any. In addition, this review found that the chief investigator was resident in Africa in only 25% of the trials, with the majority being from outside the continent, including the USA (30%) and the UK (10%), among other countries. An update to this work reported more recent trials conducted between 2004 and 2008 and identified no notable change in these trends over time.[21] These geographical dimensions highlight the continued dependence of African members of TRPs on countries and institutions in the Global North. We now turn to analyse this dependence in more detail using the examples of participant experience, expertise and infrastructure, and authorship.

Analysis

The participant experience

Clinical trials are only possible thanks to the willing participation of research participants and they should be at the centre of all debate and discussion. To date, there exists no published research that has specifically explored the perspective of participants in LMICs when it comes to the structure of global health research. During clinical trials administered through TRPs, research participants are not directly asked for their thoughts on this subject. Here we aim to provide two examples that shed light on how the experience of clinical trials in sub-Saharan Africa is permeated by colonial history and colonial power relations: rumours and informed consent.

A large portion of the ethnographic work exploring participant experience of research in LMICs has elicited data concerning rumours, most commonly in the context of blood stealing. In East and Central Africa, the historical basis for such rumours has been linked to the violent and extractive practices of colonial medical officers in the 19th and 20th centuries.[22] Today these rumours may be dismissed as expressions of ignorance or simply as being related to 'culture', but numerous social scientists have described them as forms of popular resistance.[23–25] In research within healthy volunteer studies, the generation of rumours about research studies and institutions is particularly prevalent when poor outcomes such as severe disability or death occur and, even in the absence of any clear link to the research study, there is often an apportioning of blame. These rumours often contain local interpretations of medical research ethics, especially related to the problems of resource transfers and flows of value. It has been argued that rather than ignoring rumours, engaging with them could enrich medical research ethics debates

and improve relations between medical researchers and study communities.[25]

Although the phenomenological interpretations of rumours provide an important window into the perspectives of research participants, further research exploring their experience of trials administered through TRPs is required. Individuals ought to be given the opportunity to articulate directly their perspective of how clinical trials are conducted rather than solely being interpreted from other observations (most commonly those of foreign researchers). This will also be enhanced by increased diversity within research teams and locally-led research protocols that can effectively elicit and accurately interpret research findings.

It is beyond the scope of this article to outline all the ways in which international research standards may not suit particular contexts, and in-depth research has been published elsewhere,[26,27] but let us now briefly turn to one example of informed consent. Informed consent, a product and signifier of conducting ethical research according to European standards, often falls short of successfully translating into varied research contexts outside of Europe and North America. As it is, we continue to fall short of ensuring a full and equivalent understanding of what giving consent means in the context of TRPs. These issues are magnified by the increase in genetic analyses taking place within trials and the storage of genetic material that often takes place outside the countries in which clinical trials occur.[28,29] There are already documented cases of research misconduct and exploitation in this field.[29,30] Further research is essential to understand how participants experience and interpret research ethics in a changing world.

Expertise and infrastructure

In the context of HIV research, particularly concerning HIV treatment and prevention, large, multisite trials are often conceived and designed by international research networks based in HICs. These groups then subsequently identify country leads at each site who they will then work with to recruit and train teams of researchers for that specific site. In these cases, protocol development, the design of standard operating procedures, trial oversight and data management often occur remotely to the sites, which means that local researchers implement the trial but do not necessarily gain the skills required to later run their own trials.[31] In addition, most research studies involve increasingly complex analyses of specimens—for example, genetic analysis, which can only currently be performed in a limited number of state-of-the-art laboratories that are most often found outside of sub-Saharan Africa. The location of medical infrastructures is hugely important, because infrastructures are often needed to turn knowledge into expertise and capacity, both of which are requirements for individual career progression. They are also necessary to attract future funding and the leadership of clinical trials. Over time, the development of advanced laboratory infrastructure in some LMICs has increased their competitiveness when it comes to clinical research.[32]

There is huge promise in TRPs, but there is also significant potential to create and perpetuate power imbalances both between and within individual institutions. Most commonly, chief investigators based in HICs apply to funding bodies, also often based in HICs, and collectively steer the research agenda in one direction or another. These researchers are typically employed by research institutions from HICs who measure the performance of their staff based on research funding and publications, which may distract them from the more subjective outputs of capacity building.[7] If these strategic funding decisions are not made in consultation with local researchers, there is a potential to overlook the most pressing research questions for the population as well as the opportunity to build capacity in that country.[33] The most extreme forms of this type of work are exemplified in the frequent reports of 'fly-in, fly-out' or 'parasitic' researchers who parachute into LMICs for short periods of time to collect data and samples before returning home to publish their findings, often bypassing local researchers and research needs entirely and, according to one focus group discussion, leaving institutions feeling like 'poor prostitutes'.[34–36]

Funding of clinical trials is hugely influential and there are examples of best practice whereby funding is channelled to researchers and institutions based in sub-Saharan Africa, with a focus not just on research outputs, but on institutional and individual capacity building. The European and Developing Countries Clinical Trials Partnership (EDCTP) is a notable example here.[37] The EDCTP funds clinical trials that address the most pressing public health needs within a country or region, while also providing additional funding to build capacity within research institutions. This approach requires a significant investment of time and resources, but such a model could create a future wherein TRPs occur solely between African institutions. South–South TRPs have been made more difficult given the slashing of health budgets of countries in the Global South through structural adjustment programmes in the 1980s and 1990s.[38] Going forward and where possible, governments need to integrate research funding into their healthcare budgets while balancing the demand to provide healthcare services with immediate benefits. Member states of the African Union, through the Africa Health Strategy 2007–2015, have committed to allocating 2% of their healthcare budget to research.[39] Although a situational analysis of this programme in 2017 found that target had not been met, this commitment was renewed in the Health Research and Innovation Strategy for Africa 2018–2030.[40]

The way in which success is quantified in global health research also needs to change. When individual performance is based on successful grant applications and authorship, this distracts from other meaningful outputs, such as mentorship and capacity building. International researchers are therefore, often understandably, guilty of prioritising their own research outputs rather than helping to develop the skills of their colleagues, which is an equally constructive and often more meaningful use of time. Therefore funders and research institutions need to place greater emphasis on this work in their appraisal of individuals or risk perpetuating the idea of research as a white male domain.[41]

Authorship

Another way to explore how TRPs disproportionately benefit researchers in the Global North is to look at authorship. The number of first or final author papers that an individual has is used to gauge their prominence in the field and is often the first port-of-call for funding bodies when reviewing a grant application or institutions when considering a promotion. The issue of authorship is

complex and there exist established guidelines that outline what constitutes an author or a contributor to a piece of research. In large clinical trials that employ hundreds of staff it is often impossible to list each individual, particularly when some journals place a limit on the number of authors, although this is less common than it used to be.[42] Including only individuals meeting the definition of an author may technically be fair and author positioning may be a true reflection of the workload undertaken and the 'scientific input' provided, however, it highlights further that the beneficiaries of global health research are often those based in high-income institutions. As recent studies have shown, researchers from LMICs are often 'stuck in the middle' when it comes to global health authorship resulting from international partnerships, further widening the divide between those researchers who benefit from TRPs (predominantly white and European or North American) and those who do not.[43,44] Abimbola's recent editorial on the foreign gaze in global health authorship makes an equally important point.[45] He explains the difference between the foreign and local gaze and asks us to question what the foreign gaze actually contributes to a holistic understanding of health in LMICs. These are deeply necessary questions and conversations to have and to which we hope to contribute here.

In addition, there is evidence suggesting that global health research is impacted by guest authorship, which is adding authors who did not contribute substantially to the work, and ghost authorship, which is omitting authors who have contributed substantially to the work. A survey and interview–based study solicited responses from researchers based in LMICs who were presented with various scenarios about authorship, redundant publication, plagiarism and conflict of interest and asked for their opinions and experiences of each.[46] In this study, 77% of participants reported the use of guest authorship in their institution and 41% reported occurrences of ghost authorship. There is not currently enough evidence to truly determine whether this is more common in global health research than in any other discipline, although this has been suggested,[47] and no truly comparative work has been done in high-income settings to enable a fair comparison. However, this does demonstrate a widespread unfairness in how academic work is recognised in this setting.

Authorship will always be important in research, but it is vital to factor in the contribution made by all parties and advocate for joint authorship and the most inclusive authorship policy possible, ensuring that any scientific contribution, no matter how small, is recognised. In addition, the roles that result in the more prestigious authorship positions need to be available and accessible to a more diverse group of researchers. We must also recognise to what extent we, as researchers and practitioners from or based in the Global North, have benefitted from a global health system built on colonial medicine, which continues to replicate colonial power dynamics in infrastructure, expertise and authorship.

Discussion

Decolonising TRPs

How can one work towards decolonising TRPs that, at their core, further dependence? Should we be speaking of partnerships at all? Surely the aim of decolonising TRPs should be to negate the need, motivation or opportunity for certain individuals and institutions to be involved at all. There are significant aspects of global health research that need to change and this is a process that needs to take place over time, rather than overnight, so as not to jeopardise the real benefits to health that result from this research. And it should start now.

We all have a responsibility to create an open environment whereby it is safe to discuss this issue. It is often easier for researchers in HICs to discuss neo-colonial aspects of global health research but it is far more intimidating for the majority of African researchers to do the same, particularly among their international collaborators. This reluctance is yet another colonial aspect of global health. There are intellectual decolonisation movements occurring across Africa, with the University of Cape Town being a notable example. But within TRPs there is a need for spaces and forums for debate across the continent where African and international researchers are able to have frank, open discussions about these power imbalances and develop solutions going forward. International researchers also need to embrace what is often an inconvenient truth. The London School of Hygiene and Tropical Medicine, where we work, has made a start in this regard, forming a working group that is exploring the school's historical links to colonialism and exploring how a world-renowned academic institution can undergo transformation. But each setting is nuanced and these conversations are required at the country and institutional level.

Working on the assumption that TRPs will not disappear overnight and that international researchers are likely to remain engaged in research in Africa for some time, it becomes important to focus on how they navigate through this space. This is increasingly relevant, as the trend seems to be for institutions in HICs to increasingly build links with those in LMICs. International researchers are a heterogeneous group, some of whom are respectful of institutional culture and reflective on their position within it, whereas others are less so. We all need to be culturally and racially literate when it comes to global health research and this needs to happen as early in our careers as possible. Medical schools and research institutions have a duty to generate discussion concerning the complexity of global health research and to develop, in partnership with their collaborators, guidelines for the responsible conduct of research in LMICs. It is not acceptable for researchers to assume that because they are from an international institution that they are more knowledgeable, that their work should take priority or that they deserve the premium position on papers. This is a particular risk when individuals are new to the research world or the country in which they are conducting research. A prolonged, sustained period of conducting research in a country will always be far preferable to a fly-in, fly-out approach.

Research and decolonisation

There is a need for further research into TRPs. With an increased appreciation of the potential harms and benefits of TRPs there is an urgent need for an exploration of their impact on all stakeholders. This includes ongoing quantification and monitoring of key indicators related to the three domains we have discussed as well as in-depth qualitative studies. In particular, no previous original research exploring TRPs from the perspective of researchers from both HICs and LMICs has been published. We need to

understand how research participants themselves experience the research process within these partnerships. This is the partial focus of an ongoing ethnographic study being conducted by D. S. Lawrence and colleagues (ClinicalTrials.gov: NCT04296292).

There is also a need to focus on decolonisation as the subject of research. Any research into this topic needs to be carefully planned to ensure that it does not (re)create the existing power imbalances and biases it is trying to address and is aware of its limitations. We all need to do the work to make global health truly global. This means giving voice to the global majority in global health authorship, listening to the experiences of research participants and making sure that clinical trials increasingly take place in the countries and regions whose health problems they work to alleviate. First and foremost, it means checking our own privilege and realising that as practitioners and researchers based in and affiliated with institutions in the Global North, we continue to benefit from a global health system built on colonial medicine. All research and commentary will be restricted by the lived experience of the individual researchers, this article included. Decolonising global health presents an opportunity to make global health more inclusive and work towards health justice. Let's get to it.

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