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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

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.

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Declaration of competing interest

None.

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