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Abstract

Ethics guidelines emphasise that research should be acceptable to the people invited to take part. However, acceptability is subjective and dependent on context, complicating its assessment and use as an ethical standard.

This paper examines the concept of acceptability in relation to parents' perspectives on a paediatric vaccine trial in Malawi. We examined decisions on participation and experiences of the trial through interviews with parents in 41 households invited to enrol their children, and through participant observation of trial processes. Fieldwork took place in Chikwawa, Southern Malawi from February – October 2016.

Parents were not neatly split between those who saw the trial as acceptable and those who did not; instead there were mixed and changing feelings among parents who enrolled their children, and among those who withdrew or did not take part. Some parents agreed to participate but had concerns about the trial, while others expressed satisfaction with the trial but still did not take part.

These experiences indicate substantial variation in the nature of acceptance. We describe these variations in relation to six dimensions of acceptability: how acceptable the trial is, what aspects are acceptable, changes over time, circumstances affecting acceptability, variations between people, and reasons for

participation or non-participation.

The findings illustrate the difficulty of determining whether a trial is sufficiently acceptable to potential participants. We suggest that clarifying definitions of acceptability and examining how acceptability varies in degree, between trial components, over time, and between people and contexts may help researchers generate more nuanced descriptions of acceptability that support responsive and ethical trial design.

Keywords:
acceptability, ethics, community, Malawi, medical research

Background

The acceptability of research to invited participants is essential for ethical practice. WHO identifies “acceptability to participants” as a key ethical issue in study design (WHO, 2014, p. 6), and the UK Health Research Authority suggests that defining “what is acceptable to participants” helps “make research ethical” (Involve, 2016, p. 1).Understanding and enhancing acceptability among the people invited to participate is an important function of community engagement (CIOMS, 2016; Nuffield Council on Bioethics, 2015): community input helps “in ensuring that protocol designs and procedures are […] acceptable to the trial population”, in turn “improving recruitment, retention, adherence, and other trial outcomes” (UNAIDS/AVAC, 2011, pp. 44, 20). As such, as well as holding ethical significance, acceptability affects study feasibility: adequate recruitment is unlikely if potential participants see procedures as unacceptable (Feeley et al., 2009).

While the importance of acceptability seems clear, its meaning is more ambiguous; indeed, the idea of acceptability among people affected by research has been criticised as “extremely vague” (Macdonald, 2017, p. 32). Dictionary definitions include both positive and negative situations: acceptable is defined as both “welcome, pleasing” and “barely satisfactory or adequate” (Merriam-Webster, 2017a), while accept can mean “receive willingly” or “endure without protest” (Merriam-Webster, 2017b). Discussions about the acceptability of research to invited participants often lack explicit definitions (Feeley et al., 2009). Some analyses equate acceptance with participation, contrasting this with refusal to participate, as in “deciding whether to accept or decline the research” (Mfutso-Bengo et al., 2008, p.

58; other examples include Gysels et al., 2008; Fayter et al., 2007; Moynihan et al., 2012). However, these categories of participating and refusing can hide substantial variation in views on study procedures (Fairhead et al., 2004). Further, researchers often discuss promoting “acceptance” when they mean ensuring “tolerance” or “avoiding organised opposition” (Lavery, 2017). To accommodate this variation in meaning, we adopt a working definition of acceptability as a perception among invited participants that the research design is, to varying extents, “favourab[le]” (Feeley et al., 2009, p. 86), “agreeable, palatable, or satisfactory” (Proctor et al., 2010, p. 67). This definition reflects our focus on acceptability of study designs to participants as ethically significant.

As well as ambiguity regarding its meaning, assessment of acceptability is complicated by subjectivity, variability and dependence on context. Acceptability is not a fixed property of a trial or particular research procedure, but rather determined by individual perceptions, and shaped by personal and social contexts. This influence of context is discussed explicitly in some accounts of views on research among participant communities (Fairhead et al., 2004; Kingori, 2015), and suggested by studies on willingness to participate (Cunningham et al., 2018; Gamble et al., 2012; Otwombe et al., 2011; Trauth et al., 2000) and reasons for participation or refusal (Gysels et al., 2008; Strömmer et al., 2018) that describe varied perspectives among target participants. However, the significance of contextual variability is explored more extensively in literature on acceptability of health interventions. As this literature suggests, different individual, household or group circumstances and priorities generate varied perceptions of acceptability (Heise, 1997; Montgomery et al., 2010). Research on health interventions also shows that acceptability can

change over time, for example shifting through social interactions (Cohn, 2016) or with experience (Dyer et al., 2016). Acceptability is also relative, such that views of a particular health intervention depend on the perceived suitability of any alternative interventions (Heise, 1997; Hyder and Morrow, 2006; Mcintyre et al., 2009). Finally, the degree of acceptability varies, ranging from high demand to ambivalence (SAGE Working Group on Vaccine Hesitancy, 2014).

Although existing literature points to these variations in acceptability, the concept of acceptability has not been a specific focus in discussions about research participation. We lack frameworks for examining acceptability among invited participants, and reviews of research on trial participation and acceptability call for more in-depth analysis and understanding of individual variation (O'Cathain et al., 2014; Ross et al., 1999). Some approaches to assessing acceptability may miss important variations in and reasons behind invited participants' perceptions. For example, assessing acceptability based on consent to enrol or using single timepoint questionnaires (e.g. Richards et al., 2014; Stead et al., 2005; Wallace et al., 2018) may overlook different degrees of acceptability, changes over time, or contexts affecting decisions on enrolment. Qualitative reports may also neglect underlying contexts or describe only limited areas of variation (for example, between individuals rather than over time) (e.g. Crawley et al., 2013; Gafos et al., 2017). Given the ethical importance of acceptability and its ambiguity, further work to clarify this concept may support more nuanced investigation of participant perceptions to inform responsive trial design.

Our research examines acceptability in the context of a paediatric influenza vaccine

trial in Malawi. We explore parents' decisions about enrolling their children and reasons behind these decisions, perceptions of the trial, and variation in acceptability between trial procedures, over time and between contexts and people. Our aim is to deepen understanding of the acceptability of research to potential participants, and to suggest directions for future assessment of acceptable trial design.

The vaccine trial examined whether malaria infection affects immune response to influenza vaccine in children (the FLUVAC trial, details in Peterson, 2016). The trial took place in Chikwawa, a rural district in Southern Malawi where under 5 mortality is 62 per 1000 live births and the poverty rate is 82% (compared to 73 per 1000 and 51% for Malawi overall, Government of Malawi, 2012; National Statistical Office, 2017). Approximately 1300 children aged 6 to 59 months were recruited. Participation involved three main appointments, spaced one month apart. Children received the influenza vaccine at the first two appointments, and had samples taken at all three appointments, including a venous blood sample to measure influenza serology, a finger prick blood sample to test for the malaria parasite (not in real time), and stool samples from a subset of children. A point of care rapid diagnostic test for malaria was administered to febrile children to guide treatment. Trial teams rotated between 28 villages, spending approximately two weeks at a time in each village and returning one month later for follow-up visits.

Given the age of child participants, enrolment was decided by parents. Fieldworkers and community volunteers approached parents in their homes and invited them to visit a study tent assembled in each village, where further information was provided. Trial staff gave parents an information sheet describing procedures, risks (potential

side effects and discomfort from the vaccine and blood samples) and benefits (reduced risk from influenza, malaria treatment if tested positive, and the population health benefit of additional evidence on influenza vaccination) (see supplementary file 1) **[insert online file 1 here].** Procedures, risks and benefits were also explained verbally, with time for questions. Although parents were not vaccinated, they were required to participate actively in the trial by answering questionnaires on household circumstances and their own health status, completing an adverse event diary, and accompanying their child during study appointments. The trial protocol referred to parents as participants, and consent forms completed by parents indicated their agreement “to take part in the above study”. Parents also described themselves as participating or withdrawing during interviews. Given this role, we consider parents as participants or non-participants, not just as enrolling their children.

Methods

We used qualitative research to examine parents’ experiences and decisions about trial participation. We conducted interviews with parents in 41 households invited to enrol their children, including parents who enrolled their child (21), who withdrew (9), and who did not participate (11). Most interviews involved the main carer (usually the mother), but in some cases a wife and husband were interviewed together because both wanted to be interviewed. With these joint interviews, we took care to encourage responses from both parents. Interviews were divided between nine villages where the trial took place, selected to cover variations in circumstances such as proximity to health centres, time points during the trial, and levels of uptake as reported by trial staff. Some parents were interviewed a few days after the first appointment, others midway through participation, and others after completion or

withdrawal, providing a range of experiences. Repeat interviews were conducted with three parents who were initially interviewed shortly after their first trial appointment, including one who withdrew and two who remained in the trial, to understand any changes in their experiences over time. Topic guides covered experience of the trial, decisions regarding participation, information about the trial purpose and procedures, perceived benefits and drawbacks, and issues that might affect engagement such as previous research experience (see Supplementary file 2) [INSERT LINK TO ONLINE FILE 2]. Interviews lasted approximately one hour and were conducted in Chichewa by an experienced qualitative researcher (MP). Audio recordings were transcribed verbatim and translated into English.

We also conducted participant observation of trial processes. This involved accompanying fieldworkers as they approached parents, observing informed consent procedures, attending community meetings about the trial, and holding informal discussions with trial staff and community members in trial villages. Observation was undertaken primarily by a Malawian researcher of equivalent seniority to trial staff (MP), with some visits by KG. Notes were taken during observation and expanded the same day.

Data analysis was ongoing throughout fieldwork. The research team regularly discussed emerging issues to identify aspects for further investigation, including searching for conflicting data or alternative explanations (Patton, 2002). Later analysis involved thematic coding (Gibbs, 2008) of observation notes and interview transcripts in NVivo, using a combination of emerging themes (such as concern around blood samples) and broader categories related to the research objective

(such as reasons for participation). Initial transcripts were coded independently by KG and MP, and compared to generate a common coding frame that was then adapted with further coding (see Supplementary file 3) [INSERT LINK TO ONLINE FILE 3]. We used qualitative tables that displayed codes against cases to compare perceptions between parents, and memos to capture emerging ideas (Gibbs, 2008). Interview and observation data were compared to check and extend interpretations.

During analysis, we identified multiple variations in acceptability, for example between contexts and over time. These variations were identified through a combination of reviewing coding, looking across cases and reading individual cases. For example, material coded as ‘reasons for withdrawal’ and ‘regret’ pointed to changes in acceptability over time, while reviewing the qualitative tables helped to indicate variations in acceptability between individual contexts. Initial ideas about variations were then explored further through re-reading coded sections and transcripts to check and develop our understanding. We progressively refined our categorisation of these variations to identify six dimensions of acceptability: the degree of acceptability, what is acceptable, when a trial is acceptable, variation between circumstances, variation between people, and reasons for participation. This final categorisation was developed through a process of logical analysis (Patton, 2002) that drew on variations identified inductively, and variations to which we were sensitised from literature on acceptability and our experience with the realist evaluation emphasis on “what works, how, why, for whom, to what extent and in what circumstances, in what respect and over what duration” (Wong et al., 2017, p. 21). We worked back and forth between these sensitising concepts and our data to develop a set of dimensions that matched parents’ experiences (Patton, 2002). The

realist motto helped reshape variations identified inductively into distinct categories, but our use of realist approaches was restricted to considering this pattern of outcomes, rather than steps such as explicitly identifying mechanisms.

The study was approved by the Liverpool School of Tropical Medicine and Malawi College of Medicine research ethics committees. All interview and observation participants received a written information sheet and the study purpose, requirements, benefits and risks were also explained verbally. All participants provided written informed consent.

Results

Narratives about the trial revealed diverse views among parents who enrolled their children, and among those who withdrew or did not take part. We draw out these variations in acceptability in relation to the six dimensions identified during analysis: how acceptable the trial is, what aspects are acceptable, changes over time, circumstances affecting acceptability, variations between people, and reasons for participation or non-participation. These six dimensions overlap and interact. For example, individual circumstances affect who sees a trial as acceptable, changing circumstances affect when a trial is acceptable, and the degree of acceptability is linked to reasons for participation.

How acceptable is the trial? Tolerance or satisfaction

Parents who enrolled their children in the trial reported contrasting levels of satisfaction. Some were highly enthusiastic about all trial components:

> I finished the study without any issues. The child didn't experience any problems, from the start to the end. I found it useful and I was happy with it. (Mother, participant, ID18)

The husband of this woman was equally positive, to the extent that he encouraged further research:

> If they were considering another phase of the study, based on my experience they should go ahead with it … If the child is eligible, I would enrol again. (Father, participant, ID18)

Other parents participated throughout but saw the trial as problematic and enrolled their children reluctantly. For example, one mother was concerned that blood samples would make her child sick:

> I don't think the process is good - you go today and they collect blood, you go another day and they do the same thing, so I see that they will drain blood from her body. … So we just go there, but we are not happy deep inside our hearts. (Mother, participant ID30)

Indeed, some parents had distressing experiences of the trial but still continued participating. A particular concern was difficulty encountered by trial staff in collecting blood from younger children, which sometimes meant needles were inserted several times:

> When you go, the child is pricked all over to find the veins, and that really affected me - pricking here, pricking there, and the child was just crying, to the point where I ran out of the tent. (Mother, participant, ID16)

Despite this experience, this mother planned to continue participating because she thought the trial would benefit her child's health, saying that at the next appointment,

"I will just be strong".

These contrasting experiences suggest a continuum of acceptability, from high levels of enthusiasm through to tolerance and reluctant participation. They also highlight a distinction between agreement to participate and satisfaction with trial procedures, to which we return later.

What aspects of the trial do people see as acceptable? Mixed views and misunderstandings

Most parents saw the trial as neither wholly acceptable or unacceptable; they liked some components and disliked others. For example, many parents appreciated access to the vaccine and other health services, but had concerns about blood samples, side effects, or lack of individual test results.

> This study has good parts and bad parts. The bad part is that some children fall sick after being vaccinated. The good part is that whenever the child has flu, she will have it but not very badly because she received the vaccine. (Mother, participant, ID22)

> I participated because the study will protect the child's body, but the issue where we are not getting along with them is that we still haven't received the results from the blood they collected. (Mother, participant, ID34)

Those who withdrew or did not take part also had mixed views, seeing potential benefits alongside their concerns. For example, one couple who withdrew due to fears about blood samples and perceptions of inadequate assistance in the event of side effects also described positive aspects of the trial:

> Although we withdrew, being in the study had benefits. The vaccine could prevent diseases that the child might have. … We also missed out on the mosquito nets. (Father, withdrew, ID41)

Decisions about overall acceptability and participation involved balancing positive and negative components; a judgement that the trial was welcome or that participation was worthwhile did not mean parents saw all aspects as appropriate.

Examining what parents liked or disliked about the trial also suggested that assessments sometimes reflected misconceptions of trial procedures. Despite provision of information through community engagement and consent procedures, assumptions were made, rumours circulated and some people enrolled because they expected to gain benefits that would not actually be offered. For example, the information sheet did not indicate feedback of individual test results, but as illustrated above, feedback was assumed by many parents. Similarly, one woman explained that she wanted to enrol because she thought participants would receive a solar stove, alongside the mosquito net that was actually provided:

> People said your friends are going to receive mosquito nets and solar stoves, so you will be jealous if you don't take part. So I thought I should not be the only one not getting those things, I will take part no matter what! (Mother, non-participant, ID14)

As well as misinformation about trial benefits, there were misconceptions regarding risks of both participation and refusal. This mother's wish to enrol also stemmed from an unfounded concern that refusing might restrict future healthcare access:

> I went to the study tent because I thought that if I don't take part, when I take my child to the hospital with a fever they will send me away. (Mother, non-participant,

ID14)

Others viewed the trial negatively because they believed it involved procedures that were not involved. For example, reflecting long-standing concerns around use of blood in Malawi and similar settings (Ashforth, 2014; Geissler and Pool, 2006; Schmidt, 2009), some parents saw the trial as unacceptable because they thought researchers might sell blood taken as samples:

> I refused because some people said the blood they were collecting would be sold. (Mother, non-participant, ID40)

In these examples, it is perceived rather than actual trial procedures that parents consider beneficial or problematic, complicate assessment of acceptability.

When is the study acceptable? Reassurance and regret

Views of the trial changed over time as parents gained new information and experiences of the study. Some people became increasingly positive when they learnt more about procedures or when anticipated problems did not materialise. For example, one father explained that his initial anxiety about side effects faded when his child remained healthy:

> Joining a strange study with no knowledge of its outcomes leaves you wondering, - “what are we going to see?” The heart always questions - “won’t this be dangerous for the child’s health?” But as we never experienced any of that, we’re positive about the study, and that’s why we went there again. (Father, participant, ID18)

A similar increase in enthusiasm was expressed by some parents who decided not to participate and subsequently felt this decision was based on misinformation. For

example, one mother was afraid to participate after hearing about children fainting following blood draws, but she later decided these rumours were untrue and wished she had enrolled.

> What disturbed me was that people said another child's blood was completely finished … I listened to what others were saying and didn't go there with the child. These were lies and I know we made the wrong choice. (Mother, non-participant, ID40)

Other participants became less satisfied as they learnt more about the trial or when their expectations went unmet. For example, the participants who expected to receive individual blood test results were disappointed when results were not provided. Others saw the trial as increasingly unacceptable because they felt children experienced side effects. For some, this led to withdrawal:

> When I came back home, my child had fever and diarrhoea, she was vomiting and her body was swollen. … When the researchers visited me to go for a second visit, I refused – I told them 'my child fell sick when I took her there, should I go again given that they will collect blood and my child's body will become swollen? No, it's better to stay at home.' So I dropped out. (Mother, withdrew, ID36)

These feelings of reassurance and regret show how acceptability can change over time as new information and experiences overturn previous ideas and surpass or disappoint expectations.

In what circumstances is the trial acceptable? Internal and external conditions

Perceptions of the trial were shaped by conditions within the trial and wider contexts. The influence of internal trial conditions is illustrated in the previous discussion of

changing acceptability over time: acceptability of blood samples depended partly on other trial procedures, including provision of test results. Other conditions affecting sample acceptability included adequate explanation through community engagement, assistance in the event of side effects and sufficient compensation. On the latter, one mother felt parents should receive money rather than the fruit squash and biscuits that were provided:

> Half a bottle of squash is not enough based on how they are collecting blood. … Half a bottle is very little, they are robbing us. If they were giving us money to buy food, it would have been better. (Mother, participant, ID19)

The same mother explained that she happily provided blood samples in a previous study because participants received soap and transport money; different circumstances meant a procedure was acceptable in one study but not another.

Beyond the trial, wider socioeconomic, cultural and health contexts also affected views of trial benefits and disadvantages. For example, several parents concerned about blood samples mentioned risks of anaemia or thought children would have insufficient blood, perhaps reflecting a disease context with high levels of anaemia (National Statistical Office, 2017), and a cultural understanding of blood as containing the life force (Kaspin, 1996). A context of limited access to healthcare also shaped views of the trial, and made the opportunity to receive assistance from health workers in the village an important benefit of participation:

> Because we are in a remote area, transport is a problem. Whenever she falls sick we worry, saying ‘what are we going to do? We don’t have money’, and you just move up and down looking for transport … If the doctors have left the hospital and come here, it’s an opportunity for us - whenever we have a problem, they are

going to help us. (Mother, participant, ID06)

Trial staff noted that recruitment was sometimes harder in villages close to health centres because healthcare access was relatively easy, reducing the value of services provided through the trial. Again, a study perceived as acceptable in one set of circumstances may be unacceptable in another context.

Who sees the trial as acceptable? Individual contexts and perceptions

Previous sections indicate varied views of the trial, with some parents seeing it as a welcome opportunity, and others as risky or unfair. These different views result partly from different individual contexts, reflecting the influence of circumstances on acceptability. To take one aspect, parents' previous research experience affected their views of the trial. For example, one mother wanted to enrol her child in the vaccine trial because she felt another of her children was saved through previous research:

When he was seriously ill, the malaria researchers registered him in their study. He went there and was tested and he was given medicine and they followed him until he got well. … With this study, I didn't even consider refusing because maybe it is one way that my child can be helped, the way her friend was helped. (Mother, participant, ID06)

In contrast, another mother decided against enrolling her child due to negative previous research experience:

I participated in research before when I was pregnant. … I experienced such a challenge. I would feel weak and fail to walk. … I thought the child might experience what I experienced - that's why I said I would not enrol the child.

(Mother, non-participant, ID11)

These individual experiences affect perceived risks and benefits, contributing to variations in who sees the trial as acceptable.

Why do people take part or not? Distinguishing participation and acceptability

The reluctant participation noted among some parents indicates a distinction between agreeing to participate and seeing the trial positively. This distinction was further apparent when examining reasons for participation and non-participation. Sometimes enrolment or withdrawal was based on decisions about trial benefits and risks, including aspects previously mentioned such as protection from flu, medical assistance and material compensation, or side effects, suspicion about blood samples and inadequate compensation. However, sometimes reasons for participating or not participating did not involve views of the trial. For example, some parents intended to participate but arrived at the study tent after recruitment had finished:

I went to the farm to sow first … When I went there with the child the doctor said 'you are late' … I really wanted to participate but I was told that it is done. (Mother, non-participant, ID29)

Other parents wanted to participate but were stopped by other people. For example, several women withdrew due to pressure from male partners:

This study is going well and we welcome it in our village. If there is a problem, it is between me and my husband. … I tried to convince him as I had already started the study, but he said 'no don't go there again'. So as he is the family head, I just said 'OK, I won't go again'. (Mother, withdrew, ID26)

Another mother explained that she and her husband thought the study was beneficial but community elders advised them to withdraw:

> People said a child in another village died because of the blood collection, so be careful or your child will also die. … So we just left, thinking that if we insist on continuing and something happens, people will point at us and say 'we told you but you didn't listen'. … We thought we should not disagree with the elders. …So we just left, but we thought the study was good. (Mother, withdrew, ID03)

In contrast, for some parents pressure from other people compelled participation. For example, one couple initially enrolled to avoid criticism from the village chief:

> The headman said 'I will visit the homes of those who don't go, so they can explain to me why they didn't go.' … Although he might not do anything, he would think we are being rude. (Father, withdrew, ID33)

Another mother explained that she wanted to withdraw, but remained in the trial due to persuasion from the trial team and neighbours:

> They said it's not good to drop out of something you have already started … So I went, but I wanted to tear the papers [trial documents] so I could tell them they were soaked in the rain. … If I hadn't started, I would have left. (Mother, participant, ID19)

Others continued to participate due to a sense of obligation and feeling they could not withdraw after agreeing to enrol. For example, one mother only understood that blood samples would be taken when she entered the study tent, at which point she felt it was too late to change her mind:

> They asked whether you are willing to participate, and when we said yes and entered the tent, that's when we saw they were collecting blood. So given that we

had already accepted, how could we refuse? (Mother, participant ID30)

These examples all involve situations where people's decisions about participation did not match their view of the trial's acceptability, either positive or negative. For others, participation appeared to involve passive acceptance of requests or instructions rather than active decision making and assessment of trial benefits and risks. For example, one mother who had not expected the blood samples and did not understand their purpose explained that she did not question these procedures:

I was not thinking of anything, I just take it as the way it is supposed to be, I can't stop the doctor. (Mother, participant, ID02)

While partly indicating a context of unequal power relations between researchers or health workers and the community within Malawi (Jones et al., 2013), this passive acceptance also reflected unquestioning trust in researchers (seen as health workers) as having superior knowledge. Another mother explained that her participation was voluntary – "they even said it is not something they are forcing us to do" – but her agreement appeared to follow an assumption that whatever researchers wanted must be appropriate:

They are the doctors, so if that's what they think, it's good to do it like that. … There wasn't a reason to ask them why or to caution them, they are the ones who know and that was the procedure they came with. (Mother, participant, ID05)

These experiences demonstrate participation and non-participation based on mistakes in timing, pressure from others, a sense of obligation or passive agreement; taking part did not always result from a positive view of study procedures, and not participating did not always mean seeing the trial negatively.

Discussion

The experiences and views of parents invited to enrol their children in the vaccine trial indicate multiple variations in perceived acceptability. Some were enthusiastic, while others took part reluctantly; parents liked some aspects of the trial but not others; views of the trial changed over time as experiences or information changed; parents saw the trial positively or negatively because of ideas about what would happen that did not match actual procedures; and views varied between villages and individuals. For some who took part, 'acceptance' involved a feeling of pressure or misunderstanding followed by regret, and not participating sometimes reflected lack of permission from relatives or simply arriving too late, rather than hostility to the trial.

This variable and context-dependent nature of acceptability echoes findings from other trials and ethics guidelines. Although these findings and guidelines do not explicitly examine the concept of acceptability, they suggest the dimensions of variation described for this trial in Malawi are found more widely. For example, in relation to varied levels of acceptability, work in The Gambia, Kenya and UK suggests a mix of positive and negative feelings among both those who do and do not participate (Fairhead et al., 2004; Gikonyo et al., 2008; Snowdon, 2005), with some participants experiencing anxiety and alienation (Moynihan et al., 2012). Ethics guidelines also suggest people may consent to studies they find upsetting, noting a "cultural tendency to deny or tolerate pain and suffering" as potentially making women vulnerable in research (CIOMS, 2016, p. 69).

In relation to what people find acceptable, several benefits and disadvantages perceived by invited participants for this vaccine trial are reported for other research, including appreciation of access to health care or material compensation, and concerns around blood samples (Fisher et al., 2011; Mfutso-Bengo et al., 2008, 2015; Masiye et al., 2008). Those invited to enrol weigh up these perceived benefits and risks (Fairhead et al., 2004; Fisher et al., 2011). More generally, an understanding of trials as having welcome and undesirable aspects is reflected in the emphasis on benefits, risks and burdens within ethics guidance (Emanuel et al., 2004; Nuffield Council on Bioethics, 2015). The role of rumours and misinformation or misunderstanding about trial processes is also widely documented (Kingori et al., 2010; Mitchell et al., 2002; Munalula-Nkandu et al., 2015; Ndebele et al., 2014). Misunderstanding may reflect the content and communication of trial information, but participants' experiences and interests also affect their interpretations, and decisions may involve assumptions and intuitive judgements rather than informed deliberation (Abhyankar et al., 2016; Woolfall et al., 2013).

The idea that acceptability changes over time is evident in reports of withdrawal from trials, for example in response to apparent side effects, new information or changing personal situations (Gikonyo et al., 2008; Gillies and Entwistle, 2012). Again ethics guidelines acknowledge this potential for changing views , here in relation to consent as an ongoing process and the right to withdrawal (CIOMS, 2016).

Existing literature also shows the influence of context on acceptability. In particular, research in many low income countries suggests poverty and inadequate health

services mean research becomes an opportunity to access care (Ravinetto et al., 2015), an influence highlighted in the idea of an 'empty choice' (Kingori, 2015). Variations in acceptability between individuals are also widely documented, including the influence of gender, a child's health and previous research experience (Fisher et al., 2011; Kamuya et al., 2015; Mfutso-Bengo et al., 2008), as well as the heterogeneity of research communities more generally (Marsh et al., 2011). Ethics guidelines also discuss this role of context, including study procedures, individual and household factors, and political and social environments (Nuffield Council on Bioethics, 2002).

Finally, previous research also supports a distinction between participation and acceptability of study procedures. In particular, research in Malawi and other settings shows the influence of pressure from relatives and chiefs and of competing employment obligations, such that decisions on participation reflect more than individual views of study benefits and burdens (Angwenyi et al., 2014; Fairhead et al., 2004; Magazi et al., 2014; Marsh et al., 2011; Mfutso-Bengo et al., 2008). Unquestioning faith in researchers and the role of blind trust in generating acceptability are also described in other contexts (Marsh et al., 2011), partly linked to conflated researcher and clinician roles and the influence of dependent trust on healthcare decisions more generally (Gilson, 2003; Molyneux et al., 2005). Limited understanding of the right to withdraw is also widespread (Afolabi et al., 2014). In line with these findings, theoretical discussions of research ethics note that participation "may be based on reluctant acquiescence rather than on enthusiastic co-operation" (Social Research Association, 2003, p. 29), while non-participation may result from other priorities rather than negative views of research (Hammersley,

2017).

Acceptability, then, varies in degree, between trial components, over time, and between people and places. One possible reaction is to abandon acceptability to potential participants as a principle for ethical research, as argued by some who see acceptability as too hard to define and dependent on social position to be a useful consideration (Hammersley, 2017; Hunter, 2017; Macdonald, 2017). Acceptability alone does not make a study ethical; for example high compensation might increase satisfaction but create undue inducement, and acceptability is one principle to consider alongside criteria such as scientific validity and social value (Emanuel et al., 2004). Nevertheless, we suggest the idea of acceptability remains useful in drawing attention to perceptions and experiences among potential participants. However, the variability documented here raises questions about how we define and assess acceptability. Should we only consider a trial acceptable if everyone in a community is enthusiastic about all aspects of the trial, throughout the trial and afterwards, regardless of their socio-economic circumstances, or should ‘acceptable’ simply mean there are sufficient participants to meet recruitment targets? Should a trial be considered ethical if participants are unhappy about their experience, as long as they made an informed and voluntary decision to participate?

Given the difficulty of defining a common standard above which trials are considered acceptable, a more productive focus may be the nature of insights produced through acceptability research. We suggest that researchers examining acceptability might first, clarify their definition of acceptable and any associated benchmarks to avoid ambiguity, and second, provide nuanced descriptions by examining how and why

586 acceptability varies among potential participants. This two-fold approach seems
587 more likely to enable understanding of acceptability and a trial design that responds
588 to community concerns. The appropriate definition and benchmarks of acceptability
589 will depend on the context and aim of assessment, for example, whether the aim is
590 understanding initial participation or longer trial experiences. However, useful ideas
591 can be drawn from work on vaccine acceptability. In a parallel to the gradient of
592 positive and negative views and distinction between participation and approval found
593 in our work, vaccine researchers describe a continuum of vaccine hesitancy and
594 note that failure to be vaccinated may reflect diverse situations, such as
595 procrastination rather than active concern (Hickler et al., 2017; Peretti-Watel et al.,
596 2015; SAGE Working Group on Vaccine Hesitancy, 2014). Based on this
597 understanding, some frameworks on vaccine acceptability distinguish attitudes from
598 behaviour, and look beyond uptake to a range of actions in support of vaccines, such
599 as seeking or advocating vaccination (Hickler et al., 2017; Peretti-Watel et al., 2015).
600 In the context of research participation, a similar approach might involve
601 investigating levels of satisfaction with the trial to clarify whether participation
602 involves reluctant tolerance or unequivocal enthusiasm, and identifying behaviour
603 such as taking part initially, remaining in the trial, or encouraging others to
604 participate. Some assessments of trial acceptability incorporate elements of this
605 approach. For example, research on an HIV trial asked participants whether they
606 were glad to have joined the study, intended to remain in the study, and whether
607 they were interested in joining future trials (Gafos et al., 2017). This approach avoids
608 the potentially misleading use of participation as a proxy for acceptability, and
609 elucidates different degrees of acceptance.
610

On the second step of examining how and why acceptability varies, our work revealed variations in how acceptable the trial was, what was acceptable, when, in what circumstances, to whom and why. Describing these variations and examining reasons behind both perceived acceptability and levels of participation can provide more in-depth understanding of participant views that avoids concealing ethically significant details, such as enthusiasm based on misconceptions or participation based on pressure (either of which would suggest gaps in informed, voluntary consent). Examining these dimensions of acceptability can also suggest ways to adapt trial procedures to enhance ethical practice. For example, misconceptions of trial benefits or declining acceptability as people gain new information might suggest consent processes need revising to increase awareness of trial procedures and enable more informed decisions on enrolment (for example through ensuring information is framed to promote active decision making and addresses parents' priorities (Abhyankar et al., 2016; Woolfall et al., 2013)). Participation based on pressure from others may indicate a need to reemphasise voluntary decisions in fieldworker training and community engagement, or to address other constraints on choice identified by participants (Bull and Lindegger, 2011). Discovering that people are taking part reluctantly or regret joining, and knowing which aspects people dislike, could help researchers adapt procedures in ways that encourage uptake and improve participant experiences, reducing unnecessary burden. Variations between contexts or groups might suggest ways to tailor procedures to different situations. Finally, if participation reflects limited options for healthcare, research institutions could engage in longer-term work to enhance access (Kingori, 2015). Community consultation could help design appropriate responses to such findings (UNAIDS/AVAC, 2011).

While identifying these variations in acceptability can indicate ways to strengthen trial design, there remain questions around the level of acceptability required for ethical practice, and about how to make standardised trial designs responsive when individual views vary. One proposed solution is the idea that ethics committees should decide whether research constitutes a 'fair offer', with participation involving a fair balance of benefits, burdens and risks (Nuffield Council on Bioethics, 2015). People invited to take part will make individual decisions that reflect their priorities and contexts, and may feel participation is unsatisfactory. However, by judging studies to constitute a fair offer, ethics committees provide a level of protection and reduce risks of exploitation due to limited choices among participants. Stakeholder involvement can help ethics committees determine what constitutes a fair offer (Nuffield Council on Bioethics, 2015).

Our research had limitations. Further interviews and extended participant observation across additional study villages might have deepened understanding of participant perceptions and contextual variation. We initially planned to interview more parents who did not participate or who withdrew, but these households were harder to identify, partly because overall trial participation was high and approximately 90% of those who did participate remained in the trial. Additional repeat interviews might have increased information on changing perceptions, particularly for those who withdrew. However, it was not possible to identify parents who would later withdraw in advance, and interviewing enough initial participants to obtain an adequate sample of later withdrawals was unfeasible. In addition, the repeat interviews that were conducted did not produce substantially different data,

leading us to decide against further repeat visits. Parents interviewed at later stages of the trial or after withdrawal described changes in their views, helping us to understand shifting perceptions without repeat interviews. Towards the end of data collection, similar themes were recurring within each group of interviewees (participants, non-participants and those who withdrew), suggesting that additional interviews were unlikely to produce significantly new ideas.

Conducting research alongside the trial posed challenges for relationship with trial staff and parents. As we came from the same research institution as the trial team and sometimes shared transport with them, parents might have been reluctant to speak openly. During observation, some trial staff were concerned we would monitor their activities, which may have led them to behave differently. During interviews and observation, we emphasised to parents and community members that we were not part of the trial, did not want to check or encourage their participation, and would not share information on individuals with trial staff. With trial staff, we emphasised that we were not checking procedures and would not report individual comments or behaviour to supervisors. Critical comments about the trial from both parents and trial staff suggest some success in building rapport and encouraging openness. However, the possibility of influencing responses was considered during analysis.

Conclusion

The idea that research should be acceptable to potential participants is ambiguous and complex. Being specific about what is meant by acceptability (for example, agreement to participate, or satisfaction with all trial procedures), and considering

how and why acceptability varies, could provide a more nuanced picture of acceptability that enables identification of ethical gaps and responsive trial design.

The six dimensions of acceptability described in this article - how much, what, when, under what circumstances, to whom and why – provide one set of possible areas to consider in examining acceptability. Future research could examine the value of these dimensions or other frameworks for understanding acceptability, as well as the strengths and weaknesses of different empirical methods for exploring community views.

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Six dimensions of research trial acceptability: how much, what, when, in what circumstances, to whom and why?

Research highlights

- Highlights ambiguity in the idea that research must be acceptable to invited participants
- Examines acceptability of a trial to parents invited to enrol their children
- Indicates differences between giving consent and seeing a trial as acceptable
- Acceptability varies in degree and between times, components, contexts and people
- Suggests six dimensions of variation as a guide for future acceptability research