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

3

4 **Abstract**

5

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

9

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

15

16 Parents were not neatly split between those who saw the trial as acceptable and
17 those who did not; instead there were mixed and changing feelings among parents
18 who enrolled their children, and among those who withdrew or did not take part.

19 Some parents agreed to participate but had concerns about the trial, while others
20 expressed satisfaction with the trial but still did not take part.

21

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

26 participation or non-participation.

27

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

34

35 **Keywords:**

36 acceptability, ethics, community, Malawi, medical research

37 **Background**

38

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

51

52 While the importance of acceptability seems clear, its meaning is more ambiguous;
53 indeed, the idea of acceptability among people affected by research has been
54 criticised as “extremely vague” (Macdonald, 2017, p. 32). Dictionary definitions
55 include both positive and negative situations: acceptable is defined as both
56 “welcome, pleasing” and “barely satisfactory or adequate” (Merriam-Webster,
57 2017a), while accept can mean “receive willingly” or “endure without protest”
58 (Merriam-Webster, 2017b). Discussions about the acceptability of research to invited
59 participants often lack explicit definitions (Feeley et al., 2009). Some analyses
60 equate acceptance with participation, contrasting this with refusal to participate, as in
61 “deciding whether to accept or decline the research” (Mfutso-Bengo et al., 2008, p.

62 58; other examples include Gysels et al., 2008; Fayter et al., 2007; Moynihan et al.,
63 2012). However, these categories of participating and refusing can hide substantial
64 variation in views on study procedures (Fairhead et al., 2004). Further, researchers
65 often discuss promoting “acceptance” when they mean ensuring “tolerance” or
66 “avoiding organised opposition” (Lavery, 2017). To accommodate this variation in
67 meaning, we adopt a working definition of acceptability as a perception among
68 invited participants that the research design is, to varying extents, “favourab[le]”
69 (Feeley et al., 2009, p. 86), “agreeable, palatable, or satisfactory” (Proctor et al.,
70 2010, p. 67). This definition reflects our focus on acceptability of study designs to
71 participants as ethically significant.

72
73 As well as ambiguity regarding its meaning, assessment of acceptability is
74 complicated by subjectivity, variability and dependence on context. Acceptability is
75 not a fixed property of a trial or particular research procedure, but rather determined
76 by individual perceptions, and shaped by personal and social contexts. This
77 influence of context is discussed explicitly in some accounts of views on research
78 among participant communities (Fairhead et al., 2004; Kingori, 2015), and suggested
79 by studies on willingness to participate (Cunningham et al., 2018; Gamble et al.,
80 2012; Otwombe et al., 2011; Trauth et al., 2000) and reasons for participation or
81 refusal (Gysels et al., 2008; Strömmer et al., 2018) that describe varied perspectives
82 among target participants. However, the significance of contextual variability is
83 explored more extensively in literature on acceptability of health interventions. As
84 this literature suggests, different individual, household or group circumstances and
85 priorities generate varied perceptions of acceptability (Heise, 1997; Montgomery et
86 al., 2010). Research on health interventions also shows that acceptability can

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

93
94 Although existing literature points to these variations in acceptability, the concept of
95 acceptability has not been a specific focus in discussions about research
96 participation. We lack frameworks for examining acceptability among invited
97 participants, and reviews of research on trial participation and acceptability call for
98 more in-depth analysis and understanding of individual variation (O’Cathain et al.,
99 2014; Ross et al., 1999). Some approaches to assessing acceptability may miss
100 important variations in and reasons behind invited participants’ perceptions. For
101 example, assessing acceptability based on consent to enrol or using single timepoint
102 questionnaires (e.g. Richards et al., 2014; Stead et al., 2005; Wallace et al., 2018)
103 may overlook different degrees of acceptability, changes over time, or contexts
104 affecting decisions on enrolment. Qualitative reports may also neglect underlying
105 contexts or describe only limited areas of variation (for example, between individuals
106 rather than over time) (e.g. Crawley et al., 2013; Gafos et al., 2017). Given the
107 ethical importance of acceptability and its ambiguity, further work to clarify this
108 concept may support more nuanced investigation of participant perceptions to inform
109 responsive trial design.

110

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

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

117

118 The vaccine trial examined whether malaria infection affects immune response to
119 influenza vaccine in children (the FLUVAC trial, details in Peterson, 2016). The trial
120 took place in Chikwawa, a rural district in Southern Malawi where under 5 mortality is
121 62 per 1000 live births and the poverty rate is 82% (compared to 73 per 1000 and
122 51% for Malawi overall, Government of Malawi, 2012; National Statistical Office,
123 2017). Approximately 1300 children aged 6 to 59 months were recruited.

124 Participation involved three main appointments, spaced one month apart. Children
125 received the influenza vaccine at the first two appointments, and had samples taken
126 at all three appointments, including a venous blood sample to measure influenza
127 serology, a finger prick blood sample to test for the malaria parasite (not in real time),
128 and stool samples from a subset of children. A point of care rapid diagnostic test for
129 malaria was administered to febrile children to guide treatment. Trial teams rotated
130 between 28 villages, spending approximately two weeks at a time in each village and
131 returning one month later for follow-up visits.

132

133 Given the age of child participants, enrolment was decided by parents. Fieldworkers
134 and community volunteers approached parents in their homes and invited them to
135 visit a study tent assembled in each village, where further information was provided.

136 Trial staff gave parents an information sheet describing procedures, risks (potential

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

149

150 **Methods**

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

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

172
173 We also conducted participant observation of trial processes. This involved
174 accompanying fieldworkers as they approached parents, observing informed consent
175 procedures, attending community meetings about the trial, and holding informal
176 discussions with trial staff and community members in trial villages. Observation was
177 undertaken primarily by a Malawian researcher of equivalent seniority to trial staff
178 (MP), with some visits by KG. Notes were taken during observation and expanded
179 the same day.

180
181 Data analysis was ongoing throughout fieldwork. The research team regularly
182 discussed emerging issues to identify aspects for further investigation, including
183 searching for conflicting data or alternative explanations (Patton, 2002). Later
184 analysis involved thematic coding (Gibbs, 2008) of observation notes and interview
185 transcripts in NVivo, using a combination of emerging themes (such as concern
186 around blood samples) and broader categories related to the research objective

187 (such as reasons for participation). Initial transcripts were coded independently by
188 KG and MP, and compared to generate a common coding frame that was then
189 adapted with further coding (see Supplementary file 3) [INSERT LINK TO ONLINE
190 FILE 3]. We used qualitative tables that displayed codes against cases to compare
191 perceptions between parents, and memos to capture emerging ideas (Gibbs, 2008).
192 Interview and observation data were compared to check and extend interpretations.
193
194 During analysis, we identified multiple variations in acceptability, for example
195 between contexts and over time. These variations were identified through a
196 combination of reviewing coding, looking across cases and reading individual cases.
197 For example, material coded as 'reasons for withdrawal' and 'regret' pointed to
198 changes in acceptability over time, while reviewing the qualitative tables helped to
199 indicate variations in acceptability between individual contexts. Initial ideas about
200 variations were then explored further through re-reading coded sections and
201 transcripts to check and develop our understanding. We progressively refined our
202 categorisation of these variations to identify six dimensions of acceptability: the
203 degree of acceptability, what is acceptable, when a trial is acceptable, variation
204 between circumstances, variation between people, and reasons for participation.
205 This final categorisation was developed through a process of logical analysis
206 (Patton, 2002) that drew on variations identified inductively, and variations to which
207 we were sensitised from literature on acceptability and our experience with the realist
208 evaluation emphasis on "what works, how, why, for whom, to what extent and in
209 what circumstances, in what respect and over what duration" (Wong et al., 2017, p.
210 21). We worked back and forth between these sensitising concepts and our data to
211 develop a set of dimensions that matched parents' experiences (Patton, 2002). The

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

215

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

221

222

223 **Results**

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

233

234 **How acceptable is the trial? Tolerance or satisfaction**

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

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

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

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

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

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

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

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

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

261 “I will just be strong”.

262

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

267

268

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

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

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

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

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

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

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

292

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

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

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

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

311 ID14)

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

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

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

321

322

323 **When is the study acceptable? Reassurance and regret**

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

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

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

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

339 What disturbed me was that people said another child's blood was completely
340 finished ... I listened to what others were saying and didn't go there with the child.

341 These were lies and I know we made the wrong choice. (Mother, non-participant,
342 ID40)

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

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

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

356

357

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

359 Perceptions of the trial were shaped by conditions within the trial and wider contexts.

360 The influence of internal trial conditions is illustrated in the previous discussion of

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

367 Half a bottle of squash is not enough based on how they are collecting blood. ...

368 Half a bottle is very little, they are robbing us. If they were giving us money to buy
369 food, it would have been better. (Mother, participant, ID19)

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

373

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

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

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

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

391

392

393 **Who sees the trial as acceptable? Individual contexts and perceptions**

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

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

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

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

411 (Mother, non-participant, ID11)

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

414

415

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

417 The reluctant participation noted among some parents indicates a distinction
418 between agreeing to participate and seeing the trial positively. This distinction was
419 further apparent when examining reasons for participation and non-participation.

420 Sometimes enrolment or withdrawal was based on decisions about trial benefits and
421 risks, including aspects previously mentioned such as protection from flu, medical
422 assistance and material compensation, or side effects, suspicion about blood
423 samples and inadequate compensation. However, sometimes reasons for
424 participating or not participating did not involve views of the trial. For example, some
425 parents intended to participate but arrived at the study tent after recruitment had
426 finished:

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

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

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

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

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

443
444 In contrast, for some parents pressure from other people compelled participation. For
445 example, one couple initially enrolled to avoid criticism from the village chief:

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

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

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

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

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

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

462

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

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

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

478 They are the doctors, so if that's what they think, it's good to do it like that. ...

479 There wasn't a reason to ask them why or to caution them, they are the ones who
480 know and that was the procedure they came with. (Mother, participant, ID05)

481

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

486

487

488 **Discussion**

489

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

499

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

511
512 In relation to what people find acceptable, several benefits and disadvantages
513 perceived by invited participants for this vaccine trial are reported for other research,
514 including appreciation of access to health care or material compensation, and
515 concerns around blood samples (Fisher et al., 2011; Mfutso-Bengo et al., 2008,
516 2015; Masiye et al., 2008). Those invited to enrol weigh up these perceived benefits
517 and risks (Fairhead et al., 2004; Fisher et al., 2011). More generally, an
518 understanding of trials as having welcome and undesirable aspects is reflected in the
519 emphasis on benefits, risks and burdens within ethics guidance (Emanuel et al.,
520 2004; Nuffield Council on Bioethics, 2015). The role of rumours and misinformation
521 or misunderstanding about trial processes is also widely documented (Kingori et al.,
522 2010; Mitchell et al., 2002; Munalula-Nkandu et al., 2015; Ndebele et al., 2014).
523 Misunderstanding may reflect the content and communication of trial information, but
524 participants' experiences and interests also affect their interpretations, and decisions
525 may involve assumptions and intuitive judgements rather than informed deliberation
526 (Abhyankar et al., 2016; Woolfall et al., 2013).

527
528 The idea that acceptability changes over time is evident in reports of withdrawal from
529 trials, for example in response to apparent side effects, new information or changing
530 personal situations (Gikonyo et al., 2008; Gillies and Entwistle, 2012). Again ethics
531 guidelines acknowledge this potential for changing views , here in relation to consent
532 as an ongoing process and the right to withdrawal (CIOMS, 2016).

533
534 Existing literature also shows the influence of context on acceptability. In particular,
535 research in many low income countries suggests poverty and inadequate health

536 services mean research becomes an opportunity to access care (Ravinetto et al.,
537 2015), an influence highlighted in the idea of an ‘empty choice’ (Kingori, 2015).
538 Variations in acceptability between individuals are also widely documented, including
539 the influence of gender, a child’s health and previous research experience (Fisher et
540 al., 2011; Kamuya et al., 2015; Mfutso-Bengo et al., 2008), as well as the
541 heterogeneity of research communities more generally (Marsh et al., 2011). Ethics
542 guidelines also discuss this role of context, including study procedures, individual
543 and household factors, and political and social environments (Nuffield Council on
544 Bioethics, 2002).

545

546 Finally, previous research also supports a distinction between participation and
547 acceptability of study procedures. In particular, research in Malawi and other settings
548 shows the influence of pressure from relatives and chiefs and of competing
549 employment obligations, such that decisions on participation reflect more than
550 individual views of study benefits and burdens (Angwenyi et al., 2014; Fairhead et
551 al., 2004; Magazi et al., 2014; Marsh et al., 2011; Mfutso-Bengo et al., 2008).

552 Unquestioning faith in researchers and the role of blind trust in generating
553 acceptability are also described in other contexts (Marsh et al., 2011), partly linked to
554 conflated researcher and clinician roles and the influence of dependent trust on
555 healthcare decisions more generally (Gilson, 2003; Molyneux et al., 2005). Limited
556 understanding of the right to withdraw is also widespread (Afolabi et al., 2014). In
557 line with these findings, theoretical discussions of research ethics note that
558 participation “may be based on reluctant acquiescence rather than on enthusiastic
559 co-operation” (Social Research Association, 2003, p. 29), while non-participation
560 may result from other priorities rather than negative views of research (Hammersley,

561 2017).

562

563 Acceptability, then, varies in degree, between trial components, over time, and
564 between people and places. One possible reaction is to abandon acceptability to
565 potential participants as a principle for ethical research, as argued by some who see
566 acceptability as too hard to define and dependent on social position to be a useful
567 consideration (Hammersley, 2017; Hunter, 2017; Macdonald, 2017). Acceptability
568 alone does not make a study ethical; for example high compensation might increase
569 satisfaction but create undue inducement, and acceptability is one principle to
570 consider alongside criteria such as scientific validity and social value (Emanuel et al.,
571 2004). Nevertheless, we suggest the idea of acceptability remains useful in drawing
572 attention to perceptions and experiences among potential participants. However, the
573 variability documented here raises questions about how we define and assess
574 acceptability. Should we only consider a trial acceptable if everyone in a community
575 is enthusiastic about all aspects of the trial, throughout the trial and afterwards,
576 regardless of their socio-economic circumstances, or should 'acceptable' simply
577 mean there are sufficient participants to meet recruitment targets? Should a trial be
578 considered ethical if participants are unhappy about their experience, as long as they
579 made an informed and voluntary decision to participate?

580

581 Given the difficulty of defining a common standard above which trials are considered
582 acceptable, a more productive focus may be the nature of insights produced through
583 acceptability research. We suggest that researchers examining acceptability might
584 first, clarify their definition of acceptable and any associated benchmarks to avoid
585 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

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

636

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

649

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

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

667

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

680

681

682 **Conclusion**

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

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

688

689 The six dimensions of acceptability described in this article - how much, what, when,
690 under what circumstances, to whom and why – provide one set of possible areas to
691 consider in examining acceptability. Future research could examine the value of
692 these dimensions or other frameworks for understanding acceptability, as well as the
693 strengths and weaknesses of different empirical methods for exploring community
694 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