

BMJ Paediatrics Open

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

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

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

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

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

BMJ Paediatrics Open**Cultural considerations for informed consent in pediatric research in low and middle income countries: A scoping review**

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2018-000298
Article Type:	Original article
Date Submitted by the Author:	02-Aug-2018
Complete List of Authors:	Colom, Marcela; Wuqu' Kawoq Rohloff, Peter
Keywords:	Ethics, Health services research

SCHOLARONE™
Manuscripts

Review Only

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

1 TITLE PAGE

2
3 Cultural considerations for informed consent in pediatric research in low and middle
4 income countries: A scoping review

6 Marcela Colom MD¹, Peter Rohloff MD PhD^{1,2,3}

8 ¹Wuqu' Kawoq | Maya Health Alliance, 2da Avenida 3-48 Zona 3, Barrio Patacabaj,
9 Tecpán, Chimaltenango, Guatemala

11 ²Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA

13 ³ Corresponding Author. Peter Rohloff, Brigham and Women's Hospital, 75 Francis Street,
14 Boston, MA, 02115. Phone: 617-278-0055. Fax: 888-372-2354. Email:
15 prohloff@bwh.harvard.edu

19 Word count: 3010

1
2
3 24 **ABSTRACT**
4
5
6 25

7
8 26 Introduction: Conducting research with children in low- and middle-income countries
9
10 27 (LMICs) requires consideration of socioeconomic inequalities and cultural and linguistic
11
12 28 differences. Our objective was to survey the literature on informed consent in pediatric
13
14 29 LMIC research, assessing for practical guidance for culturally- and linguistically-
15
16 30 appropriate procedures.
17
18

19 31
20
21 32 Methods: We conducted a scoping review on informed consent in pediatric LMIC research
22
23 33 searching the Pubmed, Web of Science and PsycINFO databases. Eligible articles were
24
25 34 published in English, from any date range, of any study design or format.
26
27
28 35

29
30 36 Results: The search identified 2,027 references, of which 50 were included in the analysis
31
32 37 following full-text review. Reviewed guidelines emphasized individual, informed and
33
34 38 voluntary consent from parents and caregivers. Reviewed articles provided detailed
35
36 39 practical guidance on adapting these guiding principles to LMIC settings, including
37
38 40 considerations for community engagement, verbal or other alternative consent procedures
39
40 41 for low-literacy settings or less-commonly spoken languages, and guarding against
41
42 42 therapeutic misconception by caregivers. There was uncertainty, however, on how to best
43
44 43 protect individual autonomy, especially when influenced by gender dynamics, leadership
45
46 44 hierarchies, or the social status of researchers themselves. There was, furthermore, limited
47
48 45 research discussing the special case of research involving adolescents or of procedures for
49
50 46 documenting assent by participating children.
51
52
53
54
55
56 47

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

48 Conclusions: A scoping review of pediatric research in LMICs revealed substantial
49 guidance on several features of culturally appropriate informed consent . However,
50 additional research and guidance is needed, especially in the areas of gender imbalances,
51 research with adolescents, and children’s own assent to participate in research.

Confidential: For Review Only

54 INTRODUCTION

55

56 Prior to World War II, there was little international consensus on the ethical conduct of
57 human subjects' research. The Nuremberg code, developed in 1947 during the Nuremberg
58 war crimes trials, was one of the first attempts to articulate basic ethical principles, such as
59 the right to informed consent.(1) Subsequently, the World Medical Association's (WMA)
60 Declaration of Helsinki in 1964 provided a more definitive consensus statement on the core
61 principles of ethical conduct of research--beneficence, self-determination, and informed
62 consent--which is widely considered the foundational international document in modern
63 research ethics.(2) Practical guidance on ethical practice is well codified in the joint
64 statements produced by the Council for International Organizations of Medical Sciences
65 (CIOMS) and the World Health Organization (WHO).(3)

66

67 Extension of ethical research principles to include considerations appropriate for research
68 in pediatric populations are also important, including guidance on obtaining informed
69 consent from parents or guardians, obtaining assent from children themselves, and
70 weighing the balance of risks and benefits of proposed research.(3,4) Improvements in the
71 conduct and volume of pediatric clinical trials, which have historically been few in number
72 and of lower quality than corresponding trials in adult subjects, have also recently been
73 advocated.(5)

74

75 However, there still remains uncertainty around how best to implement international ethical
76 principles of pediatric research in some settings. This is especially the case in low and
77 middle-income countries (LMICs), and in research with as indigenous populations,

1
2
3 78 speakers of less-common languages, or populations with high levels of illiteracy.
4
5 79 Practically, we experienced this recently while designing a clinical trial of a nutrition
6
7 80 intervention for indigenous Maya children in rural Guatemala, and our experience
8
9
10 81 navigating consent, literacy, and translingual adaptation in this population prompted our
11
12 82 interest in more formally exploring the topic.(6) To this end, here we conduct a scoping
13
14 83 review of the existing literature on cultural and contextual considerations for informed
15
16 84 consent in the conduct of pediatric research in LMICs. Through this review, we identify
17
18 85 evidence for specific culturally- and contextually-sensitive practices, as well as areas where
19
20 86 additional research and guideline development is needed.
21
22
23
24
25

26 88 **METHODS**

27 28 89 29 30 90 **Search and inclusion strategy**

31
32
33 91
34
35 92 To identify articles, we searched the PubMed, Web of Science and PsycINFO databases.
36
37 93 We conducted searches using a combination of the following key terms: “pediatric” or
38
39 94 “children” or “adolescents”; “research” or “biomedical research”; “consent” or “informed
40
41 95 consent” or “ethics”; “developing countries” or “low income countries” or “middle income
42
43 96 countries”; “illiteracy”; “culturally competent”. We used no date limits and included all
44
45 97 articles published through May 2018. In addition, we visited the websites of international
46
47 98 health policy organizations to identify ethics guidelines for the conduct of research in low-
48
49 99 and middle-income countries. We also manually reviewed the reference lists of articles
50
51 100 identified using the above methods. For this scoping review, of the articles identified above
52
53 101 we included for analysis any type of study design or format (original research, commentary,
54
55
56
57
58
59
60

1
2
3 102 case study, review, expert opinion), which addressed the informed consent process
4
5 103 specifically for pediatric or adolescent populations in low or middle-income
6
7 104 countries. Articles not in English were excluded.
8
9

10
11 105

12 106 **Data extraction and synthesis**

13
14 107

15
16 108 We exported identified articles into an Excel spreadsheet template which recorded location
17
18 109 of study, study type and design, study context, aspects of informed consent examined, and
19
20 110 key findings. Both authors reviewed the study titles and abstracts. After removal of articles
21
22 111 which were deemed not eligible for inclusion, one author (MC) performed a full text review
23
24 112 of all the remaining articles. As a scoping review to assess the patterns of existing
25
26 113 literature on informed consent in LMIC pediatric research, assessments of individual study
27
28 114 bias and quality were not performed. Data extracted from articles was collated in summary
29
30 115 form (Table 1), and major qualitative findings are presented in the following narrative
31
32 116 synthesis.
33
34
35
36
37

38 117

39 118 **RESULTS**

40
41 119

42 120 **Results of literature screen**

43
44 121

45
46 122 A total of 2,027 candidate titles were identified through database searches, supplemented
47
48 123 by reference list and website reviews. Of these, 1,721 did not meet eligibility criteria, and
49
50 124 306 were included for abstract review. If the abstract was not available but full text was, the
51
52 125 title was included for full text review. After abstract review, 50 duplicates were found, one
53
54
55
56
57
58
59
60

1
2
3 126 was not in English, 7 were not available (abstract nor full text), and 170 abstracts did not
4
5 127 meet inclusion criteria. 78 articles were selected for full text review, of which 24
6
7 128 subsequently did not meet inclusion criteria, one was in French, one was a duplicate, and
8
9
10 129 two did not have available full text. Therefore 50 full-text articles were included in this
11
12 130 review (Figure 1, Tables 1-2).
13
14
15 131

17 132 **Summary of guidelines and commentaries**

18
19 133
20
21 134 We selected for review five guidelines that address issues of informed consent in
22
23 135 international settings and in research involving children and summarize key
24
25 136 recommendations in Table 1. All guidelines emphasize the importance of obtaining
26
27 137 individual, informed and voluntary consent for research.(3,4,7–9) Several guidelines
28
29 138 suggest modifications appropriate for lower-resource settings, such as obtaining witnessed
30
31 139 verbal consent when literacy is a barrier. (7,9) The United States National Bioethics
32
33 140 Advisory Commission (NBAC), for example, even acknowledges that oral consent might
34
35 141 even be preferable in some circumstances.(8) However, as several commentaries on the
36
37 142 guidelines note, there is little specificity on how best operationalize these core principles,
38
39 143 such as how to formally document verbal consent.(10,11)
40
41
42
43
44
45 144

46
47
48 145 Another important consideration of LMIC research addressed in guidelines is an emphasis
49
50 146 on the need to at times obtain consent from community stakeholders and leaders, or other
51
52 147 key local decision makers. Nevertheless, all guidelines unanimously assert that community-
53
54 148 based consent can never replace individual consent. When local cultural practices around
55
56
57
58
59
60

1
2
3 149 community-based consent contradict core principles of the international consensus on the
4
5 150 informed consent process, such as the need for voluntary individual consent, researchers are
6
7 151 advised to search for culturally sensitive ways of providing all information to potential
8
9 152 participants without compromising the substantive ethical standard of informed consent, an
10
11 153 adaptive process in which local research ethics committees are expected to place a
12
13 154 substantial role. (8,10–12)
14
15
16
17
18
19

155

20 156 Finally, with respect to children or adolescents not capable of providing informed consent,
21
22 157 in addition to obtaining consent from parents or legal representatives, most guidelines also
23
24 158 reinforce the need to obtain assent from the child or adolescent in an age-appropriate way.
25
26 159 (3,4,7,9) The CIOMS guidelines on research involving children and adolescents states that
27
28 160 as adolescents reach the age of maturity, their agreement to participate may be ethically
29
30 161 considered as informed consent. However, if they legally remain minors, researchers are
31
32 162 cautioned that consent from a parent is still generally needed, but a list is provided of
33
34 163 possible situations when parental consent might be waived, such as with legally
35
36 164 emancipated adolescents, or under circumstances where obtaining parental consent is not
37
38 165 desirable because of the research topic. (3)
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

166

167

168

169

170

171

172

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

173

Confidential: For Review Only

bmjpo: first published as 10.1136/bmjpo-2018-000298 on 5 December 2018. Downloaded from <http://bmjpaedsopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

174 **Table 1 Summary of selected major guidelines, reports and reviews on ethical**
 175 **conduction of research in children**

Guideline	Core principles	Considerations for adapting to low-resource, low-literary, and minority language settings
World Medical Association, Declaration of Helsinki(7)	<ul style="list-style-type: none"> • If a research subject is not capable of giving informed consent, it should be sought from a legally authorized representative • When the subject can give assent to decisions about participation in research, assent should be sought in addition to consent. Dissent should be respected 	<ul style="list-style-type: none"> • Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information • Consent should be given preferably in writing, if not the non-written consent must be formally documented and witnessed
Council for International Organizations of Medical Sciences(3)	<ul style="list-style-type: none"> • Obtain permission from a parent or a legally authorized representative of the child • Obtain assent from the child or adolescent according to his or her capacity and after having been provided with information tailored to the child's or adolescent's level of maturity 	<ul style="list-style-type: none"> • Consult with and engage communities in the informed consent process • Obtained a signed form as evidence of informed consent, justify any exceptions to this general rule and seek approval of the research ethics committee
Standards for Research (StaR) in Child Health(4)	<ul style="list-style-type: none"> • Obtain consent and assent when age-appropriate • Provide age-appropriate, clear, concise, and on-going information for parents and children 	<ul style="list-style-type: none"> • Provide clear justification to involve a particular population and equitable sharing of benefits and risks • Community consultation can be helpful but does not replace the need for individual consent • Strengthen composition and expertise of local ethics committees
National Bioethics Advisory Commission, Ethical and policy		<ul style="list-style-type: none"> • Develop culturally appropriate ways to disclose information that is necessary for adherence to the ethical

<p>issues in international research(8)</p>		<p>standard of informed consent</p> <ul style="list-style-type: none"> • Develop procedures to ensure that participants understand the information provided in the consent process • Respect local requirements of asking permission from community representatives for approaching potential participants, but respect the requirement of individual informed consent • Ethics review committees can waive the requirements of written and signed consent in accordance with local cultural norms
<p>European Council and European Parliament Guidelines(9)</p>	<ul style="list-style-type: none"> • Consent should be sought from parents or legal representatives • Information should be provided to the minor according to its capacity of understanding • The explicit wish of a minor who is capable of forming an opinion and assessing information to refuse participation should be considered 	<ul style="list-style-type: none"> • The individual or legal representative has to give written consent. If the individual is unable to write, oral consent may be given in the presence of at least one witness, as provided for in national legislation

1
2
3 1764
5
6 177 **Thematic summary of research on consent in LMIC pediatric research**
78
9 178

10
11
12 179 Existing published work on informed consent in pediatric research in LMICs consists
13
14 180 largely of case studies describing the experience of individual research teams and
15
16 181 discussing the challenges and solutions utilized when adapting consent processes to their
17
18 182 local context. We summarize several major themes emerging from these studies here and
19
20
21 183 detail key findings from the reviewed articles in Table 2.
22
23

24 184

25
26
27 185 Understanding social norms around decision making and protecting individual autonomy
28
29

30 186 An important principle highlighted in international guidelines on informed consent
31
32 187 in LMICs is appropriate and early engagement with existing local leadership structures
33
34 188 (such as a council of elders) balanced against respect for the autonomy of individual
35
36 189 children or their caregivers.(3,8) In practice, this can be a delicate balance to maintain.
37
38
39 190 Kongsholm and colleagues, for example, describe consent processes in rural Pakistan,
40
41 191 where family structures are patriarchal and hierarchical. In this setting, consent procedures
42
43 192 involved first seeking consent from an elder, who provided initial consent for the entire
44
45 193 family. However, under this approach, the voluntariness of individual participants may be
46
47 194 undermined, and it is unclear how best to ensure that individuals still retain an “opt out”
48
49 195 mechanism.(13)
50
51

52
53
54 196
55
56
57
58
59
60

1
2
3 197 Another important consideration explored by several studies is understanding how not all
4
5 198 potential consenting caregivers may feel empowered to decline participating in research.
6
7 199 Consent procedures administered by local research personnel or by individuals with high
8
9
10 200 social status, such as physicians, may inspire trust.(13,14) However it may also make them
11
12 201 reluctant to decline participation, or to resist active participation. For example, in one study
13
14 202 in Kenya, explicit refusals to participate were often considered to be impolite. Here
15
16 203 researchers found that caregivers expressed their unwillingness to participate by delaying
17
18 204 the consent process, or by participating inconsistently in research procedures even after
19
20 205 initially having consented to the study.(15)
21
22
23
24
25
26

27 207 Adapting consent procedures to low-literate settings

28
29
30 208 There is strong consensus in international ethics guidelines that written, informed
31
32 209 consent is preferred when conducting research. In the case of pediatric research, this again
33
34 210 typically involves obtaining written consent from one or both primary caregivers.(4,9,16)
35
36 211 However, in many LMIC settings, literacy may be low or a high value may be placed on
37
38 212 oral interactions, and lack of alternative consent procedures may violate another core ethics
39
40 213 principle, namely the equitable distribution of research benefits and burdens across
41
42 214 populations.(3,14,17) Several of the studies we reviewed described these procedures, with
43
44 215 verbal consent commonly being obtained, most often in the presence of a literate witness
45
46 216 who is able to read available consent documents. (13,14,17,18) In one very thoughtful
47
48 217 piece, Kalabuanga and colleagues note, however, that ad hoc witnesses may often impose
49
50 218 their views on the consenting caregiver and their child, rather than encourage dialog and act
51
52 219 as a safeguard.(18) The authors suggest that these challenges by be mitigated by careful
53
54
55
56
57
58
59
60

1
2
3 220 vetting and training of independent witnesses or, alternatively, but allowing potential
4
5 221 consenting caregivers to use a trusted relative or friend as their witness.(18)
6
7

8 222
9

10
11 223 Working in indigenous or less-commonly-spoken languages
12
13

14 224 International ethics guidelines emphasize that research information should be
15
16 225 provided to consenting caregivers in a local language understandable to the
17
18 226 individual.(7,8,16) However, this is most commonly understood to be a working lingua
19
20 227 franca, and the issue of and practical approach to provisioning consent processes in an
21
22 228 indigenous language is largely unaddressed in LMICs.(19) This is an important
23
24 229 consideration, given that a substantial proportion of the potential pediatric research
25
26 230 population in LMICs are from populations that speak indigenous or less-commonly-spoken
27
28 231 languages.(20) In an interesting review of lessons learned in a pediatric vaccine trial in
29
30 232 West Africa, Martellet and colleagues noted difficulties in preparing consent procedures in
31
32 233 some of the less-common language groups included in the trial, where use of the written
33
34 234 form was uncommon. They describe alternative procedures, such as the preparation of
35
36 235 recordings of consent scripts in local languages and extensive practice sessions with
37
38 236 research staff obtaining consent in local languages.(17) Similarly, another vaccine trial in
39
40 237 The Gambia described the successful use of audio-visual Speaking Books in local less-
41
42 238 common languages to consent caregivers. (21)
43
44
45
46
47
48

49 239
50
51

52 240 Gender dynamics in caregiver consent
53
54
55
56
57
58
59
60

1
2
3 241 Local gender dynamics and decision making procedures when consenting male and
4
5 242 female caregivers for research is an important consideration. For example, a female
6
7 243 caregiver may be inclined to allow her child to participate, but be unable to do so if her
8
9 244 husband or another male authority figure refuses.(13) The opposite may also occur, if a
10
11 245 research study is consented by a male figure, but requires significant participatory effort
12
13 246 from the primary female for study-related activities, leading the woman to express their
14
15 247 refusal through procedural delay or inconsistent participation.(15) Given concerns about
16
17 248 gender power imbalance and potential repercussions for consenting female caregivers,
18
19 249 some studies discussed working to routinely involve fathers or male authority figures in the
20
21 250 consent process for more complex or higher-risk research interventions.(15,22) In one
22
23 251 interesting study based in India, Rajaraman and colleagues found that caregivers were
24
25 252 more likely to actively participate in the consent process when both were present. They also
26
27 253 observed, however, that this factor may have been do the fact that most study staff
28
29 254 obtaining consent were male, and they call for more research on how the gender of research
30
31 255 staff impacts the consent process.(23)
32
33
34
35
36
37
38
39
40

41 257 Disclosing potential benefits and risks of participation in research
42
43

44 258 Participation in some research studies, particularly those with a controlled design,
45
46 259 may not result in direct benefit to participants. Several studies report difficulties explaining
47
48 260 to caregivers that medical research procedures may not result in direct benefit to their
49
50 261 children. Indeed, therapeutic misconception might be hard to avoid in certain contexts, as it
51
52 262 might be affected by factors like educational level and cultural and religious beliefs about
53
54
55
56
57
58
59
60

1
2
3 263 disease.(13,18) However, explicit attention to this dynamic while designing consent
4
5 264 procedures may help to ensure caregiver comprehension.(24)
6
7

8 265
9

10
11 266 At the same time, care must be given to a culturally-appropriate degree of information
12
13 267 disclosure. For example, in several studies, caregivers—especially those of higher
14
15 268 socioeconomic or educational status—were more likely to participate when provided with
16
17 269 detailed and in-depth information about the study processes and given opportunities to ask
18
19 270 questions.(12,22,23,25) At the same time, other case studies point out how over-detailed
20
21 271 discussion of study procedures or scientific rationale may provoke unneeded reserve or
22
23 272 suspicion where such detailed disclosures by health professionals are not culturally
24
25 273 customary.(13)
26
27
28
29

30 274
31
32

33 275 Finally, in settings where access to healthcare and other important social goods may be
34
35 276 limited, even basic diagnostic or ancillary procedures that occur as part of a research study
36
37 277 may be better than the local standard of care, leading to an undue inducement for caregivers
38
39 278 to enroll their children in research, even after being informed about the experimental nature
40
41 279 or studies and the risk-benefit balance.(11,13,18) These considerations highlight the
42
43 280 importance of considering the socio-economic and cultural background of study settings
44
45 281 well before beginning research and making plans to incorporate appropriate early, equitable
46
47 282 benefit-sharing measures when possible.(18)
48
49
50

51 283
52
53

54
55 284 Adolescents
56
57
58
59
60

285

Adolescents constitute a special population with vulnerabilities different from those of adults and younger children, and they should be included in research that addresses their specific needs. However, as legal minors they often cannot give informed consent for research.(16) In research in LMICs, regulations vary significantly from country to country regarding when adolescents can provide legal consent for research.(26) For example, even when legal frameworks allow adolescents to seek, for example, contraception services without parental permission, they cannot necessarily provide consent for research on that theme.(27,28) In a scoping review of post abortion care research, Zulu and coauthors discuss how the need to balance adolescents' privacy needs and the demand for parental consent poses difficulties for researchers in this field.(29) Woollett and colleagues describe an interesting case study where they sought consent from a High Court in South Africa for research involving orphaned HIV-positive adolescents. In that study, they provide detailed recommendations for consent involving adolescents, including training staff about confidentiality requirements; recognizing immature decision-making by adolescents and developing appropriate methods for probing comprehension and consent; and utilizing methods that promote active participation in research, such as mobile phones.(28)

302

303 Assent

Pediatric research guidelines are unanimous on the need to obtain age-appropriate assent from children and adolescents who do not provide their own informed consent (Table 1). However, we found very little explicit discussion or description of procedures for

1
2
3 307 obtaining assent in the research reports we reviewed. However, one interesting qualitative
4
5 308 study on parental perceptions of assent in Jordan revealed considerable variability in
6
7 309 caregivers' perspectives about at what age assent should be solicited or, even, if assent
8
9 310 should in all cases be obtained and dissent respected.(22)
11
12
13 311

14
15 312 **Table 2. Summary of articles selected for inclusion in review. [Insert Table 2 here]**
16
17 313

Confidential: For Review Only

Reference (Year)	Study Description	Study Location	Major findings
Kongsholm N et al.(13) (2018)	Qualitative research– interviews with researchers and donors about consent experience for genetic research	Pakistan	Researchers report adaptations to consent process including use of elder and oral consent; involving literate witnesses to validate written forms; and disclosure of information adapted to educational level. Challenges include no knowledge about consent process by participants and therapeutic misconception. Donors' motivations for participating include obtaining direct benefit from their participation and a high level of trust in the research team.
Ott MA et al.(30) (2018)	Review – participation of children of minor parents in research	n/a	Discussion on international research documents and existing laws and practices regarding consent for research for children of minor parents. Few countries have regulations about the subject, which might result in exclusion of those children from research. Authors recommend involving minors in the decision-making about their children and adapting consent procedures so minor parents can participate and their children's vulnerabilities correctly addressed.
Morris M and Wilson P. (31) (2018)	Case study – research on the use of CPAP in intensive care settings	Ghana	Authors describe how consent was obtained, and express concern about the fact that there were no refusals and that this might reflect that consent was not fully informed or participation was not truly voluntary. The authors do not know to which extent parents understood randomization, or that CPAP could be used independently of study participation. They discuss how the lack of access for medical care might influence the consent process.
Zulu JM et al. (29) (2018)	Review - Ethical challenges of post-abortion	Review	Authors included 14 articles in their analysis. Regarding the consent process, challenges identified include

	care research in adolescents in LMICs		difficulties in seeking consent from parents/guardians of adolescents who are below the consent age, vulnerability of adolescents compromising ability to make decisions, fear of losing access to health care affecting informed consent process, and inadequate guidance on how and when to involve communities in the consent process.
Ward CL et al. (32) (2018)	Qualitative research – interviews with stakeholders about ethical aspects in a pediatric malaria vaccine trial	Ghana and Tanzania	Stakeholders identify the importance of community education and a well-adapted consent process in helping avoid misconception about trial benefits and healthcare service provision, as well as in preventing undue inducement by clearly stating risks and benefits.
Woollet MA et al. (28) (2017)	Case study – consent for orphaned adolescents to participate in a mental health study	South Africa	Authors present how consent for research with orphaned adolescents had to be sought from the High Court before approval was granted by academic research committees. The authors discuss how the policy results in excluding vulnerable populations from research and give recommendations for mental health research with adolescents.
Khabour O et al. (22) (2017)	Qualitative research – focus groups to explore parental perceptions about the informed consent and assent process for research	Jordan	Findings show an acceptable understanding of many aspects related to the consent process. However, some parents believed that informed consent is not necessary for questionnaire studies, there were discrepancies regarding the appropriate age for a child's assent, and some parents said they would force their child to participate regardless of child's wishes.
Mboizi R et al. (21) (2017)	Mixed methods research – recall and decay of consent information among parents	The Gambia	Recall of trial procedures and consent process was evaluated using questionnaires at two points in time. Results show overall good recall of consent when using the Speaking Book audiovisual tool. No differences were

	using and audiovisual tool		found between age, occupation, years of education, religion or family type.
Regmi P et al. (33) (2017)	Review – informed consent in health research in LMICs	Nepal	Authors discuss challenges in adapting informed consent: verbal versus written informed consent in areas of limited literacy; difficulties posed by having to translate consent documents to local languages; issues around the legal age to consent, and how clear threshold ages of consent are not clear in local guidelines.
Kalabuanga M et al. (18) (2016)	Case study – Description of the consent process during a malaria clinical trial	Democratic Republic of Congo	Authors identified misunderstanding of the informed consent process among parents. They also identified cases where culturally-accepted guardians might not have legal authority to consent for research. They discuss how the use of a witness can impair parents' autonomy by exerting social pressure. In the context of limited access to care, the ancillary benefits of participating in research may be a strong incentive to participate.
Mandava A et al. (40) (2016)	Review – comparison between consent processes in developing and developed countries	Review	Authors aimed to compare data about comprehension and voluntariness. In both settings comprehension of study information varies among participants, and comprehension of randomization and placebo use is poor. Participants in developing countries seem to be less likely to say they can refuse participation or withdraw and worry more about the consequences of doing so. Recommendations include developing validated questions to measure comprehension and voluntariness and conducting studies on the impact of cultural norms and socio-demographic characteristics on informed consent.
Joseph P et al. (45) (2016)	Qualitative research – Stakeholders' views on	n/a	Regarding the consent process, challenges identified by stakeholders include consent requirements in certain countries that conflict with adolescents'

	international pediatric clinical trials		confidentiality rights; impracticality of using long consent forms with multiple required elements, and the need for guidelines to streamline consent form production.
Joseph P et al. (46) (2016)	Review - Views of stakeholders on aspects of conducting research with children in LMICs	n/a	Regarding informed consent, stakeholders believe that disempowerment, poor education, and difficulty in translating scientific concepts were barriers to informed decision making. Authors recommend simplifying consent forms and presenting them in culturally and linguistically appropriate format with verification of parental comprehension. Authors discuss that Western ethical principles of consent and child assent, autonomy, and individualism need to be contextualized.
Embleton L et al. (34) (2015)	Case study - Ethical guidelines adaptation for three different studies with street connected youth and children	Kenya	The authors describe processes of consent for street-connected children and youth participating in three research projects. They discuss the importance of guidelines and working with local and international committees, ethicists, and the community to identify areas of special concern. Key recommendations include involving the community and working within the local sociocultural context.
Devries K et al. (24) (2015)	Qualitative research - experiences of children participating in a cluster RCT of a school-based violence prevention intervention.	Uganda	Authors describe the consent process for the RCT and present findings from interviews conducted with children after participating. They found some therapeutic misconception about potential benefits and propose that clearer language in the consent forms might help avoid it.
Martellet L et al. (17) (2015)	Case study – Informed consent for a	The Gambia, Mali, India, Senegal,	Informed consent for a vaccine trial was sought from parents/legal guardians of children 1-17 years. Written assent was taken from children

	vaccine trial	Ghana	12-17. They used literate witnesses when participants/parents were illiterate and translated consent forms to local languages. In some areas, consent was done verbally. Written consent forms were always provided. Some study sites used tools to assess understanding of the research project prior to consent.
Morrow B et al. (35) (2015)	Review – Consent for pediatric critical care research in South Africa	South Africa	Authors discuss legal issues in South Africa that create confusion for informed consent for children. They identify barriers to the consent process: impracticability of getting consent when urgent action is needed; the validity of consent in high-stress settings; addressing parents during stressful situations; sociocultural issues and the differences in communication and response to authority figures. The authors discuss alternatives to the process such as prospective informed consent or the deferred consent model.
Kamuya D et al.(15) (2015)	Qualitative – focus groups and interviews conducted with participants of RSV and malaria studies.	Kenya	Authors describe the phenomenon of silent refusal. Possible causes include avoiding conflict within households, maintaining a good relationship with the research team, and retaining study benefits. For women and young adults, it might be a way to exert agency within the patriarchal system. Authors discuss negotiations that take place during the consent process, and how ethical principles are interpreted and negotiated in a context-specific way.
MacLeod SM et al. (11) (2015)	Review – ethical issues of pediatric drug trials in LMICs	n/a	The review discusses vulnerabilities of pediatric research participants, in particular children in LMICs. Authors discuss characteristics of the consent process, and how socioeconomic status, religious belief, and distribution of power affect decisions to participate. They point to the need to consider cultural differences, and the appropriateness of obtaining

			community consent in some contexts.
--	--	--	-------------------------------------

Confidential: For Review Only

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

Serce O et al. (25) (2015)	Quantitative- Questionnaires administered to parents to assess potential participation in research	Turkey	Authors perform univariate and multivariate logistic regression to identify characteristics that might predict participation. Factors associated with willingness to consent include satisfaction with the content of the informed consent and being a business owner. Factors associated with refusal of consent were older age of parents and owning a car. Parents responded that learning more about the trial and its benefits, ensuring health coverage, and payment of transport expenses would positively influence consent.
Millum J and Emanuel E. (52) (2015)	Case study – research with abandoned children	Romania	The authors discuss how research with abandoned children might be constrained by the challenge of getting informed consent. This might result in this vulnerable group not being included in research for reasons of convenience. They argue that vulnerable groups can be protected by enrolling them in studies that pose no or minimal risks.
Swain T. (36) (2014)	Commentary- barriers to pediatric clinical drug trials in low resource settings, with emphasis in India	India	The author discusses how the consent process for research can be affected by poverty and lack of education. The author points out that the consent process should be clear and assent should be sought from children 7-18 years old, as per Indian guidelines. Consent for neonatal studies could be done in an opt-out way.
Angweny V et al. (37) (2014)	Qualitative – interviews and group discussions with researchers, community members and parents	Kenya	Authors describe and analyze the community engagement process for the trial. Concerning the consent process, they present results on parents' understanding of the trial one year after recruitment. They report low levels of understanding about the purpose of the trial and the randomisation process. There appeared to be less understanding of the trial where there was less community engagement.

Bekker L et al. (26) (2014)	Review - Ethical issues of HIV research in resource limited countries	n/a	The authors review ethical issues in HIV research with adolescents in LMICs. They point out best practices for consenting adolescents: auditing ethical-legal requirements for consent; involving adolescents in decision making; ensuring language, age, and cultural appropriateness; and giving sufficient time and resources to consent.
Ruiz-Casares M et al. (51) (2014)	Review – culturally responsive mental health research	n/a	Regarding informed consent, the author discusses how to obtain culturally appropriate consent, how to ensure adequate understanding of the consent information, consideration of community structures, documenting informed consent, and determination of decision-making capacity.
Offringa M et al. (38) (2013)	Review - Background and summary of Standards for Research (StaR) in Child Health published standards on the conduction of pediatric clinical research	n/a	Summary of first 6 StaR Child Health published standards: 1. Consent and recruitment; 2. Containing risk of bias; 3. Data monitoring committees; 4. Determining adequate sample sizes; 5. Selection, measurement, and reporting of outcomes; and 6. Age groups for pediatric trials.
Paré L et al. (47) (2013)	Mixed methods research - assessment of the relevance of the informed consent procedure in a malaria trial comparing the efficacy of two different treatments	Burkina Faso	Results showed that prior knowledge of the trial was significantly associated with the decision to participate. Common reasons for participating were the perceived aid provided by the trial, better quality of care, and better quality of the medication. Information about confidentiality, right to withdraw from the study, and potential risks was poorly retained. Randomization was poorly understood. Authors aim to show that there are other factors besides the information received during the consent process that influence parents' decision to participate in the trial.

Daley C et al. (48) (2013)	Review - ethical issues associated with ASD research in developing countries	n/a	Authors discuss ethical aspects relevant to the conduct of ASD research in developing countries. They mention challenges to informed consent such as parents' lack of knowledge about research.
Vreeman R et al. (39) (2012)	Qualitative research - analysis of community discussion sessions regarding the participation of orphaned children in research.	Kenya	Results showed positive attitudes towards the participation of orphaned children in research, mainly because adults assumed that children would be directly benefited. Consent from parents or guardians was considered necessary but getting assent from children was not. The participation of the community in the consent process was considered appropriate. Authors recommend paying attention to misconceptions about research related benefits.
Denburg A et al. (41) (2012)	Review – ethical aspects and challenges of pediatric oncology research in LMICs	n/a	Authors conducted a review of ethical issues related to standards of care, trial benefits, ethics review and informed consent. They focused on the ethical implications of drug development and intervention research. Regarding informed consent, they discuss illiteracy, social and political power imbalances, validity of consent in face of ancillary benefits of research, mistrust of foreign investigators by parents, and difficulties aligning local perspectives with international norms.
Tindana P et al. (58) (2012)	Qualitative – interviews with research staff and mothers of study participants about the informed consent process for a malaria genetics study	Ghana	The consent process was adapted to include community leaders and groups of women. For individual consent, written forms were used but information was adapted to be more relevant to parents. The timing of consent for in-patient cases was modified to obtain it after children had been stabilized. The provision of medical care and direct benefits to children was identified as a motivation for participating.

Rajamaran D et al. (23) (2011)	Mixed methods research – analysis of relation between parents’ socio-demographic characteristics and likelihood of asking questions during the consent process	India	The study looked at parents asking questions during the informed consent process. 13.4% of parents asked any questions. There was a high association between asking questions and socio-economic and educational status, and with presence of both parents. Authors conclude that consent materials should be interactive, to make comprehension easier, and that in pediatric trials effort should be made to get participation of both parents in the consent process.
Nabulsi M et al. (14) (2011)	Qualitative research – perceptions of Lebanese parents about their children’s participation in research	Lebanon	Fear of potential harm or pain caused to children was identified as a main barrier to parental consent, as were complex consent forms and misunderstanding of randomization. Perceived direct benefits of participation, trust in the doctor and the institution, financial gains or previous positive experience with research identified as motivations to participate. Authors recommend improving communication and building trust with parents to enhance recruitment.
Mystakidou K et al. (42) (2009)	Review – informed consent in human HIV research in developing countries.	n/a	In trials involving children and adolescents, authors discuss the process of enrolling subjects, including challenges in getting informed consent from parents or guardians while protecting the privacy of the subjects. Most studies on this topic involve adolescents, and there is limited data about the assent process in younger children. Authors discuss the characteristics that informed consent should have in the context of HIV trials in the developing world, including the need to address cultural differences.
Nakkash R et al. (43) (2009)	Qualitative research – observation of the consent process for a two-phase	Lebanon	Researchers identified challenges to the consent process: incomplete disclosure of study information; complexity of terms and research design, compounded by low educational levels; issues related to

	preparatory study for an RCT to test the impact of a social skill-building intervention to improve mental health in adolescents		who could provide consent for the child; and social conceptions that youth are not capable of decision making. The greatest threat to the informed consent process was lack of voluntariness.
Vreeman R et al. (49) (2009)	Case study - pediatric assent for a study on antiretroviral therapy	Kenya	Authors describe the process of getting review by both US and Kenyan IRBs, mentioning that there is no guideline about how joint review should be conducted. Authors present the differences between the two countries regarding appropriate age for obtaining assent, and discuss local laws, practices, and international guidelines.
Sarkar R et al. (54) (2009)	Mixed methods research – comprehension and recall of informed consent process in a pediatric diarrhea study	India	Findings showed low recall of study purposes four years after enrollment. Most respondents were mothers and mentioned spousal approval and free medical care for their children as main motivations to consent and remain in the study. Educational level was significantly associated with recall of study purpose. Few respondents knew they could leave the study at any time. Authors point out the need for continuous reinforcement of the consent process.
Minnies D et al. (12) (2008)	Mixed methods – Recall of the consent process for a study of immune protection against TB	South Africa	Mothers who had consented for the study then completed a questionnaire about key elements of informed consent, recall, and understanding. Most obtained scores greater than 75% for recall and understanding. 79% were aware of the risks and 64% knew participation was voluntary. A higher level of education and being consented by professional nurses were associated with higher recall. Authors suggest monitoring the quality of consent procedures periodically.

Oduro AR et al. (55) (2008)	Mixed methods research – Understanding and retention of informed consent process by parents of children participating in a malaria cohort study	Ghana	Findings show overall good recall of procedural aspects of the study. Recall about study benefits was significantly higher than about study risks. Most knew participation was voluntary, but few knew they could withdraw at any time and that information was handled confidentially. Younger parental age was associated with better recall and understanding. Free medical treatment and benefits to the participant were strong motivations for enrolling.
Krosin MT et al. (56) (2006)	Quantitative – parental understanding of the consent process for a malaria vaccine trial	Mali	By using a multiple-choice questionnaire, researchers identified poor comprehension about withdrawal criteria, study side effects, and investigational rather than therapeutic nature of the intervention. Response rate and percentage of correct answers were higher in a more urban setting than in a rural one.
Pace C et al. (50) (2005)	Qualitative – quality of parental consent in an antimalarial study	Uganda	Most respondents were mothers and had good recall of logistical aspects of the study and study purpose. Comprehension of randomization was low. The primary reason most respondents gave for enrolling their child was to obtain malaria treatment. Many parents felt pressure to enroll because their child was sick. Only 41% reported they could have refused and 65% knew they could quit.
Molyneux CS et al. (53) (2005)	Mixed methods research – community views about the informed consent process and trust	Kenya	Findings show that trust in the research institution by the community is based on the perceived quality of clinical services it provides, and less on research activities. Trust in the research unit is an important reason behind community members' agreeing to participate in research. Responders valued the informed consent process but thought that low education and being in stressful situations impaired understanding. Authors suggest modifying consent procedures by not giving all information at once and

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

			testing to improve comprehension.
--	--	--	-----------------------------------

Confidential: For Review Only

bmjpo: first published as 10.1136/bmjpo-2018-000298 on 5 December 2018. Downloaded from <http://bmjpaedsopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Molyneux CS et al. (57) (2005)	Qualitative research - Community views regarding the informed consent process, in the context of studies being carried out by the KEMRI institute in Kenya	Kenya	Results show that seeking consent from community elders is necessary but does not substitute the need for individual parental consent. Most respondents suggested males should make the decision to participate and that assent should not be sought from children before age 10-13. For inpatient studies, respondents identified illness severity, potential risks, and parents' ability to understand as factors influencing the consent process. Results of the study show some therapeutic misconception and discrepancies regarding which interventions need permission.
Bhutta Z. (10) (2004)	Review - analysis of international guidelines on the subject of informed consent	n/a	Review and discussion of guidelines for obtaining informed consent. The discussion notes that more focus is put on written documentation of consent and less understanding of the process and adaptation to local contexts, and differences regarding when and how communities should be involved in the consent process.
McClure C et al. (27) (2004)	Review - challenges to conducting HIV vaccine trials with adolescents, including in developing countries	n/a	Authors identified challenges to HIV vaccine trials with adolescents. Adolescents are minors and need parental consent for participating in research. At the same time, their autonomy and privacy need to be respected. The consent process might be affected by less perception of personal risk.
Leach A et al. (44) (1999)	Qualitative research - Attitudes of the Gambian people to consent to medical research within the context of a H. influenzae vaccine trial.	The Gambia	Semi-structured interviews were conducted with study participants and refusers in urban and rural areas. Results showed that certain points of the trial were recalled well: 90% knew the purpose of the vaccine, but only 10% understood the placebo control design. The main motive for consenting was to receive the vaccine (93%), and for refusing was that the vaccine was experimental (35%) and might have side effects (29%). In all

			cases the decision was made by just one of the parents.
--	--	--	---

314

315 **DISCUSSION**

316 Children in low-resource settings are highly vulnerable to exploitation in research, because
317 of circumstances including socioeconomic inequalities, limited access to health care, and
318 high burden of illness.(59) In addition, even where international consensus exists around
319 core ethical principles for providing protections to children as research subjects, it may be
320 unclear how best to operationalize those principles in many low-resources settings, where
321 gender norms, literacy, unfamiliarity with scientific research, and language barriers may all
322 be important adaptive barriers. (10,11)

323

324 Through a scoping review of research reports and case studies from LMICs we identified,
325 however, several core areas where existing research reports provided considerable insight
326 and operational guidance which could likely be used to guide informed consent design
327 processes in additional LMIC settings. These included: (1) *careful consideration of*
328 *community hierarchy* was important, where consent for research may first proceed through
329 a council of elders or other authority figure, prior to approaching individual caregivers; (2)
330 *guidance on developing verbal consent procedures* in settings where caregivers have low
331 literacy levels; (3) and *recognition of the challenges of consent indigenous or less-*
332 *commonly spoken languages*, particularly when that language is not commonly written and
333 where alternative procedures, such as audio recordings in the language in question, must be
334 employed; and (4) *careful consideration of the possibility of therapeutic misconception* and

1
2
3 335 of developing consent procedures that ensure caregivers' comprehension of the potential
4
5 336 benefits (or lack thereof) and risks of research procedures for their children.
6
7

8 337 However, within these four broad thematic areas, we also noted the need for additional
9
10 338 careful investigation. In particular, here is considerable uncertainty on how to ensure the
11
12 339 principle of subsequent individual informed consent when community leaders or other
13
14 340 authorities are first approached. This is especially the case when gender power imbalance is
15
16 341 at play, and female caregivers may be either unempowered to consent or to opt out of a
17
18 342 research decision made by a male authority. In addition, the social status of individuals
19
20 343 administering or witnessing consent procedures may unduly influence the decision-making
21
22 344 of caregivers, and research is needed to better understand and accommodate for the
23
24 345 interpersonal dynamics of obtaining consent.
25
26
27
28

29 346 Finally, two thematic topics seem to be particularly underrepresented in the literature on
30
31 347 pediatric LMIC research, and more work is urgently needed. First, despite extensive
32
33 348 discussions about the difficulties of conducting research with adolescents, we found only
34
35 349 few studies with practical discussions or guidance on how to navigate these difficulties.
36
37 350 More investigation of the ethical conduct of research with adolescents is needed, with a
38
39 351 broader representation of health conditions, research designs, and geographic regions.
40
41 352 Second, despite strong representation of the principle of assent in international guidelines
42
43 353 on research with children and adolescents, we found little research of cultural and regional
44
45 354 differences around notions of assent and virtually no discussion of the mechanics of
46
47 355 assessing assent in research studies. Additional research into the topic of assent for research
48
49 356 among children in LMICs should be an important priority.
50
51
52
53
54

55
56 357
57
58
59
60

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

358 **ABBREVIATIONS**

- 359 IRB: Institutional review board
- 360 LMIC: Low and middle-income country
- 361 RCT: Randomised clinical trial
- 362 STaR: Standards for Research in Child Health

Confidential: For Review Only

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

363 **FUNDING**

364 This work was unfunded.

365

Confidential: For Review Only

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

366 **COMPETING INTERESTS**

367 None.

368

Confidential: For Review Only

1
2
3 369 **AUTHOR'S CONTRIBUTIONS**
4

5
6 370 MC designed the search strategy, extracted data from articles, and wrote the first draft of
7
8 371 the manuscript. PR conceived the study, reviewed abstracts, and revised the manuscript.
9

10
11 372
12

13
14 373
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

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

374 **DATA SHARING STATEMENT**

375 Not applicable

376

Confidential: For Review Only

1
2
3 377 **ACKNOWLEDGMENTS**
4

5 378 We thank research subjects and clinical staff at Maya Health Alliance for inspiring our
6
7 379 interest in this important topic.
8
9

10 380
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

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

381 **FIGURE LEGENDS**

382 **Figure 1. Results of Literature Screen.** Flow diagram depicting results of the literature
383 search and review procedure.

384

385

386

Confidential: For Review Only

387 **REFERENCES**

- 388 1. Weindling P. The origins of informed consent: the international scientific
389 commission on medical war crimes, and the Nuremberg Code. *Bull Hist Med*
390 2001;75(1):37–71.
- 391 2. Rickham P. Human experimentation. Code of ethics of the World Medical
392 Association. Declaration of Helsinki. *Br Med J* 1964;2(5402):177.
- 393 3. Council for International Organizations of Medical Sciences (CIOMS). International
394 Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition.
395 [Internet]. 2016. Available from: [https://cioms.ch/wp-](https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf)
396 [content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf](https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf) (accessed 30 Jul
397 2018).
- 398 4. Caldwell PH, Dans L, Newman J, et al. Standard 1: consent and recruitment.
399 *Pediatrics* 2012;129:S118.
- 400 5. Klassen TP, Hartling L, Hamm M, et al. StaR Child Health: an initiative for RCTs in
401 children. *Lancet* 2009 Oct 17;374(9698):1310–2.
- 402 6. Martinez B, Webb MF, Gonzalez A, et al. Complementary feeding intervention on
403 stunted Guatemalan children : a randomised controlled trial. *BMJ Paediatr Open*
404 2018;1–8.
- 405 7. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical
406 Research Involving Human Subjects. [Internet]. 2018. Available from:
407 [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)
408 [for-medical-research-involving-human-subjects](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects) (accessed 30 Jul 2018).

- 1
2
3 409 8. National Bioethics Advisory Commission. Ethical and Policy Issues Research:
4
5 410 Clinical Trials in Developing Countries Vol. 1 [Internet]. 2001. Available from:
6
7 411 <http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf> (accessed 30 Jul 2018).
8
9
10 412 9. European Commission. Clinical Trials: Directive 2001/20/EC. [Internet]. 2001.
11
12 413 Available from: [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf)
13
14 414 [1/dir_2001_20/dir_2001_20_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf) (accessed 30 Jul 2018).
15
16
17
18 415 10. Bhutta ZA. Beyond informed consent. *Bull World Health Organ* 2004
19
20 416 Oct;82(10):771–7.
21
22
23 417 11. MacLeod SM, Knoppert DC, Stanton-Jean M, et al. Pediatric clinical drug trials in
24
25 418 low-income countries: key ethical issues. *Paediatr Drugs* 2015 Feb;17(1):83–90.
26
27
28
29 419 12. Minnies D, Hawkrigde T, Hanekom W, et al. Evaluation of the quality of informed
30
31 420 consent in a vaccine field trial in a developing country setting. *BMC Med Ethics*
32
33 421 2008;9:1–9.
34
35
36 422 13. Halmsted Kongsholm NC, Lassen J, Sandoe P. “I didn’t have anything to decide, I
37
38 423 wanted to help my kids” - An interview-based study of consent procedures for
39
40 424 sampling human biological material for genetic research in rural Pakistan. *AJOB*
41
42 425 *Empir Bioeth* 2018;4515(April 2014):1–35.
43
44
45
46 426 14. Nabulsi M, Khalil Y, Makhoul J. Parental attitudes towards and perceptions of their
47
48 427 children’s participation in clinical research: A developing-country perspective. *J*
49
50 428 *Med Ethics* 2011;37(7):420–3.
51
52
53
54 429 15. Kamuya DM, Theobald SJ, Marsh V, et al. “The one who chases you away does not
55
56 430 tell you go”: silent refusals and complex power relations in research consent
57
58
59
60

- 1
2
3 431 processes in Coastal Kenya. *PLoS One* 2015;10(5):e0126671.
- 4
5
6 432 16. Macrae DJ. The Council for International Organizations and Medical Sciences
7
8 433 (CIOMS) guidelines on ethics of clinical trials. *Proc Am Thorac Soc* 2007
9
10 434 May;4(2):176–8.
- 11
12
13 435 17. Martellet L, Sow SO, Diallo A, et al. Ethical challenges and lessons learned during
14
15 436 the clinical development of a group A meningococcal conjugate vaccine. *Clin Infect*
16
17 437 *Dis* 2015 Nov;61 Suppl 5:S422-7.
- 18
19
20
21 438 18. Kalabuanga M, Ravinetto R, Maketa V, et al. The challenges of research informed
22
23 439 consent in socio-economically vulnerable populations: a viewpoint from the
24
25 440 Democratic Republic of Congo. *Dev World Bioeth* 2016;16(2):64–9.
- 26
27
28 441 19. Fitzpatrick EFM, Martiniuk ALC, D’Antoine H, et al. Seeking consent for research
29
30 442 with indigenous communities: a systematic review. *BMC Med Ethics* 2016
31
32 443 Oct;17(1):65.
- 33
34
35
36 444 20. Flood D, Rohloff P. Indigenous languages and global health. *Lancet Glob Health*
37
38 445 2018;6(2):e134–5.
- 39
40
41 446 21. Mboizi RB, Afolabi MO, Okoye M, et al. Recall and decay of consent information
42
43 447 among parents of infants participating in a randomized controlled clinical trial using
44
45 448 an audio-visual tool in The Gambia. *Hum Vaccin Immunother* 2017
46
47 449 Sep;13(9):2185–91.
- 48
49
50
51 450 22. Khabour OF, Alomari MA, Al-Sheyab NA. Parental perceptions about informed
52
53 451 consent/assent in pediatric research in Jordan. *J Empir Res Hum Res Ethics* 2017
54
55 452 Oct;12(4):261–8.
- 56
57
58
59
60

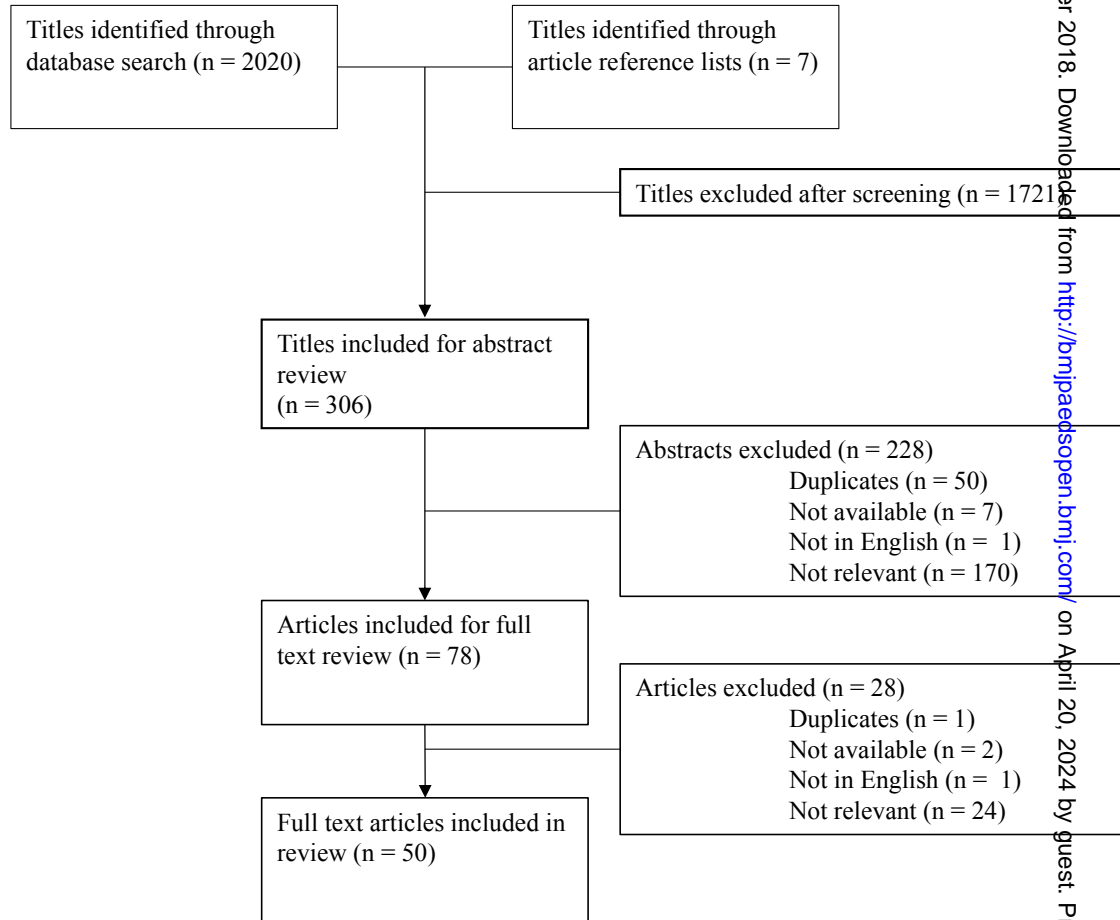
- 1
2
3 453 23. Rajaraman D, Jesuraj N, Geiter L, et al. How participatory is parental consent in low
4
5 454 literacy rural settings in low income countries? Lessons learned from a community
6
7 455 based study of infants in South India. *BMC Med Ethics* 2011 Feb;12:3.
8
9
10 456 24. Devries KM, Child JC, Elbourne D, et al. “I never expected that it would happen,
11
12 457 coming to ask me such questions”: ethical aspects of asking children about violence
13
14 458 in resource poor settings. *Trials* 2015 Nov;16:516.
15
16
17
18 459 25. Serce O, Gonen I, Bakir M. Factors influencing parental consent in a hypothetical
19
20 460 pediatric vaccine trial in a developing country setting: a questionnaire study. *Account*
21
22 461 *Res* 2015;22(1):1–13.
23
24
25
26 462 26. Bekker L, Slack C, Lee S, et al. Ethical issues in adolescent HIV research in
27
28 463 resource-limited countries. *J Acquir Immune Defic Syndr* 2014;65(Supplement
29
30 464 1):24–8.
31
32
33 465 27. McClure CA, Gray G, Rybczyk GK, et al. Challenges to conducting HIV
34
35 466 preventative vaccine trials with adolescents. *J Acquir Immune Defic Syndr* 2004
36
37 467 Jun;36(2):726–33.
38
39
40
41 468 28. Woollett N, Peter J, Cluver L, et al. Enrolling HIV-positive adolescents in mental
42
43 469 health research : a case study reflecting on legal and ethical complexities. *S Afr Med*
44
45 470 *J* 2017;107(8):679–83.
46
47
48
49 471 29. Zulu JM, Ali J, Hallez K, et al. Ethics challenges and guidance related to research
50
51 472 involving adolescent post-abortion care: A scoping review. *Reprod Health*
52
53 473 2018;15(1):1–10.
54
55
56 474 30. Ott MA, Crawley FP, Saez-Llorens X, et al. Ethical considerations for the
57
58
59
60

- 1
2
3 475 participation of children of minor parents in clinical trials. *Paediatr Drugs* 2018
4
5 476 Jun;20(3):215–22.
6
7
8 477 31. Morris MC, Wilson PT. Medical device research in resource-poor settings: a
9
10 478 paediatric case study in Ghana. *IRB* 2014;36(4):1–7.
11
12
13 479 32. Ward CL, Shaw D, Anane-Sarpong E, et al. The ethics of health care delivery in a
14
15 480 paediatric malaria vaccine trial: the perspectives of stakeholders from Ghana and
16
17 481 Tanzania. *J Empir Res Hum Res Ethics* 2018;13(1):26–41.
18
19
20
21 482 33. Regmi PR, Aryal N, Kurmi O, et al. Informed consent in health research: challenges
22
23 483 and barriers in low-and middle-income countries with specific reference to Nepal.
24
25 484 *Dev World Bioeth* 2017;17(2):84–9.
26
27
28 485 34. Embleton L, Ott MA, Wachira J, et al. Adapting ethical guidelines for adolescent
29
30 486 health research to street-connected children and youth in low- and middle-income
31
32 487 countries: a case study from western Kenya. *BMC Med Ethics* 2015;16:89.
33
34
35
36 488 35. Morrow BM, Argent AC, Kling S. Informed consent in paediatric critical care
37
38 489 research--a South African perspective. *BMC Med Ethics* 2015 Sep;16:62.
39
40
41 490 36. Swain TR. Clinical trials for children: some concerns. *Indian J Pharmacol*
42
43 491 2014;46(2):145–6.
44
45
46
47 492 37. Angwenyi V, Kamuya D, Mwachiro D, et al. Complex realities: community
48
49 493 engagement for a paediatric randomized controlled malaria vaccine trial in Kilifi,
50
51 494 Kenya. *Trials* 2014 Feb;15:65.
52
53
54 495 38. Offringa M, Needham AC, Chan WWY. StaR Child Health: Improving global
55
56
57
58
59
60

- standards for child health research. *Early Hum Dev* 2013;89(11):861–4.
39. Vreeman R, Kamaara E, Kamanda A, et al. Community perspectives on research consent involving vulnerable children in western Kenya. *J Empir Res Hum Res Ethics* 2012;7(4):44–55.
40. Mandava A, Pace C, Campbell B, et al. The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries. *J Med Ethics* 2016;38(6):356–65.
41. Denburg AE, Joffe S, Gupta S, et al. Pediatric oncology research in low income countries: ethical concepts and challenges. *Pediatr Blood Cancer* 2012 Apr;58(4):492–7.
42. Mystakidou K, Panagiotou I, Katsaragakis S, et al. Ethical and practical challenges of implementing informed consent in HIV/AIDS clinical trials in developing or resource-limited countries. *SAHARA J* 2009;6(2):46–57.
43. Nakkash R, Makhoul J, Afifi R. Obtaining informed consent: observations from community research with refugee and impoverished youth. *J Med Ethics* 2009 Oct;35(10):638–43.
44. Leach A, Hilton S, Greenwood BM, et al. An evaluation of the informed consent procedure used during a trial of a *Haemophilus influenzae* type B conjugate vaccine undertaken in The Gambia, West Africa. *Soc Sci Med* 1999;48(2):139–48.
45. Joseph PD, Craig JC, Tong A, et al. Researchers', regulators', and sponsors' views on pediatric clinical trials: a multinational study. *Pediatrics* 2016;138(4):e20161171

- 1
2
3 517 46. Joseph PD, Caldwell PH, Tong A. Stakeholder views of clinical trials in low- and
4
5 518 middle-income countries : a systematic review. *Pediatrics* 2016;137(2):e20152800.
6
7
8 519 47. Paré Toe L, Ravinetto RM, Dierickx S, et al. Could the decision of trial participation
9
10 520 precede the informed consent process? Evidence from Burkina Faso. *PLoS One*
11
12 521 2013;8(11):e80800.
13
14
15 522 48. Daley TC, Singhal N, Krishnamurthy V. Ethical considerations in conducting
16
17 523 research on autism spectrum disorders in low and middle income countries. *J Autism*
18
19 524 *Dev Disord* 2013;43(9):2002–14.
20
21
22 525 49. Vreeman RC, Nyandiko WM, Meslin EM. Pediatric assent for a study of
23
24 526 antiretroviral therapy dosing for children in western Kenya: a case study in
25
26 527 international research collaboration. *J Empir Res Hum Res Ethics* 2009;4(1):3–16.
27
28
29 528 50. Pace C, Talisuna A, Wendler D, et al. Quality of parental consent in a Ugandan
30
31 529 malaria study. *Am J Public Health* 2005;95(7):1184–9.
32
33
34 530 51. Ruiz-Casares M. Research ethics in global mental health: Advancing culturally
35
36 531 responsive mental health research. *Transcult Psychiatry* 2014;51(6):790–805.
37
38
39 532 52. Millum J, Emanuel E. The ethics of international research with abandoned children.
40
41 533 *Science* 2007;318:1874-5.
42
43
44 534 53. Molyneux CS, Peshu N, Marsh K. Trust and informed consent: insights from
45
46 535 community members on the Kenyan coast. *Soc Sci Med* 2005;61(7):1463–73.
47
48
49 536 54. Sarkar R, Grandin EW, Gladstone BP, et al. Comprehension and recall of informed
50
51 537 consent among participating families in a birth cohort study on diarrhoeal disease.
52
53
54
55
56
57
58
59
60

- 1
2
3 538 *Public Health Ethics* 2009;2(1):37–44.
4
5
6 539 55. Oduro AR, Aborigo RA, Amugsi D, et al. Understanding and retention of the
7
8 540 informed consent process among parents in rural northern Ghana. *BMC Med Ethics*
9
10 541 2008;9:12.
11
12
13 542 56. Krosin MT, Klitzman R, Levin B, et al. Problems in comprehension of informed
14
15 543 consent in rural and peri-urban Mali, west Africa. *Clin Trials* 2006;3(3):306–13.
16
17
18 544 57. Molyneux CS, Wassenaar DR, Peshu N, et al. “Even if they ask you to stand by a
19
20 545 tree all day, you will have to do it (laughter)...!”: Community voices on the notion
21
22 546 and practice of informed consent for biomedical research in developing countries.
23
24 547 *Soc Sci Med* 2005;61(2):443–54.
25
26
27
28 548 58. Tindana P, Bull S, Amenga-Etego L, et al. Seeking consent to genetic and genomic
29
30 549 research in a rural Ghanaian setting: A qualitative study of the MalariaGEN
31
32 550 experience. *BMC Med Ethics* 2012;13(1):1.
33
34
35
36 551 59. Initiative for Vaccine Research, World Health Organization. Ethical considerations
37
38 552 arising from vaccine trials conducted in paediatric populations with high disease
39
40 553 burden in developing countries. WHO/IRV Ethics Meeting, November 26–28, 2002
41
42 554 Accra, Ghana [Internet]. 2002. Available from:
43
44 555 http://www.who.int/ethics/topics/vaccinetrials_pediatric_ivr_en_2002.pdf (accessed
45
46 556 30 Jul 2018).
47
48
49
50
51 557
52
53
54 558



bmjpo-2018-000298 on 5 December 2018. Downloaded from <http://bmjpaedopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

BMJ Paediatrics Open

Cultural considerations for informed consent in pediatric research in low and middle income countries: A scoping review

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2018-000298.R1
Article Type:	Original article
Date Submitted by the Author:	26-Sep-2018
Complete List of Authors:	Colom, Marcela; Wuqu' Kawoq Rohloff, Peter
Keywords:	Ethics, Health services research

SCHOLARONE™
Manuscripts

1
2
3 1 **TITLE PAGE**
4

5 2

6
7 3 **Cultural considerations for informed consent in pediatric research in low and middle**
8 **income countries: A scoping review**
9
10 4

11 5

12
13
14 6 Marcela Colom MD¹, Peter Rohloff MD PhD^{1,2,3}
15
16

17 7

18
19 8 ¹Wuqu' Kawoq | Maya Health Alliance, 2da Avenida 3-48 Zona 3, Barrio Patacabaj,
20
21 Tecpán, Chimaltenango, Guatemala
22
23

24 10

25
26 11 ²Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA
27
28 12

29 12

30
31 13 ³ Corresponding Author. Peter Rohloff, Brigham and Women's Hospital, 75 Francis Street,
32
33 14 Boston, MA, 02115. Phone: 617-278-0055. Fax: 888-372-2354. Email:
34
35 15 prohloff@bwh.harvard.edu
36
37 16

38 16

39
40 17

41
42 18

43
44 19 Word count: 3701
45
46 20

47 20

48
49 21

50
51 22

52
53 23
54
55
56
57
58
59
60

24 WHAT IS KNOWN ABOUT THIS SUBJECT

- 25 • Conducting research with children in low- and middle-income countries (LMICs)
26 requires careful consideration of socioeconomic inequalities and cultural and
27 linguistic differences.
- 28 • Existing international standards for the conduct of ethical pediatric research advance
29 core concepts, such as informed consent, voluntariness, and assent, but there often
30 is limited guidance on how to adapt and operationalize these for LMIC settings.

31 WHAT THIS STUDY ADDS

- 32 • Through a scoping review of published literature discussing informed consent for
33 pediatric research in LMICs, we identified helpful examples and emerging
34 consensus for best practices in community engagement, verbal and alternative
35 consent procedures, and guarding against therapeutic misconception by caregivers
36 in interventional and randomized controlled trial designs.
- 37 • We also identified the need for additional research where less consensus was
38 apparent, especially around the protection of the individual autonomy of caregivers
39 and safeguarding children's own assent to participate in research.

1
2
3 **43 ABSTRACT**
4
5
6 **44**

7
8 **45** Introduction: Conducting research with children in low- and middle-income countries
9
10 **46** (LMICs) requires consideration of socioeconomic inequalities and cultural and linguistic
11
12 **47** differences. Our objective was to survey the literature on informed consent in pediatric
13
14 **48** LMIC research, assessing for practical guidance for culturally- and linguistically-
15
16 **49** appropriate procedures.
17
18

19 **50**
20
21 **51** Methods: We conducted a scoping review on informed consent in pediatric LMIC research
22
23 **52** searching the Pubmed, Web of Science and PsycINFO databases. Eligible articles were
24
25 **53** published in English, from any date range, of any study design or format.
26
27
28 **54**

29
30 **55** Results: The search identified 2,027 references, of which 50 were included in the analysis
31
32 **56** following full-text review. Reviewed guidelines emphasized individual, informed and
33
34 **57** voluntary consent from parents and caregivers. Reviewed articles provided detailed
35
36 **58** practical guidance on adapting these guiding principles to LMIC settings, including
37
38 **59** considerations for community engagement, verbal or other alternative consent procedures
39
40 **60** for low-literacy settings or less-commonly spoken languages, and guarding against
41
42 **61** therapeutic misconception by caregivers. There was uncertainty, however, on how to best
43
44 **62** protect individual autonomy, especially when influenced by gender dynamics, leadership
45
46 **63** hierarchies, or the social status of researchers themselves. There was, furthermore, limited
47
48 **64** research discussing the special case of research involving adolescents or of procedures for
49
50 **65** documenting assent by participating children.
51
52
53
54
55
56 **66**

1
2
3 67 Conclusions: A scoping review of pediatric research in LMICs revealed substantial
4
5 68 guidance on several features of culturally appropriate informed consent . However,
6
7 69 additional research and guidance is needed, especially in the areas of gender imbalances,
8
9
10 70 research with adolescents, and children's own assent to participate in research.
11
12
13 71
14
15 72
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

73 INTRODUCTION

74

75 Prior to World War II, there was little international consensus on the ethical conduct of
76 human subjects' research. The Nuremberg code, developed in 1947 during the Nuremberg
77 war crimes trials, was one of the first attempts to articulate basic ethical principles, such as
78 the right to informed consent.(1) Subsequently, the World Medical Association's (WMA)
79 Declaration of Helsinki in 1964 provided a more definitive consensus statement on the core
80 principles of ethical conduct of research--beneficence, self-determination, and informed
81 consent—which is widely considered the foundational international document in modern
82 research ethics.(2) Practical guidance on ethical practice is well codified in the joint
83 statements produced by the Council for International Organizations of Medical Sciences
84 (CIOMS) and the World Health Organization (WHO).(3)

85

86 Extension of ethical research principles to include considerations appropriate for research
87 in pediatric populations are also important, including guidance on obtaining informed
88 consent from parents or guardians, obtaining assent from children themselves, and
89 weighing the balance of risks and benefits of proposed research.(3,4) Improvements in the
90 conduct and volume of pediatric clinical trials, which have historically been few in number
91 and of lower quality than corresponding trials in adult subjects, have also recently been
92 advocated.(5)

93

94 However, there still remains uncertainty around how best to implement international ethical
95 principles of pediatric research in some settings. This is especially the case in low and
96 middle-income countries (LMICs), and in research with groups such as indigenous

1
2
3 97 populations, speakers of less-common languages, or populations with high levels of
4
5 98 illiteracy. Practically, we experienced this recently while designing a clinical trial of a
6
7
8 99 nutrition intervention for indigenous Maya children in rural Guatemala, and our experience
9
10 100 navigating consent, literacy, and translingual adaptation in this population prompted our
11
12 101 interest in more formally exploring the topic.(6) To this end, here we conduct a scoping
13
14 102 review of the existing literature on cultural and contextual considerations for informed
15
16 103 consent in the conduct of pediatric research in LMICs. Through this review, we identify
17
18 104 evidence for specific culturally- and contextually-sensitive practices, as well as areas where
19
20 105 additional research and guideline development is needed.
21
22
23
24 106

26 107 **METHODS**

30 109 **Search and inclusion strategy**

31
32
33 110
34
35 111 To identify articles, we searched the PubMed, Web of Science and PsycINFO databases.
36
37 112 We conducted searches using a combination of the following key terms: “pediatric” or
38
39 113 “children” or “adolescents”; “research” or “biomedical research”; “consent” or “informed
40
41 114 consent” or “ethics”; “developing countries” or “low income countries” or “middle income
42
43 115 countries”; “illiteracy”; “culturally competent”. We used no date limits and included all
44
45 116 articles published through May 2018. In addition, we visited the websites of international
46
47 117 health policy organizations to identify ethics guidelines for the conduct of research in low-
48
49 118 and middle-income countries. We also manually reviewed the reference lists of articles
50
51 119 identified using the above methods. For this scoping review, of the articles identified above
52
53
54 120 we included for analysis any type of study design or format (original research, commentary,
55
56
57
58
59
60

121 case study, review, expert opinion), which addressed the informed consent process
122 specifically for pediatric or adolescent populations in low or middle-income
123 countries. Articles not in English were excluded.

125 **Data extraction and synthesis**

126
127 We exported identified articles into an Excel spreadsheet template which recorded location
128 of study, study type and design, study context, aspects of informed consent examined, and
129 key findings. Both authors reviewed the study titles and abstracts. After removal of articles
130 which were deemed not eligible for inclusion, one author (MC) performed a full text review
131 of all the remaining articles. As a scoping review to assess the patterns of existing
132 literature on informed consent in LMIC pediatric research, assessments of individual study
133 bias and quality were not performed. Data extracted from articles was collated in summary
134 form (Table 1), and major qualitative findings are presented in the following narrative
135 synthesis.

137 **RESULTS**

139 **Results of literature screen**

140
141 A total of 2,027 candidate titles were identified through database searches, supplemented
142 by reference list and website reviews. Of these, 1,721 did not meet eligibility criteria, and
143 306 were included for abstract review. If the abstract was not available but full text was, the
144 title was included for full text review. After abstract review, 50 duplicates were found, one

1
2
3 145 was not in English, 7 were not available (abstract nor full text), and 170 abstracts did not
4
5 146 meet inclusion criteria. 78 articles were selected for full text review, of which 24
6
7 147 subsequently did not meet inclusion criteria, one was in French, one was a duplicate, and
8
9 148 two did not have available full text. Therefore 50 full-text articles were included in this
10
11 149 review (Figure 1, Table 1, Supplementary Table 1). Of the articles excluded at the abstract
12
13 150 and full text review stages, the most common reasons for exclusion were: no mention of the
14
15 151 informed consent process for research with pediatric or adolescent populations; research
16
17 152 not taking place in a low- or middle-income country; articles on pediatric research in low-
18
19 153 or middle-income countries that did not discuss the informed consent process
20
21
22
23
24
25

26 155 **Summary of guidelines and commentaries**

27
28 156
29
30 157 We identified seven guidelines that addressed issues of informed consent in international
31
32 158 settings and in research involving children in our scoping review. Of these, we selected for
33
34 159 detailed review five that were most comprehensive, summarizing key recommendations in
35
36 160 Table 1. All guidelines emphasize the importance of obtaining individual, informed and
37
38 161 voluntary consent for research.(3,4,7–9) Importantly, however, the guidelines do not
39
40 162 necessarily specify in detail how best to operationalize assessment of these core principles.
41
42 163 For example, the Declaration of Helsinki comments only that informed consent requires
43
44 164 that a subject be adequately informed of the “aims, methods, sources of funding, any
45
46 165 possible conflicts of interest, institutional affiliations of the researcher, the anticipated
47
48 166 benefits and potential risks of the study and the discomfort it may entail, post-study
49
50 167 provisions and any other relevant aspects of the study” (Article 26). (7) Similarly, on
51
52
53
54
55
56
57
58
59
60

1
2
3 168 voluntariness, the CIOMS guidelines note only that consent is voluntary if “an individual’s
4
5 169 decision to participate is free of undue influence” (p. 35). (3)
6
7

8
9 170

10
11 171 Some of the guidelines do suggest modifications appropriate for lower-resource settings,
12
13 172 such as obtaining witnessed verbal consent when literacy is a barrier. (7,9) The United
14
15 173 States National Bioethics Advisory Commission (NBAC) also acknowledges that oral
16
17 174 consent might even be preferable in some circumstances.(8) However, as other
18
19 175 commentaries note, there is little specificity on how best to operationalize these
20
21 176 suggestions, such as how to formally document verbal consent or characteristics of a
22
23 177 qualified witness.(10,11)
24
25
26

27
28 178

29
30
31 179 Another important consideration of LMIC research addressed in guidelines is an emphasis
32
33 180 on the need to at times obtain consent from community stakeholders and leaders, or other
34
35 181 key local decision makers. Nevertheless, all guidelines unanimously assert that community-
36
37 182 based consent can never replace individual consent. When local cultural practices around
38
39 183 community-based consent contradict core principles of the international consensus on the
40
41 184 informed consent process, such as the need for voluntary individual consent, researchers are
42
43 185 advised to search for culturally sensitive ways of providing all information to potential
44
45 186 participants without compromising the substantive ethical standard of informed consent, an
46
47 187 adaptive process in which local research ethics committees are expected to place a
48
49 188 substantial role. (8,10–12)
50
51
52

53
54
55 189
56
57
58
59
60

1
2
3 190 Finally, with respect to children or adolescents not capable of providing informed consent,
4
5 191 in addition to obtaining consent from parents or legal representatives, most guidelines also
6
7 192 reinforce the need to obtain assent from the child or adolescent in an age-appropriate way.
8
9
10 193 (3,4,7,9) The CIOMS guidelines note that assent is “a process...not merely the absence of
11
12 194 dissent” and requires “meaningful[1] engage[ment] in the research discussion in accordance
13
14 195 with...capacities” (p. 67). (3) They also note that as adolescents reach the age of maturity,
15
16 196 their agreement to participate may be ethically considered as informed consent. However, if
17
18 197 they legally remain minors, researchers are cautioned that consent from a parent is still
19
20 198 generally needed, but a list is provided of possible situations when parental consent might
21
22 199 be waived, such as with legally emancipated adolescents, or under circumstances where
23
24 200 obtaining parental consent is not desirable because of the research topic. (3)
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

209 **Table 1 Summary of selected major guidelines, reports and reviews on ethical**
 210 **conduction of research in children**

Guideline	Core principles	Considerations for adapting to low-resource, low-literary, and minority language settings
World Medical Association, Declaration of Helsinki(7)	<ul style="list-style-type: none"> • If a research subject is not capable of giving informed consent, it should be sought from a legally authorized representative • When the subject can give assent to decisions about participation in research, assent should be sought in addition to consent. Dissent should be respected 	<ul style="list-style-type: none"> • Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information • Consent should be given preferably in writing, if not the non-written consent must be formally documented and witnessed
Council for International Organizations of Medical Sciences(3)	<ul style="list-style-type: none"> • Obtain permission from a parent or a legally authorized representative of the child • Obtain assent from the child or adolescent according to his or her capacity and after having been provided with information tailored to the child's or adolescent's level of maturity 	<ul style="list-style-type: none"> • Consult with and engage communities in the informed consent process • Obtained a signed form as evidence of informed consent, justify any exceptions to this general rule and seek approval of the research ethics committee
Standards for Research (StaR) in Child Health(4)	<ul style="list-style-type: none"> • Obtain consent and assent when age-appropriate • Provide age-appropriate, clear, concise, and on-going information for parents and children 	<ul style="list-style-type: none"> • Provide clear justification to involve a particular population and equitable sharing of benefits and risks • Community consultation can be helpful but does not replace the need for individual consent • Strengthen composition and expertise of local ethics committees
National Bioethics Advisory Commission, Ethical and policy		<ul style="list-style-type: none"> • Develop culturally appropriate ways to disclose information that is necessary for adherence to the ethical

<p>issues in international research(8)</p>		<p>standard of informed consent</p> <ul style="list-style-type: none"> • Develop procedures to ensure that participants understand the information provided in the consent process • Respect local requirements of asking permission from community representatives for approaching potential participants, but respect the requirement of individual informed consent • Ethics review committees can waive the requirements of written and signed consent in accordance with local cultural norms
<p>European Council and European Parliament Guidelines(9)</p>	<ul style="list-style-type: none"> • Consent should be sought from parents or legal representatives • Information should be provided to the minor according to its capacity of understanding • The explicit wish of a minor who is capable of forming an opinion and assessing information to refuse participation should be considered 	<ul style="list-style-type: none"> • The individual or legal representative has to give written consent. If the individual is unable to write, oral consent may be given in the presence of at least one witness, as provided for in national legislation

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

211

212 Thematic summary of research on consent in LMIC pediatric research

213

214 Existing published work on informed consent in pediatric research in LMICs consists
215 largely of case studies describing the experience of individual research teams and
216 discussing the challenges and solutions utilized when adapting consent processes to their
217 local context. We summarize several major themes emerging from these studies here and
218 detail key findings from the reviewed articles in Supplementary Table 1.

219

220 Understanding social norms around decision making and protecting individual autonomy

221 An important principle highlighted in international guidelines on informed consent
222 in LMICs is appropriate and early engagement with existing local leadership structures
223 (such as a council of elders) balanced against respect for the autonomy of individual
224 children or their caregivers.(3,8) In practice, this can be a delicate balance to maintain.
225 Kongsholm and colleagues, for example, describe consent processes in rural Pakistan,
226 where family structures are patriarchal and hierarchical. In this setting, consent procedures
227 involved first seeking consent from an elder, who provided initial consent for the entire
228 family. However, under this approach, the voluntariness of individual participants may be
229 undermined, and it is unclear how best to ensure that individuals still retain an “opt out”
230 mechanism or, conversely, the right to participate in research if they wish to do so but the
231 elder declines.(13)

232

1
2
3 233 Another important consideration explored by some studies is understanding how not all
4
5 234 potential consenting caregivers may feel empowered to decline participating in research.
6
7 235 Consent procedures administered by local research personnel or by individuals with high
8
9 236 social status, such as physicians, may inspire trust.(13,14) However it may also make them
10
11 237 reluctant to decline participation, or to resist active participation. For example, in one study
12
13 238 in Kenya, explicit refusals to participate were often considered to be impolite. Here
14
15 239 researchers found that caregivers expressed their unwillingness to participate by delaying
16
17 240 the consent process, or by participating inconsistently in research procedures even after
18
19 241 initially having consented to the study.(15)
20
21
22
23
24
25

242

243 Adapting consent procedures to low-literate settings

244 There is strong consensus in international ethics guidelines that written, informed
245 consent is preferred when conducting research. In the case of pediatric research, this again
246 typically involves obtaining written consent from one or both primary caregivers.(4,9,16)
247 However, in many LMIC settings, literacy may be low or a high value may be placed on
248 oral interactions, and lack of alternative consent procedures may violate another core ethics
249 principle, namely the equitable distribution of research benefits and burdens across
250 populations.(3,14,17) Some of the studies we reviewed described these procedures, with
251 verbal consent commonly being obtained, most often in the presence of a literate witness
252 who is able to read available consent documents. (13,14,17,18) In one very thoughtful
253 piece, Kalabuanga and colleagues note, however, that witnesses may often impose their
254 views on the consenting caregiver and their child, rather than encourage dialog and act as a
255 safeguard, especially since they are often recruited in an ad hoc fashion (e.g., other literate

1
2
3 256 patients or ancillary hospital staff).(18) Kalabuanga et al. go on to suggest that these
4
5 257 challenges may be mitigated by careful vetting and training of independent witnesses or,
6
7 258 alternatively, by allowing potential consenting caregivers to use a trusted relative or friend
8
9
10 259 as their witness.(18)

11
12
13 260 Another issue identified in the review is that of emerging new mandates in some
14
15 261 LMICs to document consent procedures. For example, in India, audiovisual documentation
16
17 262 of obtaining informed consent is now required for most clinical trials if participants are
18
19 263 low-literate. This introduced significant new logistical challenges and costs related to
20
21 264 obtaining and archiving recordings, and it may also pose a barrier to potential research
22
23 265 subjects who may distrust or refuse to be recorded.(19)

24
25
26
27 266

28
29
30 267 Working in indigenous or less-commonly-spoken languages

31
32
33 268 International ethics guidelines emphasize that research information should be
34
35 269 provided to consenting caregivers in a local language understandable to the
36
37 270 individual.(7,8,16) However, this is most commonly understood to be a working lingua
38
39 271 franca, and the issue of and practical approach to provisioning consent processes in an
40
41 272 indigenous language is largely unaddressed in LMICs.(20) This is an important
42
43 273 consideration, given that a substantial proportion of the potential pediatric research
44
45 274 population in LMICs are from populations that speak indigenous or less-commonly-spoken
46
47 275 languages.(21) In an interesting review of lessons learned in a pediatric vaccine trial in
48
49 276 West Africa, Martellet and colleagues noted challenges in preparing consent procedures in
50
51 277 some of the less-common language groups included in the trial, where use of the written
52
53
54
55
56
57
58
59
60

1
2
3 278 form was uncommon, where substantial need to rely on metaphor and paraphrase made
4
5 279 back-translation difficult, and where written documents were perceived as not being
6
7 280 dynamic enough in cultures which valued interactivity and person-to-person exchange.
8
9 281 They describe alternative procedures, such as the preparation of recordings of consent
10
11 282 scripts in local languages and extensive practice sessions with research staff obtaining
12
13 283 consent in local languages.(17) Similarly, another vaccine trial in The Gambia described
14
15 284 the successful use of audio-visual Speaking Books in local less-common languages to
16
17 285 consent caregivers. (22)
18
19
20
21
22
23
24

25 287 Gender dynamics in caregiver consent

26
27
28 288 Local gender dynamics and decision making procedures when consenting male and
29
30 289 female caregivers for research is an important consideration. For example, when consenting
31
32 290 with caregiving couples or within an extended family unit, instances are discussed where a
33
34 291 female caregiver wishes to allow her child to participate, but is unable to do so because her
35
36 292 husband or another male authority figure refuses.(13) The opposite may also occur, if a
37
38 293 research study is consented by a male figure, but requires significant participatory effort
39
40 294 from the primary female for study-related activities, leading the woman to express their
41
42 295 refusal through procedural delay or inconsistent participation.(15) Given concerns about
43
44 296 gender power imbalance and potential repercussions for consenting female caregivers,
45
46 297 some studies discussed working to routinely involve fathers or male authority figures in the
47
48 298 consent process for more complex or higher-risk research interventions.(15,23) In one
49
50 299 interesting study based in India, Rajaraman and colleagues found that caregivers were
51
52 300 more likely to actively participate in the consent process when both were present. They also
53
54
55
56
57
58
59
60

1
2
3 301 observed, however, that this factor may have been due the fact that most study staff
4
5 302 obtaining consent were male, and they call for more research on how the gender of research
6
7
8 303 staff impacts the consent process.(24)
9

10
11 304 It is important to note that most discussions of gender dynamics that we reviewed
12
13 305 were limited in nuance, tending to focus on instances of overt overriding of female
14
15 306 decision-making by male authorities. A broader consideration of the range of ways in
16
17 307 which female caregivers communicate, influence, and negotiate decision-making with male
18
19 308 family members and other community authorities is an obvious point for future
20
21 309 investigation.
22
23
24
25 310

28 311 Disclosing potential benefits and risks of participation in research

30
31 312 Participation in some research studies, particularly those with a randomized
32
33 313 controlled design or those with differing intervention arms, may not result in direct benefit
34
35 314 to all participants. Several studies report difficulties explaining to caregivers that medical
36
37 315 research procedures may not result in direct benefit to their children, and in verifying that
38
39 316 caregivers comprehended the substance of randomization or control procedures. (25–28)
40
41 317 Others noted the need to address issues of information recall and retention, particularly with
42
43 318 complex study procedures or consent forms, and to emphasize the right of study withdrawal
44
45 319 and the ongoing reaffirmation of consent throughout a study. (26–29) Furthermore, other
46
47 320 reports discussed how therapeutic misconception—the perception by research subjects that
48
49 321 participation in any component of a multiple-arm, controlled trial, will result in therapeutic
50
51
52
53
54
55
56
57
58
59
60

1
2
3 322 benefits—might be hard to avoid in certain contexts, as it might be affected by factors like
4
5 323 educational level and cultural and religious beliefs about disease.(13,18)
6
7
8
9 324

10
11 325 At the same time, care must be given to a culturally-appropriate degree of information
12
13 326 disclosure. For example, in several studies, caregivers—especially those of higher
14
15 327 socioeconomic or educational status—were more likely to participate when provided with
16
17 328 detailed and in-depth information about the study processes and given opportunities to ask
18
19 329 questions.(12,23,24,30) At the same time, other case studies point out how over-detailed
20
21 330 discussion of study procedures or scientific rationale may provoke unneeded reserve or
22
23 331 suspicion where such detailed disclosures by health professionals are not culturally
24
25 332 customary.(13)
26
27
28
29

30 333
31
32
33 334 Finally, in settings where access to healthcare and other important social goods may be
34
35 335 limited, even basic diagnostic or ancillary procedures that occur as part of a research
36
37 336 studies may be better than the local standard of care, leading to an undue inducement or
38
39 337 highly compelling incentives for caregivers to enroll their children in research, even after
40
41 338 being informed about the experimental nature or studies and the risk-benefit
42
43 339 balance.(11,13,18) These considerations highlight the importance of considering the socio-
44
45 340 economic and cultural background of study settings well before beginning research and
46
47 341 making plans to incorporate appropriate early, equitable benefit-sharing measures when
48
49 342 possible, such as using study resources to improve community-level care not just care for
50
51 343 eligible trial participants.(18)
52
53
54
55
56
57
58
59
60

344

345 Adolescents

346

347 Adolescents constitute a special population with vulnerabilities different from those
348 of adults and younger children, and they should be included in research that addresses their
349 specific needs. However, as legal minors they often cannot give informed consent for
350 research.(16) In research in LMICs, regulations vary significantly from country to country
351 regarding when adolescents can provide legal consent for research.(31) For example, even
352 when legal frameworks allow adolescents to seek, for example, contraception services
353 without parental permission, they cannot necessarily provide consent for research on that
354 theme.(32,33) In a scoping review of post abortion care research, Zulu and coauthors
355 discuss how the need to balance adolescents' privacy needs and the demand for parental
356 consent poses difficulties for researchers in this field.(34) Woollett and colleagues describe
357 an interesting case study where they sought consent from a High Court in South Africa for
358 research involving orphaned HIV-positive adolescents. In that study, they provide detailed
359 recommendations for consent involving adolescents, including training staff about
360 confidentiality requirements; recognizing immature decision-making by adolescents and
361 developing appropriate methods for probing comprehension and consent, and utilizing
362 methods that promote active participation in research, such as mobile phones.(33)

363

364 Assent

1
2
3 365 Pediatric research guidelines are unanimous on the need to obtain age-appropriate
4
5 366 assent from children and adolescents who do not provide their own informed consent
6
7 367 (Table 1). However, we found little explicit discussion or description of procedures for
8
9 368 obtaining assent in the research reports we reviewed. (35,36) One interesting qualitative
10
11 369 study on parental perceptions of assent in Jordan revealed considerable variability in
12
13 370 caregivers' perspectives about at what age assent should be solicited or, even, if assent
14
15 371 should in all cases be obtained and dissent respected.(23)
16
17
18
19

20 372
21 373 **DISCUSSION**
22 374

23 375 Children in low-resource settings are highly vulnerable to exploitation in research, because
24
25 376 of circumstances including socioeconomic inequalities, limited access to health care, and
26
27 377 high burden of illness.(60) In addition, even where international consensus exists around
28
29 378 core ethical principles for providing protections to children as research subjects, it may be
30
31 379 unclear how best to operationalize those principles in many low-resources settings, where
32
33 380 gender norms, literacy, unfamiliarity with scientific research, and language barriers may all
34
35 381 be important adaptive barriers. (10,11)
36
37
38
39

40 382
41
42
43 383 Through a scoping review of research reports and case studies from LMICs we identified,
44
45 384 however, several core areas where existing research reports provided considerable insight
46
47 385 and operational guidance which could be used to guide informed consent design processes
48
49 386 in additional LMIC settings. These included: (1) *careful consideration of community*
50
51 387 *hierarchy*, where consent for research may first proceed through a council of elders or other
52
53 388 authority figure, prior to approaching individual caregivers; (2) *guidance on developing*
54
55
56
57
58
59
60

1
2
3 389 *verbal consent procedures* in settings where caregivers have low literacy levels; (3) and
4
5 390 *recognition of the challenges of consent in indigenous or less-commonly spoken languages,*
6
7 391 particularly when that language is not commonly written and where alternative procedures,
8
9
10 392 such as audio recordings in the language, must be employed; and (4) *careful consideration*
11
12 393 *of the possibility of therapeutic misconception* and of developing consent procedures that
13
14 394 ensure caregivers' comprehension of the potential benefits (or lack thereof) and risks of
15
16 395 research procedures for their children.
17
18
19
20 396

21
22
23 397 However, within these four broad thematic areas, we also noted the need for additional
24
25 398 careful investigation. In particular, there is considerable uncertainty on how to ensure the
26
27 399 principle of subsequent individual informed consent when community leaders or other
28
29 400 authorities are approached first. This is especially the case when gender power imbalance is
30
31 401 at play, and female caregivers may be either unempowered to consent or to opt out of a
32
33 402 research decision made by a male authority. In addition, the social status of individuals
34
35 403 administering or witnessing consent procedures may unduly influence the decision-making
36
37 404 of caregivers, and research is needed to better understand and accommodate for the
38
39 405 interpersonal dynamics of obtaining consent.
40
41
42
43
44 406

45
46
47 407 Finally, two thematic topics seem to be particularly underrepresented in the literature on
48
49 408 pediatric LMIC research, and more work is urgently needed. First, despite extensive
50
51 409 discussions about the difficulties of conducting research with adolescents, we found only
52
53 410 few studies with practical discussions or guidance on how to navigate these difficulties.
54
55
56
57
58
59
60

1
2
3 411 More investigation of the ethical conduct of research with adolescents is needed, with a
4
5 412 broader representation of health conditions, research designs, and geographic regions.
6
7 413 Second, despite strong representation of the principle of assent in international guidelines
8
9 414 on research with children and adolescents, we found little research of cultural and regional
10
11 415 differences around notions of assent and virtually no discussion of the mechanics of
12
13 416 assessing assent in research studies. Additional research into the topic of assent for research
14
15 417 among children in LMICs should be an important priority.
16
17
18
19
20 418

21
22
23 419 Our review has two important limitations that must be considered. First, we included only
24
25 420 articles published in English in major indexing databases. We believe this approach is
26
27 421 justified, given our desire to provide a high-level overview of the topic without focusing
28
29 422 specifically on any geographic region. Nevertheless, our review has undoubtedly missed
30
31 423 resources in other languages or within the grey literature, which could be taken up in more
32
33 424 detailed region-specific work on this topic. Second, given the diversity and heterogeneity of
34
35 425 the literature reviewed, it was not possible to detail many of the practical insights and tips
36
37 426 given in the individual articles. Nevertheless, given the annotation and thematic
38
39 427 organization provided in Supplementary Table 1, we are confident that readers will be able
40
41 428 to identify areas of particular interest for more in-depth examination.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

429 **ABBREVIATIONS**

- 430 IRB: Institutional review board
- 431 LMIC: Low and middle-income country
- 432 RCT: Randomized clinical trial
- 433 STaR: Standards for Research in Child Health

Confidential: For Review Only

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

434 **FUNDING**

435 This work was unfunded.

436

Confidential: For Review Only

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

437 **COMPETING INTERESTS**

438 None.

439

Confidential: For Review Only

1
2
3 440 **AUTHOR'S CONTRIBUTIONS**
4
5

6 441 MC designed the search strategy, extracted data from articles, and wrote the first draft of
7
8 442 the manuscript. PR conceived the study, reviewed abstracts, and revised the manuscript.
9

10
11 443
12

13
14 444
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

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

445 **DATA SHARING STATEMENT**

446 Not applicable

447

Confidential: For Review Only

1
2
3 448 **ACKNOWLEDGMENTS**
4

5 449 We thank research subjects and clinical staff at Maya Health Alliance for inspiring our
6
7
8 450 interest in this important topic.
9

10
11 451
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

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

452 **FIGURE LEGENDS**

453 **Figure 1. Results of Literature Screen.** Flow diagram depicting results of the literature
454 search and review procedure.

455
456
457

Confidential: For Review Only

bmjpo: first published as 10.1136/bmjpo-2018-000298 on 5 December 2018. Downloaded from <http://bmjpaedsopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

458 **REFERENCES**

- 459 1. Weindling P. The Origins of Informed Consent: The International Scientific
460 Commission on Medical War Crimes, and the Nuremberg Code. *Bull Hist Med.*
461 2001;75(1):37–71.
- 462 2. Rickham P. Human Experimentation. Code of Ethics of the World Medical
463 Association. Declaration of Helsinki. *Br Med J.* 1964;2 (5402)(177).
- 464 3. Council for International Organizations of Medical Sciences (CIOMS). International
465 Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition.
466 [Internet]. 2016. Available from:
467 [http://www.sciencedirect.com/science/article/B6VC6-45F5X02-](http://www.sciencedirect.com/science/article/B6VC6-45F5X02-9C/2/e44bc37a6e392634b1cf436105978f01)
468 [9C/2/e44bc37a6e392634b1cf436105978f01](http://www.sciencedirect.com/science/article/B6VC6-45F5X02-9C/2/e44bc37a6e392634b1cf436105978f01)
- 469 4. Caldwell PHY, Dans L, Newman J, Sammons H, Spriggs M, Tambe P, et al. StaR
470 Child Health Standard 1 : Consent and Recruitment. *Pediatrics.* 2012.
- 471 5. Klassen TP, Hartling L, Hamm M, van der Lee JH, Ursum J, Offringa M. StaR Child
472 Health: an initiative for RCTs in children. *Lancet* [Internet]. 2009 Oct
473 17;374(9698):1310–2. Available from: [http://dx.doi.org/10.1016/S0140-](http://dx.doi.org/10.1016/S0140-6736(09)61803-1)
474 [6736\(09\)61803-1](http://dx.doi.org/10.1016/S0140-6736(09)61803-1)
- 475 6. Martinez B, Webb MF, Gonzalez A, Douglas K, Grazioso P, Rohloff P, et al.
476 Complementary feeding intervention on stunted Guatemalan children : a randomised
477 controlled trial. *BMJ Paediatr Open.* 2018;1–8.
- 478 7. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for
479 Medical Research Invol...: . 2017;(June 1964):1–9. Available from:

- 1
2
3 480 <http://eds.b.ebscohost.com/eds/pdfviewer/pdfviewer?sid=a4bced6b-7270-457a->
4
5 481 [9730-e5a47e439a7a%40sessionmgr105&vid=6&hid=126](http://eds.b.ebscohost.com/eds/pdfviewer/pdfviewer?sid=a4bced6b-7270-457a-9730-e5a47e439a7a%40sessionmgr105&vid=6&hid=126)
6
7
8 482 8. National Bioethics Advisory Commission. Ethical and Policy Issues Research:
9
10 483 Clinical Trials in Developing Countries Vol. 1 [Internet]. 2001. 59 p. Available
11
12 484 from: <http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf>
13
14
15
16 485 9. European Commission. EU Directive 2001/20/EC. Off J Eur Communities.
17
18 486 2001;2001(April):1–15.
19
20
21 487 10. Bhutta ZA. Beyond informed consent. Bull World Health Organ. 2004
22
23 488 Oct;82(10):771–7.
24
25
26 489 11. MacLeod SM, Knoppert DC, Stanton-Jean M, Avarad D. Pediatric clinical drug trials
27
28 490 in low-income countries: key ethical issues. Paediatr Drugs. 2015 Feb;17(1):83–90.
29
30
31 491 12. Minnies D, Hawkrigde T, Hanekom W, Ehrlich R, London L, Hussey G. Evaluation
32
33 492 of the quality of informed consent in a vaccine field trial in a developing country
34
35 493 setting. BMC Med Ethics. 2008;9:1–9.
36
37
38
39 494 13. Halmsted Kongsholm NC, Lassen J, Sandoe P. “I didn’t have anything to decide, I
40
41 495 wanted to help my kids” - An interview-based study of consent procedures for
42
43 496 sampling human biological material for genetic research in rural Pakistan. AJOB
44
45 497 Empir Bioeth. 2018;4515(April 2014):1–35.
46
47
48
49 498 14. Nabulsi M, Khalil Y, Makhoul J. Parental attitudes towards and perceptions of their
50
51 499 children’s participation in clinical research: A developing-country perspective. J
52
53 500 Med Ethics. 2011;37(7):420–3.

- 1
2
3 501 15. Kamuya DM, Theobald SJ, Marsh V, Parker M, Geissler WP, Molyneux SC. “The
4 one who chases you away does not tell you go”: silent refusals and complex power
5 502 relations in research consent processes in Coastal Kenya. PLoS One.
6
7 503
8
9 504 2015;10(5):e0126671.
- 10
11
12 505 16. Macrae DJ. The Council for International Organizations and Medical Sciences
13 (CIOMS) guidelines on ethics of clinical trials. Proc Am Thorac Soc. 2007
14 506 May;4(2):176–8, discussion 178-9.
15
16
17 507
- 18 508 17. Martellet L, Sow SO, Diallo A, Hodgson A, Kampmann B, Hirve S, et al. Ethical
19 Challenges and Lessons Learned During the Clinical Development of a Group A
20 509 Meningococcal Conjugate Vaccine. Clin Infect Dis. 2015 Nov;61 Suppl 5:S422-7.
21
22
23 510
- 24 511 18. Kalabuanga M, Ravinetto R, Maketa V, Muhindo Mavoko H, Fungula B, Inocência
25 da Luz R, et al. The Challenges of Research Informed Consent in Socio-
26 512 Economically Vulnerable Populations: A Viewpoint From the Democratic Republic
27 of Congo. Dev World Bioeth. 2016;16(2):64–9.
28
29
30 513
- 31 514
- 32 515 19. Shetty P, Maurya M, Figer B, Thatte U, Gogtay N. Audiovisual recording of the
33 consenting process in clinical research: Experiences from a tertiary referral center.
34 516 Perspect Clin Res [Internet]. 2018 Jan 1;9(1):44–7. Available from:
35 517 <http://www.picronline.org/article.asp?issn=2229-3485>
36
37 518
- 38 519 20. Fitzpatrick EFM, Martiniuk ALC, D’Antoine H, Oscar J, Carter M, Elliott EJ.
39 Seeking consent for research with indigenous communities: a systematic review.
40 520 BMC Med Ethics. 2016 Oct;17(1):65.
41
42
43 521
- 44 522 21. Flood D, Rohloff P. Indigenous languages and global health. Lancet Glob Heal

- 1
2
3 523 [Internet]. 2018;6(2):e134–5. Available from: <http://dx.doi.org/10.1016/S2214->
4
5 524 109X(17)30493-X
6
7
8 525 22. Mboizi RB, Afolabi MO, Okoye M, Kampmann B, Roca A, Idoko OT. Recall and
9
10 526 decay of consent information among parents of infants participating in a randomized
11
12 527 controlled clinical trial using an audio-visual tool in The Gambia. *Hum Vaccin*
13
14
15 528 *Immunother.* 2017 Sep;13(9):2185–91.
16
17
18 529 23. Khabour OF, Alomari MA, Al-Sheyab NA. Parental Perceptions About Informed
19
20 530 Consent/Assent in Pediatric Research in Jordan. *J Empir Res Hum Res Ethics.* 2017
21
22 531 Oct;12(4):261–8.
23
24
25 532 24. Rajaraman D, Jesuraj N, Geiter L, Bennett S, Grewal HM, Vaz M. How
26
27 533 participatory is parental consent in low literacy rural settings in low income
28
29 534 countries? Lessons learned from a community based study of infants in South India.
30
31 535 *BMC Med Ethics.* 2011 Feb;12:3.
32
33
34
35 536 25. Leach A, Hilton S, Greenwood BM, Manneh E, Dibba B, Wilkins A, et al. An
36
37 537 evaluation of the informed consent procedure used during a trial of a *Haemophilus*
38
39 538 *influenzae* type B conjugate vaccine undertaken in The Gambia, West Africa. *Soc*
40
41 539 *Sci Med.* 1999;48(2):139–48.
42
43
44
45 540 26. Pace C, Talisuna A, Wendler D, Maiso F, Wabwire-Mangen F, Bakyaite N, et al.
46
47 541 Quality of parental consent in a Ugandan malaria study. *Am J Public Health.*
48
49 542 2005;95(7):1184–9.
50
51
52
53 543 27. Paré Toe L, Ravinetto RM, Dierickx S, Gryseels C, Tinto H, Rouamba N, et al.
54
55 544 Could the decision of trial participation precede the informed consent process?

- 1
2
3 545 Evidence from Burkina Faso. *PLoS One*. 2013;8(11):1–10.
4
5
6 546 28. Angwenyi V, Kamuya D, Mwachiro D, Kalama B, Marsh V, Njuguna P, et al.
7
8 547 Complex realities: community engagement for a paediatric randomized controlled
9
10 548 malaria vaccine trial in Kilifi, Kenya. *Trials*. 2014 Feb;15:65.
11
12
13 549 29. Sarkar R, Grandin EW, Gladstone BP, Muliyl J, Kang G. Comprehension and recall
14
15 550 of informed consent among participating families in a birth cohort study on
16
17 551 diarrhoeal disease. *Public Health Ethics*. 2009;2(1):37–44.
18
19
20
21 552 30. Serce O, Gonen I, Bakir M. Factors Influencing Parental Consent in a Hypothetical
22
23 553 Pediatric Vaccine Trial in a Developing Country Setting: A Questionnaire Study.
24
25 554 Account Res [Internet]. 2015;22(1):1–13. Available from:
26
27 555 <http://dx.doi.org/10.1080/08989621.2014.882779>
28
29
30
31 556 31. Bekker L, Slack C, Lee S, Shah S, Kapogiannis B. Ethical Issues in Adolescent HIV
32
33 557 Research in Resource-Limited Countries. *J Acquir Immune Defic Syndr*.
34
35 558 2014;65(Supplement 1):24–8.
36
37
38 559 32. McClure CA, Gray G, Rybczyk GK, Wright PF. Challenges to conducting HIV
39
40 560 preventative vaccine trials with adolescents. *J Acquir Immune Defic Syndr*. 2004
41
42 561 Jun;36(2):726–33.
43
44
45
46 562 33. Woollett N, Psychology MA, Th A, Peter J, Cluver L, Brahmabhatt H. Enrolling
47
48 563 HIV-positive adolescents in mental health research : A case study re fl ecting on
49
50 564 legal and ethical complexities. 2017;107(8):679–83.
51
52
53
54 565 34. Zulu JM, Ali J, Hallez K, Kass N, Michelo C, Hyder AA. Ethics challenges and
55
56 566 guidance related to research involving adolescent post-abortion care: A scoping
57
58
59
60

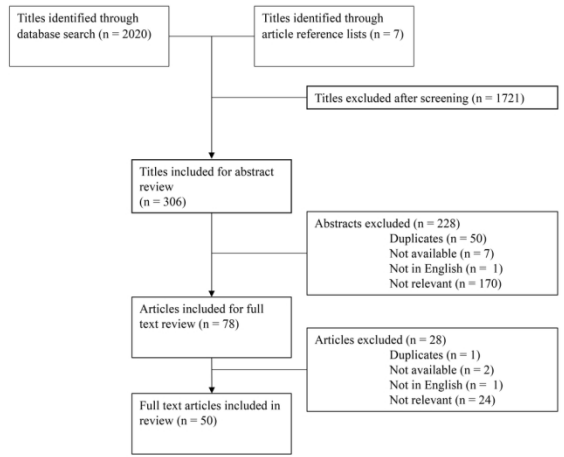
- 1
2
3 567 review. *Reprod Health*. 2018;15(1):1–10.
4
5
6 568 35. Vreeman RC, Nyandiko WM, Meslin EM. Pediatric Assent for a Study of
7
8 569 Antiretroviral Therapy Dosing for Children in Western Kenya: A Case Study in
9
10 570 International Research Collaboration. *J Empir Res Hum Res Ethics* [Internet].
11
12 571 2009;4(1):3–16. Available from: <http://www.jstor.org/stable/10.1525/jer.2009.4.1.3>
13
14
15
16 572 36. Molyneux CS, Wassenaar DR, Peshu N, Marsh K. “Even if they ask you to stand by
17
18 573 a tree all day, you will have to do it (laughter)...!”: Community voices on the notion
19
20 574 and practice of informed consent for biomedical research in developing countries.
21
22 575 *Soc Sci Med*. 2005;61(2):443–54.
23
24
25
26 576 37. Ott MA, Crawley FP, Saez-Llorens X, Owusu-Agyei S, Neubauer D, Dubin G, et al.
27
28 577 Ethical Considerations for the Participation of Children of Minor Parents in Clinical
29
30 578 Trials. *Paediatr Drugs*. 2018 Jun;20(3):215–22.
31
32
33 579 38. Regmi PR, Aryal N, Kurmi O, Pant PR, van Teijlingen E, Wasti SP. Informed
34
35 580 Consent in Health Research: Challenges and Barriers in Low-and Middle-Income
36
37 581 Countries with Specific Reference to Nepal. *Dev World Bioeth*. 2017;17(2):84–9.
38
39
40
41 582 39. Mandava A, Pace C, Campbell B, Emanuel E. The quality of informed consent:
42
43 583 mapping the landscape. A review of empirical data from developing and developed
44
45 584 countries. *J Med Ethics*. 2016;38(6):356–65.
46
47
48 585 40. Joseph PD, Caldwell PHY, Tong A. Stakeholder Views of Clinical Trials in Low-
49
50 586 and Middle-Income Countries : A Systematic Review. 2016;137(2).
51
52
53
54 587 41. Morrow BM, Argent AC, Kling S. Informed consent in paediatric critical care
55
56 588 research--a South African perspective. *BMC Med Ethics*. 2015 Sep;16:62.
57
58
59
60

- 1
2
3 589 42. Swain TR. Clinical trials for children: some concerns. *Indian J Pharmacol* [Internet].
4
5 590 2014;46(2):145–6. Available from:
6
7 591 <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N>
8
9 &AN=24741182
10 592
- 11
12
13 593 43. Ruiz-Casares M. Research ethics in global mental health: Advancing culturally
14
15 594 responsive mental health research. *Transcult Psychiatry*. 2014;51(6):790–805.
- 16
17
18 595 44. Offringa M, Needham AC, Chan WWY. StaR Child Health: Improving global
19
20 596 standards for child health research. *Early Hum Dev* [Internet]. 2013;89(11):861–4.
21
22 597 Available from: <http://dx.doi.org/10.1016/j.earlhumdev.2013.09.011>
- 23
24
25 598 45. Daley TC, Singhal N, Krishnamurthy V. Ethical considerations in conducting
26
27 599 research on autism spectrum disorders in low and middle income countries. *J Autism*
28
29 600 *Dev Disord*. 2013;43(9):2002–14.
- 30
31
32
33 601 46. Denburg AE, Joffe S, Gupta S, Howard SC, Ribeiro RC, Antillon FA, et al. Pediatric
34
35 602 oncology research in low income countries: ethical concepts and challenges. *Pediatr*
36
37 603 *Blood Cancer*. 2012 Apr;58(4):492–7.
- 38
39
40
41 604 47. Mystakidou K, Panagiotou I, Katsaragakis S, Tsilika E, Parpa. Ethical and practical
42
43 605 challenges of implementing informed consent in HIV/AIDS clinical trials in
44
45 606 developing or resource-limited countries. *J Soc Asp HIV/AIDS*. 2009;6(2):46–57.
- 46
47
48 607 48. Embleton L, Ott MA, Wachira J, Naanyu V, Kamanda A, Makori D, et al. Adapting
49
50 608 ethical guidelines for adolescent health research to street-connected children and
51
52 609 youth in low- and middle-income countries: A case study from western Kenya. *BMC*
53
54 610 *Med Ethics*. 2015;

- 1
2
3 611 49. Millum J, Emanuel E. The Ethics of International Research with Abandoned
4
5 612 Children. 2015;35(1):30–7.
6
7
8 613 50. Vreeman R, Kamaara E, Kamanda A, Ayuku D, Nyandiko W, Atwoli L, et al.
9
10 614 Community Perspectives on Research Consent Involving Vulnerable Children in
11
12 615 Western Kenya. *J Empir Res Hum Res Ethics* [Internet]. 2012;7(4):44–55. Available
13
14 616 from: <http://journals.sagepub.com/doi/10.1525/jer.2012.7.4.44>
15
16
17
18 617 51. Tindana P, Bull S, Amenga-Etego L, De Vries J, Aborigo R, Koram K, et al.
19
20 618 Seeking consent to genetic and genomic research in a rural Ghanaian setting: A
21
22 619 qualitative study of the MalariaGEN experience. *BMC Med Ethics* [Internet].
23
24 620 2012;13(1):1. Available from: BMC Medical Ethics
25
26
27
28 621 52. Morris MC, Wilson PT. Medical Device Research in Resource-Poor Settings: A
29
30 622 Pediatric Case Study in Ghana. *IRB Ethics Hum Res*. 2018;36(4):1–7.
31
32
33 623 53. Ward CL, Shaw D, Anane-Sarpong E, Sankoh O, Tanner M, Elger B. The Ethics of
34
35 624 Health Care Delivery in a Pediatric Malaria Vaccine Trial: The Perspectives of
36
37 625 Stakeholders From Ghana and Tanzania. *J Empir Res Hum Res Ethics*.
38
39 626 2018;13(1):26–41.
40
41
42
43 627 54. Devries KM, Child JC, Elbourne D, Naker D, Heise L. “I never expected that it
44
45 628 would happen, coming to ask me such questions”: Ethical aspects of asking children
46
47 629 about violence in resource poor settings. *Trials*. 2015 Nov;16:516.
48
49
50
51 630 55. Oduro AR, Aborigo RA, Amugsi D, Anto F, Anyorigiya T, Atuguba F, et al.
52
53 631 Understanding and retention of the informed consent process among parents in rural
54
55 632 northern Ghana. *BMC Med Ethics*. 2008;9:1–9.
56
57
58
59
60

- 1
2
3 633 56. Krosin MT, Klitzman R, Levin B, Cheng J, Ranney ML. Problems in comprehension
4
5 634 of informed consent in rural and peri-urban Mali, West Africa. *Clin Trials*.
6
7 635 2006;3(3):306–13.
8
9
10 636 57. Molyneux CS, Peshu N, Marsh K. Trust and informed consent: Insights from
11
12 637 community members on the Kenyan coast. *Soc Sci Med*. 2005;61(7):1463–73.
13
14
15 638 58. Joseph PD, Craig JC, Tong A, Caldwell PHY. Researchers, Regulators, and
16
17 639 Sponsors Views on Pediatric Clinical Trials: A Multinational Study. *Pediatrics*
18
19 640 [Internet]. 2016;138(4):e20161171–e20161171. Available from:
20
21 641 <http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2016-1171>
22
23
24
25 642 59. Nakkash R, Makhoul J, Afifi R. Obtaining informed consent: observations from
26
27 643 community research with refugee and impoverished youth. *J Med Ethics*. 2009
28
29 644 Oct;35(10):638–43.
30
31
32
33 645 60. Initiative for Vaccine Research of the Department of Vaccines and Biologicals World
34
35 646 Health Organization. Ethical considerations arising from vaccine trials conducted in
36
37 647 paediatric populations with high disease burden in developing countries. In:
38
39 648 WHO/IRV ethics meeting November 26-28, 2002 Accra, Ghana [Internet]. 2002.
40
41 649 Available from: www.who.int/vaccines-documents
42
43
44
45
46 650

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



152x85mm (300 x 300 DPI)

Supplementary Table 1. Summary of articles selected for inclusion in review.

Confidential: For Review Only

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

Reference (Year)	Study Description	Study Location	Major findings
Reviews and Opinion Articles¹			
Ott MA et al.(37) (2018)	Review – participation of children of minor parents in research	Multiple	Discussion on international research documents and existing laws and practices regarding consent for research for children of minor parents. Few countries have regulations about the subject, which might result in exclusion of those children from research. Authors recommend involving minors in the decision-making about their children and adapting consent procedures so minor parents can participate and their children's vulnerabilities correctly addressed.
Zulu JM et al. (34) (2018)	Review - Ethical challenges of post-abortion care research in adolescents in LMICs	Multiple	Authors included 14 articles in their analysis. Regarding the consent process, challenges identified include difficulties in seeking consent from parents/guardians of adolescents who are below the consent age, vulnerability of adolescents compromising ability to make decisions, fear of losing access to health care affecting informed consent process, and inadequate guidance on how and when to involve communities in the consent process.
Regmi P et al. (38) (2017)	Review – informed consent in health research in LMICs	Multiple, but focused on Nepal	Authors discuss challenges in adapting informed consent: verbal versus written informed consent in areas of limited literacy; difficulties posed by having to translate consent documents to local languages; issues around the legal age to consent, and how clear threshold ages of consent are not clear in local guidelines.
Mandava A et al. (39) (2016)	Review – comparison between consent processes in developing and developed countries	Multiple	Authors aimed to compare data about comprehension and voluntariness. In both settings comprehension of study information varies among participants, and comprehension of randomization and placebo use is poor. Participants in developing countries seem to be less likely to say they can refuse participation or withdraw and worry more about the consequences of doing so. Recommendations include developing validated questions to measure comprehension and voluntariness and conducting studies on the impact of cultural norms and socio-demographic characteristics on informed consent.

Joseph P et al. (40) (2016)	Review - Views of stakeholders on aspects of conducting research with children in LMICs	Multiple	Regarding informed consent, stakeholders believe that disempowerment, poor education, and difficulty in translating scientific concepts were barriers to informed decision making. Authors recommend simplifying consent forms and presenting them in culturally and linguistically appropriate format with verification of parental comprehension. Authors discuss that Western ethical principles of consent and child assent, autonomy, and individualism need to be contextualized.
Morrow B et al. (41) (2015)	Opinion – Consent for pediatric critical care research in South Africa	South Africa	Authors discuss legal issues in South Africa that create confusion for informed consent for children. They identify barriers to the consent process: impracticability of getting consent when urgent action is needed; the validity of consent in high-stress settings; addressing parents during stressful situations; sociocultural issues and the differences in communication and response to authority figures. The authors discuss alternatives to the prospective informed consent, such as the deferred consent model.
MacLeod SM et al. (11) (2015)	Review – ethical issues of pediatric drug trials in LMICs	Multiple	The review discusses vulnerabilities of pediatric research participants, in particular children in LMICs. Authors discuss characteristics of the consent process, and how socioeconomic status, religious belief, and distribution of power affect decisions to participate. They point to the need to consider cultural differences, and the appropriateness of obtaining community consent in some contexts.
Swain T. (42) (2014)	Opinion - barriers to pediatric clinical drug trials in low resource settings, with emphasis in India	India	The author discusses how the consent process for research can be affected by poverty and lack of education. The author points out that the consent process should be clear and assent should be sought from children 7-18 years old, as per Indian guidelines. Deferred consent for neonatal intensive care studies and other high-acuity settings may reduce caregiver stress and be preferred.
Bekker L et al. (31) (2014)	Review - Ethical issues of HIV research in resource limited countries	Multiple	The authors review ethical issues in HIV research with adolescents in LMICs. They point out best practices for consenting adolescents: auditing ethical-legal requirements for consent; involving adolescents in decision making; ensuring

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

			language, age, and cultural appropriateness; and giving sufficient time and resources to consent.
--	--	--	---

Confidential: For Review Only

bmjpo- first published as 10.1136/bmjpo-2018-000298 on 5 December 2018. Downloaded from <http://bmjpaedopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Ruiz-Casares M et al. (43) (2014)	Review – culturally responsive mental health research	Multiple	Regarding informed consent, the author discusses how to obtain culturally appropriate consent, how to ensure adequate understanding of the consent information, consideration of community structures, documenting informed consent, and determination of decision-making capacity.
Offringa M et al. (44) (2013)	Review - Background and summary of Standards for Research (StaR) in Child Health published standards on the conduction of pediatric clinical research	n/a	Summary of first 6 StaR Child Health published standards: 1. Consent and recruitment; 2. Containing risk of bias; 3. Data monitoring committees; 4. Determining adequate sample sizes; 5. Selection, measurement, and reporting of outcomes; and 6. Age groups for pediatric trials.
Daley C et al. (45) (2013)	Review - ethical issues associated with autism spectrum disorders research in developing countries	Multiple	Authors discuss ethical aspects relevant to the conduct of autism spectrum disorders research in developing countries. They mention challenges to informed consent such as parents' lack of knowledge about research.
Denburg A et al. (46) (2012)	Review – ethical aspects and challenges of pediatric oncology research in LMICs	Multiple	Authors conducted a review of ethical issues related to standards of care, trial benefits, ethics review and informed consent. They focused on the ethical implications of drug development and intervention research. Regarding informed consent, they discuss illiteracy, social and political power imbalances, validity of consent in face of ancillary benefits of research, mistrust of foreign investigators by parents, and difficulties aligning local perspectives with international norms.
Mystakidou K et al. (47) (2009)	Review – informed consent in human HIV research in developing countries.	Multiple	In trials involving children and adolescents, authors discuss the process of enrolling subjects, including challenges in getting informed consent from parents or guardians while protecting the privacy of the subjects. Most studies on this topic involve adolescents, and there is limited data about the assent process in younger children. Authors discuss the characteristics that informed consent should have in the context of HIV trials in the developing world, including the need to address cultural differences.
Bhutta Z. (10) (2004)	Review - analysis of international guidelines on the subject of informed	Multiple	Review and discussion of guidelines for obtaining informed consent. The discussion notes that more focus is put on written documentation of consent and less

	consent		understanding of the process and adaptation to local contexts, and differences regarding when and how communities should be involved in the consent process.
McClure C et al. (32) (2004)	Review - challenges to conducting HIV vaccine trials with adolescents, including in developing countries	Multiple	Authors identified challenges to HIV vaccine trials with adolescents. Adolescents are minors and need parental consent for participating in research. At the same time, their autonomy and privacy need to be respected. The consent process might be affected by less perception of personal risk.
Social Norms, Decision Making, and Autonomy			

Kongsholm N et al.(13) (2018)	Qualitative research– interviews with researchers and donors about consent experience for genetic research	Pakistan	Researchers report adaptations to consent process including use of elder and oral consent; involving literate witnesses to validate written forms; and disclosure of information adapted to educational level. Challenges include no knowledge about consent process by participants and therapeutic misconception. Donors' motivations for participating include obtaining direct benefit from their participation and a high level of trust in the research team.
Embleton L et al. (48) (2015)	Case study - Ethical guidelines adaptation for three different studies with street connected youth and children	Kenya	The authors describe processes of consent for street-connected children and youth participating in three research projects. They discuss the importance of guidelines and working with local and international committees, ethicists, and the community to identify areas of special concern. Key recommendations include involving the community and working within the local sociocultural context.
Millum J and Emanuel E. (49) (2015)	Case study – research with abandoned children	Romania	The authors discuss how research with abandoned children might be constrained by the challenge of getting informed consent. This might result in this vulnerable group not being included in research for reasons of convenience. They argue that vulnerable groups can be protected by enrolling them in studies that pose no or minimal risks.
Vreeman R et al. (50) (2012)	Qualitative research - analysis of community discussion sessions regarding the participation of orphaned children in research.	Kenya	Results showed positive attitudes towards the participation of orphaned children in research, mainly because adults assumed that children would be directly benefited. Consent from parents or guardians was considered necessary but getting assent from children was not. The participation of the community in the consent process was considered appropriate. Authors recommend paying attention to misconceptions about research related benefits.
Molyneux CS et al. (36) (2005)	Qualitative research - Community views regarding the informed consent process, in the context of studies being carried out by the KEMRI institute in Kenya	Kenya	Results show that seeking consent from community elders is necessary but does not substitute the need for individual parental consent. Most respondents suggested males should make the decision to participate and that assent should not be sought from children before age 10-13. For inpatient studies, respondents identified illness severity, potential risks, and parents' ability to

			understand as factors influencing the consent process. Results of the study show some therapeutic misconception and discrepancies regarding which interventions need permission.
Working in low-literate setting and with indigenous/less-commonly-spoken languages			
Mboizi R et al. (22) (2017)	Mixed methods research – recall and decay of consent information among parents using and audiovisual tool	The Gambia	Recall of trial procedures and consent process was evaluated using questionnaires at two points in time. Results show overall good recall of consent when using the Speaking Book audiovisual tool. No differences were found between age, occupation, years of education, religion or family type.
Kalabuanga M et al. (18) (2016)	Case study – Description of the consent process during a malaria clinical trial	Democratic Republic of Congo	Authors identified misunderstanding of the informed consent process among parents. They also identified cases where culturally-accepted guardians might not have legal authority to consent for research. They discuss how the use of a witness can impair parents' autonomy by exerting social pressure. In the context of limited access to care, the ancillary benefits of participating in research may be a strong incentive to participate.
Martellet L et al. (17) (2015)	Case study – Informed consent for a vaccine trial	The Gambia, Mali, India, Senegal, Ghana	Informed consent for a vaccine trial was sought from parents/legal guardians of children 1-17 years. Written assent was taken from children 12-17. They used literate witnesses when participants/parents were illiterate and translated consent forms to local languages. In some areas, consent was done verbally. Written consent forms were always provided. Some study sites used tools to assess understanding of the research project prior to consent.
Tindana P et al. (51) (2012)	Qualitative – interviews with research staff and mothers of study participants about the informed consent process for a malaria genetics study	Ghana	The consent process was adapted to include community leaders and groups of women. For individual consent, written forms were used but information was adapted to be more relevant to parents. The timing of consent for in-patient cases was modified to obtain it after children had been stabilized. The provision of medical care and direct benefits to children was identified as a motivation for participating.
Gender			

Kamuya D et al.(15) (2015)	Qualitative – focus groups and interviews conducted with participants of RSV and malaria studies.	Kenya	Authors describe the phenomenon of silent refusal. Possible causes include avoiding conflict within households, maintaining a good relationship with the research team, and retaining study benefits. For women and young adults, it might be a way to exert agency within the patriarchal system. Authors discuss negotiations that take place during the consent process, and how ethical principles are interpreted and negotiated in a context-specific way.
Sarkar R et al. (29) (2009)	Mixed methods research – comprehension and recall of informed consent process in a pediatric diarrhea study	India	Findings showed low recall of study purposes four years after enrollment. Most respondents were mothers and mentioned spousal approval and free medical care for their children as main motivations to consent and remain in the study. Educational level was significantly associated with recall of study purpose. Few respondents knew they could leave the study at any time. Authors point out the need for continuous reinforcement of the consent process.
Minnies D et al. (12) (2008)	Mixed methods – Recall of the consent process for a study of immune protection against TB	South Africa	Mothers who had consented for the study then completed a questionnaire about key elements of informed consent, recall, and understanding. Most obtained scores greater than 75% for recall and understanding. 79% were aware of the risks and 64% knew participation was voluntary. A higher level of education and being consented by professional nurses were associated with higher recall. Authors suggest monitoring the quality of consent procedures periodically.
Communicating about Risks and Benefits of Research			

Morris M and Wilson P. (52) (2018)	Case study – research on the use of CPAP in intensive care settings	Ghana	Authors describe how consent was obtained, and express concern about the fact that there were no refusals and that this might reflect that consent was not fully informed or participation was not truly voluntary. The authors do not know to which extent parents understood randomization, or that CPAP could be used independently of study participation. They discuss how the lack of access for medical care might influence the consent process.
Ward CL et al. (53) (2018)	Qualitative research – interviews with stakeholders about ethical aspects in a pediatric malaria vaccine trial	Ghana and Tanzania	Stakeholders identify the importance of community education and a well-adapted consent process in helping avoid misconception about trial benefits and healthcare service provision, as well as in preventing undue inducement by clearly stating risks and benefits.
Devries K et al. (54) (2015)	Qualitative research - experiences of children participating in a cluster RCT of a school-based violence prevention intervention.	Uganda	Authors describe the consent process for the RCT and present findings from interviews conducted with children after participating. They found some therapeutic misconception about potential benefits and propose that clearer language in the consent forms might help avoid it.
Serce O et al. (30) (2015)	Quantitative- Questionnaires administered to parents to assess potential participation in research	Turkey	Authors perform univariate and multivariate logistic regression to identify characteristics that might predict participation. Factors associated with willingness to consent include satisfaction with the content of the informed consent and being a business owner. Factors associated with refusal of consent were older age of parents and owning a car. Parents responded that learning more about the trial and its benefits, ensuring health coverage, and payment of transport expenses would positively influence consent.
Angweny V et al. (28) (2014)	Qualitative – interviews and group discussions with researchers, community members and parents	Kenya	Authors describe and analyze the community engagement process for the trial. Concerning the consent process, they present results on parents' understanding of the trial one year after recruitment. They report low levels of understanding about the purpose of the trial and the randomisation process. There appeared to be less understanding of the trial where there was less community engagement.
Paré L et al. (27) (2013)	Mixed methods research - assessment of the relevance of the informed	Burkina Faso	Results showed that prior knowledge of the trial was significantly associated with the decision to participate. Common reasons for

	consent procedure in a malaria trial comparing the efficacy of two different treatments		participating were the perceived aid provided by the trial, better quality of care, and better quality of the medication. Information about confidentiality, right to withdraw from the study, and potential risks was poorly retained. Randomization was poorly understood. Authors aim to show that there are other factors besides the information received during the consent process that influence parents' decision to participate in the trial.
Rajamaran D et al. (24) (2011)	Mixed methods research – analysis of relation between parents' socio-demographic characteristics and likelihood of asking questions during the consent process	India	The study looked at parents asking questions during the informed consent process. 13.4% of parents asked any questions. There was a high association between asking questions and socio-economic and educational status, and with presence of both parents. Authors conclude that consent materials should be interactive, to make comprehension easier, and that in pediatric trials effort should be made to get participation of both parents in the consent process.
Nabulsi M et al. (14) (2011)	Qualitative research – perceptions of Lebanese parents about their children's participation in research	Lebanon	Fear of potential harm or pain caused to children was identified as a main barrier to parental consent, as were complex consent forms and misunderstanding of randomization. Perceived direct benefits of participation, trust in the doctor and the institution, financial gains or previous positive experience with research identified as motivations to participate. Authors recommend improving communication and building trust with parents to enhance recruitment.
Oduro AR et al. (55) (2008)	Mixed methods research – Understanding and retention of informed consent process by parents of children participating in a malaria cohort study	Ghana	Findings show overall good recall of procedural aspects of the study. Recall about study benefits was significantly higher than about study risks. Most knew participation was voluntary, but few knew they could withdraw at any time and that information was handled confidentially. Younger parental age was associated with better recall and understanding. Free medical treatment and benefits to the participant were strong motivations for enrolling.
Krosin MT et al. (56) (2006)	Quantitative – parental understanding of the consent process for a malaria vaccine trial	Mali	By using a multiple-choice questionnaire, researchers identified poor comprehension about withdrawal criteria, study side effects, and investigational rather than therapeutic nature of the intervention. Response rate and percentage of correct answers were higher in a more urban setting than in a rural one.

Pace C et al. (26) (2005)	Qualitative – quality of parental consent in an antimalarial study	Uganda	Most respondents were mothers and had good recall of logistical aspects of the study and study purpose. Comprehension of randomization was low. The primary reason most respondents gave for enrolling their child was to obtain malaria treatment. Many parents felt pressure to enroll because their child was sick. Only 41% reported they could have refused and 65% knew they could quit.
Molyneux CS et al. (57) (2005)	Mixed methods research – community views about the informed consent process and trust	Kenya	Findings show that trust in the research institution by the community is based on the perceived quality of clinical services it provides, and less on research activities. Trust in the research unit is an important reason behind community members' agreeing to participate in research. Responders valued the informed consent process but thought that low education and being in stressful situations impaired understanding. Authors suggest modifying consent procedures by not giving all information at once and testing to improve comprehension.
Leach A et al. (25) (1999)	Qualitative research - Attitudes of the Gambian people to consent to medical research within the context of a H. influenzae vaccine trial.	The Gambia	Semi-structured interviews were conducted with study participants and refusers in urban and rural areas. Results showed that certain points of the trial were recalled well: 90% knew the purpose of the vaccine, but only 10% understood the placebo control design. The main motive for consenting was to receive the vaccine (93%), and for refusing was that the vaccine was experimental (35%) and might have side effects (29%). In all cases the decision was made by just one of the parents.
Research with Adolescents			

Woollet MA et al. (33) (2017)	Case study – consent for orphaned adolescents to participate in a mental health study	South Africa	Authors present how consent for research with orphaned adolescents had to be sought from the High Court before approval was granted by academic research committees. The authors discuss how the policy results in excluding vulnerable populations from research and give recommendations for mental health research with adolescents.
Joseph P et al. (58) (2016)	Qualitative research – Stakeholders' views on international pediatric clinical trials	n/a	Regarding the consent process, challenges identified by stakeholders include consent requirements in certain countries that conflict with adolescents' confidentiality rights; impracticality of using long consent forms with multiple required elements, and the need for guidelines to streamline consent form production.
Nakkash R et al. (59) (2009)	Qualitative research – observation of the consent process for a two-phase preparatory study for an RCT to test the impact of a social skill-building intervention to improve mental health in adolescents	Lebanon	Researchers identified challenges to the consent process: incomplete disclosure of study information; complexity of terms and research design, compounded by low educational levels; issues related to who could provide consent for the child; and social conceptions that youth are not capable of decision making. The greatest threat to the informed consent process was lack of voluntariness.
Assent			
Khabour O et al. (23) (2017)	Qualitative research – focus groups to explore parental perceptions about the informed consent and assent process for research	Jordan	Findings show an acceptable understanding of many aspects related to the consent process. However, some parents believed that informed consent is not necessary for questionnaire studies, there were discrepancies regarding the appropriate age for a child's assent, and some parents said they would force their child to participate regardless of child's wishes.
Vreeman R et al. (35) (2009)	Case study - pediatric assent for a study on antiretroviral therapy	Kenya	Authors describe the process of getting review by both US and Kenyan IRBs, mentioning that there is no guideline about how joint review should be conducted. Authors present the differences between the two countries regarding appropriate age for obtaining assent, and discuss local laws, practices, and international guidelines.

¹Major thematic groupings for articles in Table 2 are provided. Most articles discuss multiple themes, but are grouped here based on the most prominent or significant theme identified in the review.

BMJ Paediatrics Open

Cultural considerations for informed consent in pediatric research in low and middle income countries: A scoping review

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2018-000298.R2
Article Type:	Original article
Date Submitted by the Author:	24-Oct-2018
Complete List of Authors:	Colom, Marcela; Wuqu' Kawoq Rohloff, Peter
Keywords:	Ethics, Health services research

SCHOLARONE™
Manuscripts

1
2
3 1 **TITLE PAGE**
4

5 2

6
7 3 **Cultural considerations for informed consent in pediatric research in low and middle**
8 **income countries: A scoping review**
9
10 4

11
12 5
13
14 6 Marcela Colom MD¹, Peter Rohloff MD PhD^{1,2,3}
15
16
17 7

18
19 8 ¹Wuqu' Kawoq | Maya Health Alliance, 2da Avenida 3-48 Zona 3, Barrio Patacabaj, Tecpán,
20
21 Chimaltenango, Guatemala
22
23

24 10
25
26 11 ²Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA
27
28
29 12

30
31 13 ³ Corresponding Author. Peter Rohloff, Brigham and Women's Hospital, 75 Francis Street,
32
33 14 Boston, MA, 02115. Phone: 617-278-0055. Fax: 888-372-2354. Email:
34
35 15 prohloff@bwh.harvard.edu
36
37
38 16
39
40 17
41
42 18
43

44 19 Word count: 3701
45
46
47 20
48
49 21
50
51 22
52
53
54 23
55
56
57
58
59
60

24 WHAT IS KNOWN ABOUT THIS SUBJECT

- 25 • Conducting research with children in low- and middle-income countries (LMICs)
26 requires careful consideration of socioeconomic inequalities and cultural and
27 linguistic differences.
- 28 • Existing international standards for the conduct of ethical pediatric research advance
29 core concepts, such as informed consent, voluntariness, and assent, but there often
30 is limited guidance on how to adapt and operationalize these for LMIC settings.

31 WHAT THIS STUDY ADDS

- 32 • Helpful examples and emerging consensus for best practices in community
33 engagement, verbal and alternative consent procedures, and guarding against
34 therapeutic misconception by caregivers in interventional and randomized
35 controlled trial designs.
- 36 • The need for additional research where less consensus was apparent, especially
37 around the protection of the individual autonomy of caregivers and safeguarding
38 children's own assent to participate in research.

1
2
3 42 **ABSTRACT**
4
5
6 43

7
8 44 Introduction: Conducting research with children in low- and middle-income countries
9
10 45 (LMICs) requires consideration of socioeconomic inequalities and cultural and linguistic
11
12 46 differences. Our objective was to survey the literature on informed consent in pediatric LMIC
13
14 47 research, assessing for practical guidance for culturally- and linguistically-appropriate
15
16 48 procedures.
17
18

19 49
20
21 50 Methods: We conducted a scoping review on informed consent in pediatric LMIC research
22
23 51 searching the Pubmed, Web of Science and PsycINFO databases. Eligible articles were
24
25 52 published in English, from any date range, of any study design or format.
26
27
28 53

29
30 54 Results: The search identified 2,027 references, of which 50 were included in the analysis
31
32 55 following full-text review. Reviewed guidelines emphasized individual, informed and
33
34 56 voluntary consent from parents and caregivers. Reviewed articles provided detailed practical
35
36 57 guidance on adapting these guiding principles to LMIC settings, including considerations for
37
38 58 community engagement, verbal or other alternative consent procedures for low-literacy
39
40 59 settings or less-commonly spoken languages, and guarding against therapeutic
41
42 60 misconception by caregivers. There was uncertainty, however, on how to best protect
43
44 61 individual autonomy, especially when influenced by gender dynamics, leadership
45
46 62 hierarchies, or the social status of researchers themselves. There was, furthermore, limited
47
48 63 research discussing the special case of research involving adolescents or of procedures for
49
50 64 documenting assent by participating children.
51
52
53
54
55
56 65

1
2
3 66 Conclusions: A scoping review of pediatric research in LMICs revealed substantial guidance
4
5 67 on several features of culturally appropriate informed consent . However, additional research
6
7 68 and guidance is needed, especially in the areas of gender imbalances, research with
8
9 69 adolescents, and children’s own assent to participate in research.
10
11
12
13 70
14
15 71
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

72 INTRODUCTION

73

74 Prior to World War II, there was little international consensus on the ethical conduct of
75 human subjects' research. The Nuremberg code, developed in 1947 during the Nuremberg
76 war crimes trials, was one of the first attempts to articulate basic ethical principles, such as
77 the right to informed consent.(1) Subsequently, the World Medical Association's (WMA)
78 Declaration of Helsinki in 1964 provided a more definitive consensus statement on the core
79 principles of ethical conduct of research--beneficence, self-determination, and informed
80 consent—which is widely considered the foundational international document in modern
81 research ethics.(2) Practical guidance on ethical practice is well codified in the joint
82 statements produced by the Council for International Organizations of Medical Sciences
83 (CIOMS) and the World Health Organization (WHO).(3)

84

85 Extension of ethical research principles to include considerations appropriate for research in
86 pediatric populations are also important, including guidance on obtaining informed consent
87 from parents or guardians, obtaining assent from children themselves, and weighing the
88 balance of risks and benefits of proposed research.(3,4) Improvements in the conduct and
89 volume of pediatric clinical trials, which have historically been few in number and of lower
90 quality than corresponding trials in adult subjects, have also recently been advocated.(5)

91

92 However, there still remains uncertainty around how best to implement international ethical
93 principles of pediatric research in some settings. This is especially the case in low and
94 middle-income countries (LMICs), and in research with groups such as indigenous
95 populations, speakers of less-common languages, or populations with high levels of

1
2
3 96 illiteracy. Practically, we experienced this recently while designing a clinical trial of a
4
5 97 nutrition intervention for indigenous Maya children in rural Guatemala, and our experience
6
7 98 navigating consent, literacy, and translingual adaptation in this population prompted our
8
9
10 99 interest in more formally exploring the topic.(6) To this end, here we conduct a scoping
11
12 100 review of the existing literature on cultural and contextual considerations for informed
13
14 101 consent in the conduct of pediatric research in LMICs. Through this review, we identify
15
16 102 evidence for specific culturally- and contextually-sensitive practices, as well as areas where
17
18 103 additional research and guideline development is needed.
19
20
21
22 104

23 105 **METHODS**

24 106 25 26 107 **Search and inclusion strategy**

27
28 108
29
30
31 109 To identify articles, we searched the PubMed, Web of Science and PsycINFO databases. We
32
33 110 conducted searches using a combination of the following key terms: “pediatric” or “children”
34
35 111 or “adolescents”; “research” or “biomedical research”; “consent” or “informed consent” or
36
37 112 “ethics”; “developing countries” or “low income countries” or “middle income countries”;
38
39 113 “illiteracy”; “culturally competent”. We used no date limits and included all articles
40
41 114 published through May 2018. In addition, we visited the websites of international health
42
43 115 policy organizations to identify ethics guidelines for the conduct of research in low- and
44
45 116 middle-income countries. We also manually reviewed the reference lists of articles identified
46
47 117 using the above methods. For this scoping review, of the articles identified above we included
48
49 118 for analysis any type of study design or format (original research, commentary, case study,
50
51 119 review, expert opinion), which addressed the informed consent process specifically for
52
53
54
55
56
57
58
59
60

1
2
3 120 pediatric or adolescent populations in low or middle-income countries. Articles not in
4
5 121 English were excluded.
6
7
8 122

9 10 123 **Data extraction and synthesis**

11
12 124
13
14 125 We exported identified articles into an Excel spreadsheet template which recorded location
15
16 126 of study, study type and design, study context, aspects of informed consent examined, and
17
18 127 key findings. Both authors reviewed the study titles and abstracts. After removal of articles
19
20 128 which were deemed not eligible for inclusion, one author (MC) performed a full text review
21
22 129 of all the remaining articles. As a scoping review to assess the patterns of existing literature
23
24 130 on informed consent in LMIC pediatric research, assessments of individual study bias and
25
26 131 quality were not performed. Data extracted from articles was collated in summary form
27
28 132 (Table 1), and major qualitative findings are presented in the following narrative synthesis.
29
30
31
32
33
34

35 134 **RESULTS**

36 37 135 38 39 136 **Results of literature screen**

40
41 137
42
43
44 138 A total of 2,027 candidate titles were identified through database searches, supplemented by
45
46 139 reference list and website reviews. Of these, 1,721 did not meet eligibility criteria, and 306
47
48 140 were included for abstract review. If the abstract was not available but full text was, the title
49
50 141 was included for full text review. After abstract review, 50 duplicates were found, one was
51
52 142 not in English, 7 were not available (abstract nor full text), and 170 abstracts did not meet
53
54 143 inclusion criteria. 78 articles were selected for full text review, of which 24 subsequently did
55
56
57
58
59
60

1
2
3 144 not meet inclusion criteria, one was in French, one was a duplicate, and two did not have
4
5 145 available full text. Therefore 50 full-text articles were included in this review (Figure 1, Table
6
7 146 1, Supplementary Table 1). Of the articles excluded at the abstract and full text review stages,
8
9 147 the most common reasons for exclusion were: no mention of the informed consent process
10
11 148 for research with pediatric or adolescent populations; research not taking place in a low- or
12
13 149 middle-income country; articles on pediatric research in low- or middle-income countries
14
15 150 that did not discuss the informed consent process
16
17
18
19
20
21

22 152 **Summary of guidelines and commentaries**

23
24 153
25
26 154 We identified seven guidelines that addressed issues of informed consent in international
27
28 155 settings and in research involving children in our scoping review. Of these, we selected for
29
30 156 detailed review five that were most comprehensive, summarizing key recommendations in
31
32 157 Table 1. All guidelines emphasize the importance of obtaining individual, informed and
33
34 158 voluntary consent for research.(3,4,7–9) Importantly, however, the guidelines do not
35
36 159 necessarily specify in detail how best to operationalize assessment of these core principles.
37
38 160 For example, the Declaration of Helsinki comments only that informed consent requires that
39
40 161 a subject be adequately informed of the “aims, methods, sources of funding, any possible
41
42 162 conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and
43
44 163 potential risks of the study and the discomfort it may entail, post-study provisions and any
45
46 164 other relevant aspects of the study” (Article 26). (7) Similarly, on voluntariness, the CIOMS
47
48 165 guidelines note only that consent is voluntary if “an individual’s decision to participate is
49
50 166 free of undue influence” (p. 35). (3)
51
52
53
54
55
56
57
58
59
60

167

168 Some of the guidelines do suggest modifications appropriate for lower-resource settings,
169 such as obtaining witnessed verbal consent when literacy is a barrier. (7,9) The United States
170 National Bioethics Advisory Commission (NBAC) also acknowledges that oral consent
171 might even be preferable in some circumstances.(8) However, as other commentaries note,
172 there is little specificity on how best to operationalize these suggestions, such as how to
173 formally document verbal consent or characteristics of a qualified witness.(10,11)

174

175 Another important consideration of LMIC research addressed in guidelines is an emphasis
176 on the need to at times obtain consent from community stakeholders and leaders, or other
177 key local decision makers. Nevertheless, all guidelines unanimously assert that community-
178 based consent can never replace individual consent. When local cultural practices around
179 community-based consent contradict core principles of the international consensus on the
180 informed consent process, such as the need for voluntary individual consent, researchers are
181 advised to search for culturally sensitive ways of providing all information to potential
182 participants without compromising the substantive ethical standard of informed consent, an
183 adaptive process in which local research ethics committees are expected to place a substantial
184 role. (8,10–12)

185

186 Finally, with respect to children or adolescents not capable of providing informed consent,
187 in addition to obtaining consent from parents or legal representatives, most guidelines also
188 reinforce the need to obtain assent from the child or adolescent in an age-appropriate way.

189 (3,4,7,9) The CIOMS guidelines note that assent is “a process...not merely the absence of
 190 dissent” and requires “meaningful[1] engage[ment] in the research discussion in accordance
 191 with...capacities” (p. 67). (3) They also note that as adolescents reach the age of maturity,
 192 their agreement to participate may be ethically considered as informed consent. However, if
 193 they legally remain minors, researchers are cautioned that consent from a parent is still
 194 generally needed, but a list is provided of possible situations when parental consent might be
 195 waived, such as with legally emancipated adolescents, or under circumstances where
 196 obtaining parental consent is not desirable because of the research topic. (3)

197 **Table 1 Summary of selected major guidelines on ethical conduct of research in children**

Guideline	Core principles	Considerations for adapting to low-resource, low-literary, and minority language settings
World Medical Association, Declaration of Helsinki(7)	<ul style="list-style-type: none"> • If a research subject is not capable of giving informed consent, it should be sought from a legally authorized representative • When the subject can give assent to decisions about participation in research, assent should be sought in addition to consent. Dissent should be respected 	<ul style="list-style-type: none"> • Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information • Consent should be given preferably in writing, if not the non-written consent must be formally documented and witnessed
Council for International Organizations of Medical Sciences(3)	<ul style="list-style-type: none"> • Obtain permission from a parent or a legally authorized representative of the child • Obtain assent from the child or adolescent according to his or her capacity and after having been provided with information tailored to the child’s or adolescent’s level of maturity 	<ul style="list-style-type: none"> • Consult with and engage communities in the informed consent process • Obtained a signed form as evidence of informed consent, justify any exceptions to this general rule and seek approval of the research ethics committee
Standards for Research (StaR) in Child Health(4)	<ul style="list-style-type: none"> • Obtain consent and assent when age-appropriate • Provide age-appropriate, clear, concise, and on-going information for parents and children 	<ul style="list-style-type: none"> • Provide clear justification to involve a particular population and equitable sharing of benefits and risks • Community consultation can be helpful but does not replace the need for individual consent • Strengthen composition and

<p>National Bioethics Advisory Commission, Ethical and policy issues in international research(8)</p>		<p>expertise of local ethics committees</p> <ul style="list-style-type: none"> • Develop culturally appropriate ways to disclose information that is necessary for adherence to the ethical standard of informed consent • Develop procedures to ensure that participants understand the information provided in the consent process • Respect local requirements of asking permission from community representatives for approaching potential participants, but respect the requirement of individual informed consent • Ethics review committees can waive the requirements of written and signed consent in accordance with local cultural norms
<p>European Council and European Parliament Guidelines(9)</p>	<ul style="list-style-type: none"> • Consent should be sought from parents or legal representatives • Information should be provided to the minor according to its capacity of understanding • The explicit wish of a minor who is capable of forming an opinion and assessing information to refuse participation should be considered 	<ul style="list-style-type: none"> • The individual or legal representative has to give written consent. If the individual is unable to write, oral consent may be given in the presence of at least one witness, as provided for in national legislation

199 **Thematic summary of research on consent in LMIC pediatric research**

200

201 Existing published work on informed consent in pediatric research in LMICs includes a
 202 number of review and opinion articles (Table 2) as well as case studies describing the
 203 experience of individual research teams and discussing the challenges and solutions utilized
 204 when adapting consent processes to their local context. We summarize several major themes
 205 emerging from these studies here in narrative form and provide detailed key findings from
 206 the reviewed articles in the accompanying Tables.

207 [insert Table 2 here]

208 **Table 2 Summary of review and opinion articles on ethical conduct of research in**
 209 **children**

Reference (Year)	Study Description	Study Location	Major findings
Ott MA et al.(37) (2018)	Review – participation of children of minor parents in research	Multiple	Discussion on international research documents and existing laws and practices regarding consent for research for children of minor parents. Few countries have regulations about the subject, which might result in exclusion of those children from research. Authors recommend involving minors in the decision-making about their children and adapting consent procedures so minor parents can participate and their children's vulnerabilities correctly addressed.
Zulu JM et al. (34) (2018)	Review - Ethical challenges of post-abortion care research in adolescents in LMICs	Multiple	Authors included 14 articles in their analysis. Regarding the consent process, challenges identified include difficulties in seeking consent from parents/guardians of adolescents who are below the consent age, vulnerability of adolescents compromising ability to make decisions, fear of losing access to health care affecting informed consent process, and inadequate guidance on how and when to involve communities in the consent process.

1 2 3 4 5 6 7 8 9 10 11	Regmi P et al. (38) (2017)	Review – informed consent in health research in LMICs	Multiple, but focused on Nepal	Authors discuss challenges in adapting informed consent: verbal versus written informed consent in areas of limited literacy; difficulties posed by having to translate consent documents to local languages; issues around the legal age to consent, and how clear threshold ages of consent are not clear in local guidelines.
12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27	Mandava A et al. (39) (2016)	Review – comparison between consent processes in developing and developed countries	Multiple	Authors aimed to compare data about comprehension and voluntariness. In both settings comprehension of study information varies among participants, and comprehension of randomization and placebo use is poor. Participants in developing countries seem to be less likely to say they can refuse participation or withdraw and worry more about the consequences of doing so. Recommendations include developing validated questions to measure comprehension and voluntariness and conducting studies on the impact of cultural norms and socio-demographic characteristics on informed consent.
28 29 30 31 32 33 34 35 36 37 38 39 40 41	Joseph P et al. (40) (2016)	Review - Views of stakeholders on aspects of conducting research with children in LMICs	Multiple	Regarding informed consent, stakeholders believe that disempowerment, poor education, and difficulty in translating scientific concepts were barriers to informed decision making. Authors recommend simplifying consent forms and presenting them in culturally and linguistically appropriate format with verification of parental comprehension. Authors discuss that Western ethical principles of consent and child assent, autonomy, and individualism need to be contextualized.
42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Morrow B et al. (41) (2015)	Opinion – Consent for pediatric critical care research in South Africa	South Africa	Authors discuss legal issues in South Africa that create confusion for informed consent for children. They identify barriers to the consent process: impracticability of getting consent when urgent action is needed; the validity of consent in high-stress settings; addressing parents during stressful situations; sociocultural issues and the differences in communication and response to authority figures. The authors discuss alternatives to the prospective informed consent, such as the deferred consent model.

MacLeod SM et al. (11) (2015)	Review – ethical issues of pediatric drug trials in LMICs	Multiple	The review discusses vulnerabilities of pediatric research participants, in particular children in LMICs. Authors discuss characteristics of the consent process, and how socioeconomic status, religious belief, and distribution of power affect decisions to participate. They point to the need to consider cultural differences, and the appropriateness of obtaining community consent in some contexts.
Swain T. (42) (2014)	Opinion - barriers to pediatric clinical drug trials in low resource settings, with emphasis in India	India	The author discusses how the consent process for research can be affected by poverty and lack of education. The author points out that the consent process should be clear and assent should be sought from children 7-18 years old, as per Indian guidelines. Deferred consent for neonatal intensive care studies and other high-acuity settings may reduce caregiver stress and be preferred.
Bekker L et al. (31) (2014)	Review - Ethical issues of HIV research in resource limited countries	Multiple	The authors review ethical issues in HIV research with adolescents in LMICs. They point out best practices for consenting adolescents: auditing ethical-legal requirements for consent; involving adolescents in decision making; ensuring language, age, and cultural appropriateness; and giving sufficient time and resources to consent.
Ruiz-Casares M et al. (43) (2014)	Review – culturally responsive mental health research	Multiple	Regarding informed consent, the author discusses how to obtain culturally appropriate consent, how to ensure adequate understanding of the consent information, consideration of community structures, documenting informed consent, and determination of decision-making capacity.
Offringa M et al. (44) (2013)	Review - Background and summary of Standards for Research (StaR) in Child Health published standards on the conduction of pediatric clinical research	n/a	Summary of first 6 StaR Child Health published standards: 1. Consent and recruitment; 2. Containing risk of bias; 3. Data monitoring committees; 4. Determining adequate sample sizes; 5. Selection, measurement, and reporting of outcomes; and 6. Age groups for pediatric trials.
Daley C et al. (45) (2013)	Review - ethical issues associated with autism spectrum disorders research in developing countries	Multiple	Authors discuss ethical aspects relevant to the conduct of autism spectrum disorders research in developing countries. They mention challenges to informed consent such as parents' lack of knowledge about research.

Denburg A et al. (46) (2012)	Review – ethical aspects and challenges of pediatric oncology research in LMICs	Multiple	Authors conducted a review of ethical issues related to standards of care, trial benefits, ethics review and informed consent. They focused on the ethical implications of drug development and intervention research. Regarding informed consent, they discuss illiteracy, social and political power imbalances, validity of consent in face of ancillary benefits of research, mistrust of foreign investigators by parents, and difficulties aligning local perspectives with international norms.
Mystakidou K et al. (47) (2009)	Review – informed consent in human HIV research in developing countries.	Multiple	In trials involving children and adolescents, authors discuss the process of enrolling subjects, including challenges in getting informed consent from parents or guardians while protecting the privacy of the subjects. Most studies on this topic involve adolescents, and there is limited data about the assent process in younger children. Authors discuss the characteristics that informed consent should have in the context of HIV trials in the developing world, including the need to address cultural differences.
Bhutta Z. (10) (2004)	Review - analysis of international guidelines on the subject of informed consent	Multiple	Review and discussion of guidelines for obtaining informed consent. The discussion notes that more focus is put on written documentation of consent and less understanding of the process and adaptation to local contexts, and differences regarding when and how communities should be involved in the consent process.
McClure C et al. (32) (2004)	Review - challenges to conducting HIV vaccine trials with adolescents, including in developing countries	Multiple	Authors identified challenges to HIV vaccine trials with adolescents. Adolescents are minors and need parental consent for participating in research. At the same time, their autonomy and privacy need to be respected. The consent process might be affected by less perception of personal risk.

210

211

212

213 Understanding social norms around decision making and protecting individual autonomy

214

215 An important principle highlighted in international guidelines on informed consent in
216 LMICs is appropriate and early engagement with existing local leadership structures (such
217 as a council of elders) balanced against respect for the autonomy of individual children or
218 their caregivers.(3,8) In practice, this can be a delicate balance to maintain (Table 3).
219 Kongsholm and colleagues, for example, describe consent processes in rural Pakistan, where
220 family structures are patriarchal and hierarchical. In this setting, consent procedures involved
221 first seeking consent from an elder, who provided initial consent for the entire family.
222 However, under this approach, the voluntariness of individual participants may be
223 undermined, and it is unclear how best to ensure that individuals still retain an “opt out”
224 mechanism or, conversely, the right to participate in research if they wish to do so but the elder
225 declines.(13)

226

227 Another important consideration explored by some studies is understanding how not all
228 potential consenting caregivers may feel empowered to decline participating in research.
229 Consent procedures administered by local research personnel or by individuals with high
230 social status, such as physicians, may inspire trust.(13,14) However it may also make them
231 reluctant to decline participation, or to resist active participation. For example, in one study
232 in Kenya, explicit refusals to participate were often considered to be impolite. Here
233 researchers found that caregivers expressed their unwillingness to participate by delaying the
234 consent process, or by participating inconsistently in research procedures even after initially
235 having consented to the study.(15)

236 [insert Table 3 here]

237 **Table 3 Summary of articles discussing Social Norms, Decision Making, and**
 238 **Autonomy¹**

Kongsholm N et al.(13) (2018)	Qualitative research– interviews with researchers and donors about consent experience for genetic research	Pakistan	Researchers report adaptations to consent process including use of elder and oral consent; involving literate witnesses to validate written forms; and disclosure of information adapted to educational level. Challenges include no knowledge about consent process by participants and therapeutic misconception. Donors’ motivations for participating include obtaining direct benefit from their participation and a high level of trust in the research team.
Embleton L et al. (48) (2015)	Case study - Ethical guidelines adaptation for three different studies with street connected youth and children	Kenya	The authors describe processes of consent for street-connected children and youth participating in three research projects. They discuss the importance of guidelines and working with local and international committees, ethicists, and the community to identify areas of special concern. Key recommendations include involving the community and working within the local sociocultural context.
Millum J and Emanuel E. (49) (2015)	Case study – research with abandoned children	Romania	The authors discuss how research with abandoned children might be constrained by the challenge of getting informed consent. This might result in this vulnerable group not being included in research for reasons of convenience. They argue that vulnerable groups can be protected by enrolling them in studies that pose no or minimal risks.
Vreeman R et al. (50) (2012)	Qualitative research - analysis of community discussion sessions regarding the participation of orphaned children in research.	Kenya	Results showed positive attitudes towards the participation of orphaned children in research, mainly because adults assumed that children would be directly benefited. Consent from parents or guardians was considered necessary but getting assent from children was not. The participation of the community in the consent process was considered appropriate. Authors recommend paying attention to misconceptions about research related benefits.
Molyneux CS et al. (36) (2005)	Qualitative research - Community views regarding the informed consent process, in the	Kenya	Results show that seeking consent from community elders is necessary but does not substitute the need for individual parental consent. Most respondents

	context of studies being carried out by the KEMRI institute in Kenya	suggested males should make the decision to participate and that assent should not be sought from children before age 10-13. For inpatient studies, respondents identified illness severity, potential risks, and parents' ability to understand as factors influencing the consent process. Results of the study show some therapeutic misconception and discrepancies regarding which interventions need permission.
--	--	--

239 ¹In this and subsequent tables, articles are presented by major thematic groupings. Most articles
 240 discuss multiple themes, but are grouped here based on the most prominent or significant theme
 241 identified in the review.

242

243 Adapting consent procedures to low-literate settings

244

245 There is strong consensus in international ethics guidelines that written, informed
 246 consent is preferred when conducting research (Table 4). In the case of pediatric research,
 247 this again typically involves obtaining written consent from one or both primary
 248 caregivers.(4,9,16) However, in many LMIC settings, literacy may be low or a high value
 249 may be placed on oral interactions, and lack of alternative consent procedures may violate
 250 another core ethics principle, namely the equitable distribution of research benefits and
 251 burdens across populations.(3,14,17) Some of the studies we reviewed described these
 252 procedures, with verbal consent commonly being obtained, most often in the presence of a
 253 literate witness who is able to read available consent documents. (13,14,17,18) In one very
 254 thoughtful piece, Kalabuanga and colleagues note, however, that witnesses may often impose
 255 their views on the consenting caregiver and their child, rather than encourage dialog and act
 256 as a safeguard, especially since they are often recruited in an ad hoc fashion (e.g., other
 257 literate patients or ancillary hospital staff).(18) Kalabuanga et al. go on to suggest that these

258 challenges may be mitigated by careful vetting and training of independent witnesses or,
 259 alternatively, by allowing potential consenting caregivers to use a trusted relative or friend
 260 as their witness.(18)

261

262 Another issue identified in the review is that of emerging new mandates in some LMICs to
 263 document consent procedures. For example, in India, audiovisual documentation of obtaining
 264 informed consent is now required for most clinical trials if participants are low-literate. This
 265 introduced significant new logistical challenges and costs related to obtaining and archiving
 266 recordings, and it may also pose a barrier to potential research subjects who may distrust or
 267 refuse to be recorded.(19)

268 [insert Table 4 here]

269 **Table 4 Summary of articles discussing working in low-literate settings, and with**
 270 **indigenous or less-commonly-spoken languages**

Mboizi R et al. (22) (2017)	Mixed methods research – recall and decay of consent information among parents using and audiovisual tool	The Gambia	Recall of trial procedures and consent process was evaluated using questionnaires at two points in time. Results show overall good recall of consent when using the Speaking Book audiovisual tool. No differences were found between age, occupation, years of education, religion or family type.
Kalabuanga M et al. (18) (2016)	Case study – Description of the consent process during a malaria clinical trial	Democratic Republic of Congo	Authors identified misunderstanding of the informed consent process among parents. They also identified cases where culturally-accepted guardians might not have legal authority to consent for research. They discuss how the use of a witness can impair parents' autonomy by exerting social pressure. In the context of limited access to care, the ancillary benefits of participating in research may be a strong incentive to participate.
Martellet L et al. (17) (2015)	Case study – Informed consent for a vaccine trial	The Gambia, Mali, India, Senegal, Ghana	Informed consent for a vaccine trial was sought from parents/legal guardians of children 1-17 years. Written assent was taken from children 12-17. They used

			literate witnesses when participants/parents were illiterate and translated consent forms to local languages. In some areas, consent was done verbally. Written consent forms were always provided. Some study sites used tools to assess understanding of the research project prior to consent.
Tindana P et al. (51) (2012)	Qualitative – interviews with research staff and mothers of study participants about the informed consent process for a malaria genetics study	Ghana	The consent process was adapted to include community leaders and groups of women. For individual consent, written forms were used but information was adapted to be more relevant to parents. The timing of consent for in-patient cases was modified to obtain it after children had been stabilized. The provision of medical care and direct benefits to children was identified as a motivation for participating.

271

272 Working in indigenous or less-commonly-spoken languages

273

274 International ethics guidelines emphasize that research information should be
 275 provided to consenting caregivers in a local language understandable to the individual (Table
 276 4).(7,8,16) However, this is most commonly understood to be a working lingua franca, and
 277 the issue of and practical approach to provisioning consent processes in an indigenous
 278 language is largely unaddressed in LMICs.(20) This is an important consideration, given that
 279 a substantial proportion of the potential pediatric research population in LMICs are from
 280 populations that speak indigenous or less-commonly-spoken languages.(21) In an interesting
 281 review of lessons learned in a pediatric vaccine trial in West Africa, Martellet and colleagues
 282 noted challenges in preparing consent procedures in some of the less-common language
 283 groups included in the trial, where use of the written form was uncommon, where substantial
 284 need to rely on metaphor and paraphrase made back-translation difficult, and where written
 285 documents were perceived as not being dynamic enough in cultures which valued

1
2
3 286 interactivity and person-to-person exchange. They describe alternative procedures, such as
4
5 287 the preparation of recordings of consent scripts in local languages and extensive practice
6
7 288 sessions with research staff obtaining consent in local languages.(17) Similarly, another
8
9 289 vaccine trial in The Gambia described the successful use of audio-visual Speaking Books in
10
11 290 local less-common languages to consent caregivers. (22)
12
13
14
15
16
17

18 291

19 292 Gender dynamics in caregiver consent
20
21
22
23

24 293

25 294 Local gender dynamics and decision making procedures when consenting male and
26
27 295 female caregivers for research is an important consideration (Table 5). For example, when
28
29 296 consenting with caregiving couples or within an extended family unit, instances are discussed
30
31 297 where a female caregiver wishes to allow her child to participate, but is unable to do so
32
33 298 because her husband or another male authority figure refuses.(13) The opposite may also
34
35 299 occur, if a research study is consented by a male figure, but requires significant participatory
36
37 300 effort from the primary female for study-related activities, leading the woman to express their
38
39 301 refusal through procedural delay or inconsistent participation.(15) Given concerns about
40
41 302 gender power imbalance and potential repercussions for consenting female caregivers, some
42
43 303 studies discussed working to routinely involve fathers or male authority figures in the consent
44
45 304 process for more complex or higher-risk research interventions.(15,23) In one interesting
46
47 305 study based in India, Rajaraman and colleagues found that caregivers were more likely to
48
49 306 actively participate in the consent process when both were present. They also observed,
50
51 307 however, that this factor may have been due the fact that most study staff obtaining consent
52
53
54
55
56
57
58
59
60

308 were male, and they call for more research on how the gender of research staff impacts the
 309 consent process.(24)

310

311 It is important to note that most discussions of gender dynamics that we reviewed were
 312 limited in nuance, tending to focus on instances of overt overriding of female decision-
 313 making by male authorities. A broader consideration of the range of ways in which female
 314 caregivers communicate, influence, and negotiate decision-making with male family
 315 members and other community authorities is an obvious point for future investigation.

316 [insert Table 5 here]

317 **Table 5 Summary of articles discussing gender**

Kamuya D et al.(15) (2015)	Qualitative – focus groups and interviews conducted with participants of RSV and malaria studies.	Kenya	Authors describe the phenomenon of silent refusal. Possible causes include avoiding conflict within households, maintaining a good relationship with the research team, and retaining study benefits. For women and young adults, it might be a way to exert agency within the patriarchal system. Authors discuss negotiations that take place during the consent process, and how ethical principles are interpreted and negotiated in a context-specific way.
Sarkar R et al. (29) (2009)	Mixed methods research – comprehension and recall of informed consent process in a pediatric diarrhea study	India	Findings showed low recall of study purposes four years after enrollment. Most respondents were mothers and mentioned spousal approval and free medical care for their children as main motivations to consent and remain in the study. Educational level was significantly associated with recall of study purpose. Few respondents knew they could leave the study at any time. Authors point out the need for continuous reinforcement of the consent process.
Minnies D et al. (12) (2008)	Mixed methods – Recall of the consent process for a study of immune protection	South Africa	Mothers who had consented for the study then completed a questionnaire about key elements of informed consent, recall, and understanding. Most obtained scores greater than 75% for recall and

	against TB		understanding. 79% were aware of the risks and 64% knew participation was voluntary. A higher level of education and being consented by professional nurses were associated with higher recall. Authors suggest monitoring the quality of consent procedures periodically.
--	------------	--	--

318

319 Disclosing potential benefits and risks of participation in research

320

321 Participation in some research studies, particularly those with a randomized
 322 controlled design or those with differing intervention arms, may not result in direct benefit
 323 to all participants. Several studies report difficulties explaining to caregivers that medical
 324 research procedures may not result in direct benefit to their children, and in verifying that
 325 caregivers comprehended the substance of randomization or control procedures (Table 6).
 326 (25–28) Others noted the need to address issues of information recall and retention,
 327 particularly with complex study procedures or consent forms, and to emphasize the right of
 328 study withdrawal and the ongoing reaffirmation of consent throughout a study. (26–29)
 329 Furthermore, other reports discussed how therapeutic misconception—the perception by
 330 research subjects that participation in any component of a multiple-arm, controlled trial, will
 331 result in therapeutic benefits—might be hard to avoid in certain contexts, as it might be
 332 affected by factors like educational level and cultural and religious beliefs about
 333 disease.(13,18)

334

335 At the same time, care must be given to a culturally-appropriate degree of information
 336 disclosure. For example, in several studies, caregivers—especially those of higher

337 socioeconomic or educational status—were more likely to participate when provided with
 338 detailed and in-depth information about the study processes and given opportunities to ask
 339 questions.(12,23,24,30) At the same time, other case studies point out how over-detailed
 340 discussion of study procedures or scientific rationale may provoke unneeded reserve or
 341 suspicion where such detailed disclosures by health professionals are not culturally
 342 customary.(13)

343

344 Finally, in settings where access to healthcare and other important social goods may be
 345 limited, even basic diagnostic or ancillary procedures that occur as part of a research studies
 346 may be better than the local standard of care, leading to an undue inducement or highly
 347 compelling incentives for caregivers to enroll their children in research, even after being
 348 informed about the experimental nature or studies and the risk-benefit balance.(11,13,18)
 349 These considerations highlight the importance of considering the socio-economic and
 350 cultural background of study settings well before beginning research and making plans to
 351 incorporate appropriate early, equitable benefit-sharing measures when possible, such as
 352 using study resources to improve community-level care not just care for eligible trial
 353 participants.(18)

354 [insert Table 6 here]

355 **Table 6 Summary of articles discussing communicating about risks and benefits of**
 356 **research**

Morris M and Wilson P. (52) (2018)	Case study – research on the use of CPAP in intensive care settings	Ghana	Authors describe how consent was obtained, and express concern about the fact that there were no refusals and that this might reflect that consent was not fully informed or participation was not truly voluntary. The authors do not know to which extent parents understood
------------------------------------	---	-------	--

			randomization, or that CPAP could be used independently of study participation. They discuss how the lack of access for medical care might influence the consent process.
Ward CL et al. (53) (2018)	Qualitative research – interviews with stakeholders about ethical aspects in a pediatric malaria vaccine trial	Ghana and Tanzania	Stakeholders identify the importance of community education and a well-adapted consent process in helping avoid misconception about trial benefits and healthcare service provision, as well as in preventing undue inducement by clearly stating risks and benefits.
Devries K et al. (54) (2015)	Qualitative research - experiences of children participating in a cluster RCT of a school-based violence prevention intervention.	Uganda	Authors describe the consent process for the RCT and present findings from interviews conducted with children after participating. They found some therapeutic misconception about potential benefits and propose that clearer language in the consent forms might help avoid it.
Serce O et al. (30) (2015)	Quantitative- Questionnaires administered to parents to assess potential participation in research	Turkey	Authors perform univariate and multivariate logistic regression to identify characteristics that might predict participation. Factors associated with willingness to consent include satisfaction with the content of the informed consent and being a business owner. Factors associated with refusal of consent were older age of parents and owning a car. Parents responded that learning more about the trial and its benefits, ensuring health coverage, and payment of transport expenses would positively influence consent.
Angweny V et al. (28) (2014)	Qualitative – interviews and group discussions with researchers, community members and parents	Kenya	Authors describe and analyze the community engagement process for the trial. Concerning the consent process, they present results on parents' understanding of the trial one year after recruitment. They report low levels of understanding about the purpose of the trial and the randomisation process. There appeared to be less understanding of the trial where there was less community engagement.
Paré L et al. (27) (2013)	Mixed methods research - assessment of the relevance of the informed consent procedure in a malaria trial comparing the efficacy of two different treatments	Burkina Faso	Results showed that prior knowledge of the trial was significantly associated with the decision to participate. Common reasons for participating were the perceived aid provided by the trial, better quality of care, and better quality of the medication. Information about confidentiality, right to withdraw from the study, and potential risks was poorly

			retained. Randomization was poorly understood. Authors aim to show that there are other factors besides the information received during the consent process that influence parents' decision to participate in the trial.
Rajamaran D et al. (24) (2011)	Mixed methods research – analysis of relation between parents' socio-demographic characteristics and likelihood of asking questions during the consent process	India	The study looked at parents asking questions during the informed consent process. 13.4% of parents asked any questions. There was a high association between asking questions and socio-economic and educational status, and with presence of both parents. Authors conclude that consent materials should be interactive, to make comprehension easier, and that in pediatric trials effort should be made to get participation of both parents in the consent process.
Nabulsi M et al. (14) (2011)	Qualitative research – perceptions of Lebanese parents about their children's participation in research	Lebanon	Fear of potential harm or pain caused to children was identified as a main barrier to parental consent, as were complex consent forms and misunderstanding of randomization. Perceived direct benefits of participation, trust in the doctor and the institution, financial gains or previous positive experience with research identified as motivations to participate. Authors recommend improving communication and building trust with parents to enhance recruitment.
Oduro AR et al. (55) (2008)	Mixed methods research – Understanding and retention of informed consent process by parents of children participating in a malaria cohort study	Ghana	Findings show overall good recall of procedural aspects of the study. Recall about study benefits was significantly higher than about study risks. Most knew participation was voluntary, but few knew they could withdraw at any time and that information was handled confidentially. Younger parental age was associated with better recall and understanding. Free medical treatment and benefits to the participant were strong motivations for enrolling.
Krosin MT et al. (56) (2006)	Quantitative – parental understanding of the consent process for a malaria vaccine trial	Mali	By using a multiple-choice questionnaire, researchers identified poor comprehension about withdrawal criteria, study side effects, and investigational rather than therapeutic nature of the intervention. Response rate and percentage of correct answers were higher in a more urban setting than in a rural one.
Pace C et al. (26) (2005)	Qualitative – quality of parental consent in an antimalarial study	Uganda	Most respondents were mothers and had good recall of logistical aspects of the study and study purpose. Comprehension of randomization was low. The primary reason most respondents gave for

			enrolling their child was to obtain malaria treatment. Many parents felt pressure to enroll because their child was sick. Only 41% reported they could have refused and 65% knew they could quit.
Molyneux CS et al. (57) (2005)	Mixed methods research – community views about the informed consent process and trust	Kenya	Findings show that trust in the research institution by the community is based on the perceived quality of clinical services it provides, and less on research activities. Trust in the research unit is an important reason behind community members' agreeing to participate in research. Responders valued the informed consent process but thought that low education and being in stressful situations impaired understanding. Authors suggest modifying consent procedures by not giving all information at once and testing to improve comprehension.
Leach A et al. (25) (1999)	Qualitative research - Attitudes of the Gambian people to consent to medical research within the context of a H. influenzae vaccine trial.	The Gambia	Semi-structured interviews were conducted with study participants and refusers in urban and rural areas. Results showed that certain points of the trial were recalled well: 90% knew the purpose of the vaccine, but only 10% understood the placebo control design. The main motive for consenting was to receive the vaccine (93%), and for refusing was that the vaccine was experimental (35%) and might have side effects (29%). In all cases the decision was made by just one of the parents.

357

358 Adolescents

359

360 Adolescents constitute a special population with vulnerabilities different from those
 361 of adults and younger children, and they should be included in research that addresses their
 362 specific needs (Table 7). However, as legal minors they often cannot give informed consent
 363 for research.(16) In research in LMICs, regulations vary significantly from country to country
 364 regarding when adolescents can provide legal consent for research.(31) For example, even
 365 when legal frameworks allow adolescents to seek, for example, contraception services

without parental permission, they cannot necessarily provide consent for research on that theme.(32,33) In a scoping review of post abortion care research, Zulu and coauthors discuss how the need to balance adolescents' privacy needs and the demand for parental consent poses difficulties for researchers in this field.(34) Woollett and colleagues describe an interesting case study where they sought consent from a High Court in South Africa for research involving orphaned HIV-positive adolescents. In that study, they provide detailed recommendations for consent involving adolescents, including training staff about confidentiality requirements; recognizing immature decision-making by adolescents and developing appropriate methods for probing comprehension and consent; and utilizing methods that promote active participation in research, such as mobile phones.(33)

[insert Table 7 here]

Table 7 Summary of articles discussing research with adolescents

Woollet MA et al. (33) (2017)	Case study – consent for orphaned adolescents to participate in a mental health study	South Africa	Authors present how consent for research with orphaned adolescents had to be sought from the High Court before approval was granted by academic research committees. The authors discuss how the policy results in excluding vulnerable populations from research and give recommendations for mental health research with adolescents.
Joseph P et al. (58) (2016)	Qualitative research – Stakeholders' views on international pediatric clinical trials	n/a	Regarding the consent process, challenges identified by stakeholders include consent requirements in certain countries that conflict with adolescents' confidentiality rights; impracticality of using long consent forms with multiple required elements, and the need for guidelines to streamline consent form production.
Nakkash R et al. (59) (2009)	Qualitative research – observation of the consent process for a two-phase preparatory study for an RCT to test the impact of a social skill-building	Lebanon	Researchers identified challenges to the consent process: incomplete disclosure of study information; complexity of terms and research design, compounded by low educational levels; issues related to who could provide consent for the child; and social conceptions that youth

	intervention to improve mental health in adolescents		are not capable of decision making. The greatest threat to the informed consent process was lack of voluntariness.
--	--	--	--

378

379 Assent

380

381 Pediatric research guidelines are unanimous on the need to obtain age-appropriate
 382 assent from children and adolescents who do not provide their own informed consent (Table
 383 1). However, we found little explicit discussion or description of procedures for obtaining
 384 assent in the research reports we reviewed (Table 8). (35,36) One interesting qualitative study
 385 on parental perceptions of assent in Jordan revealed considerable variability in caregivers'
 386 perspectives about at what age assent should be solicited or, even, if assent should in all cases
 387 be obtained and dissent respected.(23)

388 [insert Table 8 here]

389 **Table 8 Summary of articles discussing assent**

390

40 Khabour O et al. (23) (2017)	41 Qualitative research – 42 focus groups to 43 explore parental 44 perceptions about the 45 informed consent and 46 assent process for 47 research	48 Jordan	49 Findings show an acceptable 50 understanding of many aspects related to 51 the consent process. However, some 52 parents believed that informed consent is 53 not necessary for questionnaire studies, 54 there were discrepancies regarding the 55 appropriate age for a child's assent, and 56 some parents said they would force their 57 child to participate regardless of child's 58 wishes.
59 Vreeman R et al. (35) (2009)	60 Case study - pediatric 61 assent for a study on 62 antiretroviral therapy	63 Kenya	64 Authors describe the process of getting 65 review by both US and Kenyan IRBs, 66 mentioning that there is no guideline 67 about how joint review should be 68 conducted. Authors present the 69 differences between the two countries 70 regarding appropriate age for obtaining

			assent, and discuss local laws, practices, and international guidelines.
--	--	--	--

391

392

DISCUSSION

393

394

395

396 Children in low-resource settings are highly vulnerable to exploitation in research, because
397 of circumstances including socioeconomic inequalities, limited access to health care, and
398 high burden of illness.(60) In addition, even where international consensus exists around core
399 ethical principles for providing protections to children as research subjects, it may be unclear
400 how best to operationalize those principles in many low-resources settings, where gender
401 norms, literacy, unfamiliarity with scientific research, and language barriers may all be
402 important adaptive barriers. (10,11)

403

404 Through a scoping review of research reports and case studies from LMICs we identified,
405 however, several core areas where existing research reports provided considerable insight
406 and operational guidance which could be used to guide informed consent design processes in
407 additional LMIC settings. These included: (1) *careful consideration of community hierarchy*,
408 where consent for research may first proceed through a council of elders or other authority
409 figure, prior to approaching individual caregivers; (2) *guidance on developing verbal consent*
410 *procedures* in settings where caregivers have low literacy levels; (3) and *recognition of the*
411 *challenges of consent in indigenous or less-commonly spoken languages*, particularly when
412 that language is not commonly written and where alternative procedures, such as audio
413 recordings in the language, must be employed; and (4) *careful consideration of the possibility*

1
2
3 414 *of therapeutic misconception* and of developing consent procedures that ensure caregivers'
4
5 415 comprehension of the potential benefits (or lack thereof) and risks of research procedures for
6
7 416 their children.
8
9

10 417

11
12
13 418 However, within these four broad thematic areas, we also noted the need for additional
14
15 419 careful investigation. In particular, there is considerable uncertainty on how to ensure the
16
17 420 principle of subsequent individual informed consent when community leaders or other
18
19 421 authorities are approached first. This is especially the case when gender power imbalance is
20
21 422 at play, and female caregivers may be either unempowered to consent or to opt out of a
22
23 423 research decision made by a male authority. In addition, the social status of individuals
24
25 424 administering or witnessing consent procedures may unduly influence the decision-making
26
27 425 of caregivers, and research is needed to better understand and accommodate for the
28
29 426 interpersonal dynamics of obtaining consent.
30
31
32
33
34

35 427

36
37
38 428 Finally, two thematic topics seem to be particularly underrepresented in the literature on
39
40 429 pediatric LMIC research, and more work is urgently needed. First, despite extensive
41
42 430 discussions about the difficulties of conducting research with adolescents, we found only few
43
44 431 studies with practical discussions or guidance on how to navigate these difficulties. More
45
46 432 investigation of the ethical conduct of research with adolescents is needed, with a broader
47
48 433 representation of health conditions, research designs, and geographic regions. Second,
49
50 434 despite strong representation of the principle of assent in international guidelines on research
51
52 435 with children and adolescents, we found little research of cultural and regional differences
53
54
55
56
57
58
59
60

1
2
3 436 around notions of assent and virtually no discussion of the mechanics of assessing assent in
4
5 437 research studies. Additional research into the topic of assent for research among children in
6
7
8 438 LMICs should be an important priority.
9

10
11 439

12
13 440 Our review has two important limitations that must be considered. First, we included only
14
15 441 articles published in English in major indexing databases. We believe this approach is
16
17 442 justified, given our desire to provide a high-level overview of the topic without focusing
18
19 443 specifically on any geographic region. Nevertheless, our review has undoubtedly missed
20
21 444 resources in other languages or within the grey literature, which could be taken up in more
22
23 445 detailed region-specific work on this topic. Second, given the diversity and heterogeneity of
24
25 446 the literature reviewed, it was not possible to detail many of the practical insights and tips
26
27 447 given in the individual articles. Nevertheless, given the annotation and thematic
28
29 448 organization provided in Supplementary Table 1, we are confident that readers will be able
30
31 449 to identify areas of particular interest for more in-depth examination.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

450 **ABBREVIATIONS**

- 451 IRB: Institutional review board
- 452 LMIC: Low and middle-income country
- 453 RCT: Randomized clinical trial
- 454 STaR: Standards for Research in Child Health

Confidential: For Review Only

1
2
3 455 **FUNDING**4
5
6 456 This work was unfunded.
78
9 457
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

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

458 **COMPETING INTERESTS**

459 None.

460

Confidential: For Review Only

1
2
3 461 **AUTHOR'S CONTRIBUTIONS**
4
5

6 462 MC designed the search strategy, extracted data from articles, and wrote the first draft of the
7
8 463 manuscript. PR conceived the study, reviewed abstracts, and revised the manuscript.
9

10
11 464
12

13
14 465
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

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

466 **DATA SHARING STATEMENT**

467 Not applicable

468

Confidential: For Review Only

1
2
3 469 **ACKNOWLEDGMENTS**

4
5 470 We thank research subjects and clinical staff at Maya Health Alliance for inspiring our
6
7 471 interest in this important topic.
8

9
10 472
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Confidential: For Review Only

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

473 **FIGURE LEGENDS**

474 **Figure 1. Results of Literature Screen.** Flow diagram depicting results of the literature
475 search and review procedure.

476
477
478

Confidential: For Review Only

479 **REFERENCES**

- 480 1. Weindling P. The Origins of Informed Consent: The International Scientific
481 Commission on Medical War Crimes, and the Nuremberg Code. *Bull Hist Med.*
482 2001;75(1):37–71.
- 483 2. Rickham P. Human Experimentation. Code of Ethics of the World Medical
484 Association. Declaration of Helsinki. *Br Med J.* 1964;2 (5402)(177).
- 485 3. Council for International Organizations of Medical Sciences (CIOMS). International
486 Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition.
487 [Internet]. 2016. Available from:
488 [http://www.sciencedirect.com/science/article/B6VC6-45F5X02-](http://www.sciencedirect.com/science/article/B6VC6-45F5X02-9C/2/e44bc37a6e392634b1cf436105978f01)
489 [9C/2/e44bc37a6e392634b1cf436105978f01](http://www.sciencedirect.com/science/article/B6VC6-45F5X02-9C/2/e44bc37a6e392634b1cf436105978f01)
- 490 4. Caldwell PHY, Dans L, Newman J, Sammons H, Spriggs M, Tambe P, et al. StaR
491 Child Health Standard 1 : Consent and Recruitment. *Pediatrics.* 2012.
- 492 5. Klassen TP, Hartling L, Hamm M, van der Lee JH, Ursum J, Offringa M. StaR Child
493 Health: an initiative for RCTs in children. *Lancet* [Internet]. 2009 Oct
494 17;374(9698):1310–2. Available from: [http://dx.doi.org/10.1016/S0140-](http://dx.doi.org/10.1016/S0140-6736(09)61803-1)
495 [6736\(09\)61803-1](http://dx.doi.org/10.1016/S0140-6736(09)61803-1)
- 496 6. Martinez B, Webb MF, Gonzalez A, Douglas K, Grazioso P, Rohloff P, et al.
497 Complementary feeding intervention on stunted Guatemalan children : a randomised
498 controlled trial. *BMJ Paediatr Open.* 2018;1–8.
- 499 7. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for
500 Medical Research Invol...: . 2017;(June 1964):1–9. Available from:

- 1
2
3 501 <http://eds.b.ebscohost.com/eds/pdfviewer/pdfviewer?sid=a4bced6b-7270-457a->
4
5 502 [9730-e5a47e439a7a%40sessionmgr105&vid=6&hid=126](http://eds.b.ebscohost.com/eds/pdfviewer/pdfviewer?sid=a4bced6b-7270-457a-9730-e5a47e439a7a%40sessionmgr105&vid=6&hid=126)
6
7
8 503 8. National Bioethics Advisory Commission. Ethical and Policy Issues Research:
9
10 504 Clinical Trials in Developing Countries Vol. 1 [Internet]. 2001. 59 p. Available
11
12 505 from: <http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf>
13
14
15
16 506 9. European Commission. EU Directive 2001/20/EC. Off J Eur Communities.
17
18 507 2001;2001(April):1–15.
19
20
21 508 10. Bhutta ZA. Beyond informed consent. Bull World Health Organ. 2004
22
23 509 Oct;82(10):771–7.
24
25
26 510 11. MacLeod SM, Knoppert DC, Stanton-Jean M, Avarad D. Pediatric clinical drug trials
27
28 511 in low-income countries: key ethical issues. Paediatr Drugs. 2015 Feb;17(1):83–90.
29
30
31 512 12. Minnies D, Hawkrigde T, Hanekom W, Ehrlich R, London L, Hussey G. Evaluation
32
33 513 of the quality of informed consent in a vaccine field trial in a developing country
34
35 514 setting. BMC Med Ethics. 2008;9:1–9.
36
37
38
39 515 13. Halmsted Kongsholm NC, Lassen J, Sandoe P. “I didn’t have anything to decide, I
40
41 516 wanted to help my kids” - An interview-based study of consent procedures for
42
43 517 sampling human biological material for genetic research in rural Pakistan. AJOB
44
45 518 Empir Bioeth. 2018;4515(April 2014):1–35.
46
47
48
49 519 14. Nabulsi M, Khalil Y, Makhoul J. Parental attitudes towards and perceptions of their
50
51 520 children’s participation in clinical research: A developing-country perspective. J
52
53 521 Med Ethics. 2011;37(7):420–3.
54
55
56
57
58
59
60

- 1
2
3 522 15. Kamuya DM, Theobald SJ, Marsh V, Parker M, Geissler WP, Molyneux SC. “The
4
5 523 one who chases you away does not tell you go”: silent refusals and complex power
6
7 524 relations in research consent processes in Coastal Kenya. PLoS One.
8
9 525 2015;10(5):e0126671.
- 10
11
12
13 526 16. Macrae DJ. The Council for International Organizations and Medical Sciences
14
15 527 (CIOMS) guidelines on ethics of clinical trials. Proc Am Thorac Soc. 2007
16
17 528 May;4(2):176–8, discussion 178-9.
- 18
19
20
21 529 17. Martellet L, Sow SO, Diallo A, Hodgson A, Kampmann B, Hirve S, et al. Ethical
22
23 530 Challenges and Lessons Learned During the Clinical Development of a Group A
24
25 531 Meningococcal Conjugate Vaccine. Clin Infect Dis. 2015 Nov;61 Suppl 5:S422-7.
- 26
27
28 532 18. Kalabuanga M, Ravinetto R, Maketa V, Muhindo Mavoko H, Fungula B, Inocência
29
30 533 da Luz R, et al. The Challenges of Research Informed Consent in Socio-
31
32 534 Economically Vulnerable Populations: A Viewpoint From the Democratic Republic
33
34 535 of Congo. Dev World Bioeth. 2016;16(2):64–9.
- 35
36
37
38 536 19. Shetty P, Maurya M, Figer B, Thatte U, Gogtay N. Audiovisual recording of the
39
40 537 consenting process in clinical research: Experiences from a tertiary referral center.
41
42 538 Perspect Clin Res [Internet]. 2018 Jan 1;9(1):44–7. Available from:
43
44 539 <http://www.picronline.org/article.asp?issn=2229-3485>
- 45
46
47
48 540 20. Fitzpatrick EFM, Martiniuk ALC, D’Antoine H, Oscar J, Carter M, Elliott EJ.
49
50 541 Seeking consent for research with indigenous communities: a systematic review.
51
52 542 BMC Med Ethics. 2016 Oct;17(1):65.
- 53
54
55 543 21. Flood D, Rohloff P. Indigenous languages and global health. Lancet Glob Heal

- 1
2
3 544 [Internet]. 2018;6(2):e134–5. Available from: <http://dx.doi.org/10.1016/S2214->
4
5 545 109X(17)30493-X
6
7
8 546 22. Mboizi RB, Afolabi MO, Okoye M, Kampmann B, Roca A, Idoko OT. Recall and
9
10 547 decay of consent information among parents of infants participating in a randomized
11
12 548 controlled clinical trial using an audio-visual tool in The Gambia. *Hum Vaccin*
13
14 549 *Immunother.* 2017 Sep;13(9):2185–91.
15
16
17
18 550 23. Khabour OF, Alomari MA, Al-Sheyab NA. Parental Perceptions About Informed
19
20 551 Consent/Assent in Pediatric Research in Jordan. *J Empir Res Hum Res Ethics.* 2017
21
22 552 Oct;12(4):261–8.
23
24
25
26 553 24. Rajaraman D, Jesuraj N, Geiter L, Bennett S, Grewal HM, Vaz M. How
27
28 554 participatory is parental consent in low literacy rural settings in low income
29
30 555 countries? Lessons learned from a community based study of infants in South India.
31
32 556 *BMC Med Ethics.* 2011 Feb;12:3.
33
34
35
36 557 25. Leach A, Hilton S, Greenwood BM, Manneh E, Dibba B, Wilkins A, et al. An
37
38 558 evaluation of the informed consent procedure used during a trial of a *Haemophilus*
39
40 559 *influenzae* type B conjugate vaccine undertaken in The Gambia, West Africa. *Soc*
41
42 560 *Sci Med.* 1999;48(2):139–48.
43
44
45
46 561 26. Pace C, Talisuna A, Wendler D, Maiso F, Wabwire-Mangen F, Bakyaita N, et al.
47
48 562 Quality of parental consent in a Ugandan malaria study. *Am J Public Health.*
49
50 563 2005;95(7):1184–9.
51
52
53 564 27. Paré Toe L, Ravinetto RM, Dierickx S, Gryseels C, Tinto H, Rouamba N, et al.
54
55 565 Could the decision of trial participation precede the informed consent process?

- 1
2
3 566 Evidence from Burkina Faso. *PLoS One*. 2013;8(11):1–10.
4
5
6 567 28. Angwenyi V, Kamuya D, Mwachiro D, Kalama B, Marsh V, Njuguna P, et al.
7
8 568 Complex realities: community engagement for a paediatric randomized controlled
9
10 569 malaria vaccine trial in Kilifi, Kenya. *Trials*. 2014 Feb;15:65.
11
12
13 570 29. Sarkar R, Grandin EW, Gladstone BP, Muliyl J, Kang G. Comprehension and recall
14
15 571 of informed consent among participating families in a birth cohort study on
16
17 572 diarrhoeal disease. *Public Health Ethics*. 2009;2(1):37–44.
18
19
20
21 573 30. Serce O, Gonen I, Bakir M. Factors Influencing Parental Consent in a Hypothetical
22
23 574 Pediatric Vaccine Trial in a Developing Country Setting: A Questionnaire Study.
24
25 575 Account Res [Internet]. 2015;22(1):1–13. Available from:
26
27 576 <http://dx.doi.org/10.1080/08989621.2014.882779>
28
29
30
31 577 31. Bekker L, Slack C, Lee S, Shah S, Kapogiannis B. Ethical Issues in Adolescent HIV
32
33 578 Research in Resource-Limited Countries. *J Acquir Immune Defic Syndr*.
34
35 579 2014;65(Supplement 1):24–8.
36
37
38 580 32. McClure CA, Gray G, Rybczyk GK, Wright PF. Challenges to conducting HIV
39
40 581 preventative vaccine trials with adolescents. *J Acquir Immune Defic Syndr*. 2004
41
42 582 Jun;36(2):726–33.
43
44
45
46 583 33. Woollett N, Psychology MA, Th A, Peter J, Cluver L, Brahmabhatt H. Enrolling
47
48 584 HIV-positive adolescents in mental health research : A case study re flecting on
49
50 585 legal and ethical complexities. 2017;107(8):679–83.
51
52
53
54 586 34. Zulu JM, Ali J, Hallez K, Kass N, Michelo C, Hyder AA. Ethics challenges and
55
56 587 guidance related to research involving adolescent post-abortion care: A scoping
57
58
59
60

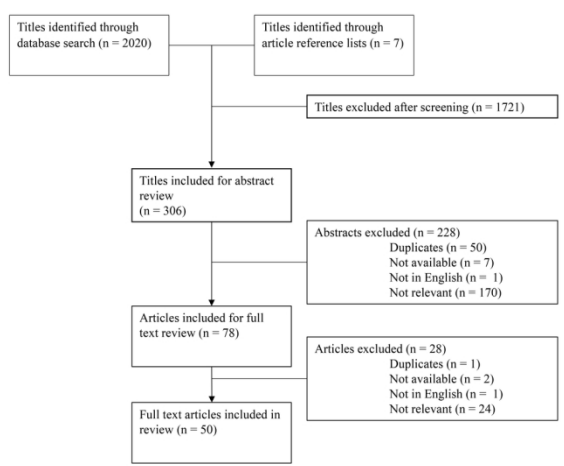
- 1
2
3 588 review. *Reprod Health*. 2018;15(1):1–10.
4
5
6 589 35. Vreeman RC, Nyandiko WM, Meslin EM. Pediatric Assent for a Study of
7
8 590 Antiretroviral Therapy Dosing for Children in Western Kenya: A Case Study in
9
10 591 International Research Collaboration. *J Empir Res Hum Res Ethics* [Internet].
11
12 592 2009;4(1):3–16. Available from: <http://www.jstor.org/stable/10.1525/jer.2009.4.1.3>
13
14
15
16 593 36. Molyneux CS, Wassenaar DR, Peshu N, Marsh K. “Even if they ask you to stand by
17
18 594 a tree all day, you will have to do it (laughter)...!”: Community voices on the notion
19
20 595 and practice of informed consent for biomedical research in developing countries.
21
22 596 *Soc Sci Med*. 2005;61(2):443–54.
23
24
25
26 597 37. Ott MA, Crawley FP, Saez-Llorens X, Owusu-Agyei S, Neubauer D, Dubin G, et al.
27
28 598 Ethical Considerations for the Participation of Children of Minor Parents in Clinical
29
30 599 Trials. *Paediatr Drugs*. 2018 Jun;20(3):215–22.
31
32
33 600 38. Regmi PR, Aryal N, Kurmi O, Pant PR, van Teijlingen E, Wasti SP. Informed
34
35 601 Consent in Health Research: Challenges and Barriers in Low-and Middle-Income
36
37 602 Countries with Specific Reference to Nepal. *Dev World Bioeth*. 2017;17(2):84–9.
38
39
40
41 603 39. Mandava A, Pace C, Campbell B, Emanuel E. The quality of informed consent:
42
43 604 mapping the landscape. A review of empirical data from developing and developed
44
45 605 countries. *J Med Ethics*. 2016;38(6):356–65.
46
47
48 606 40. Joseph PD, Caldwell PHY, Tong A. Stakeholder Views of Clinical Trials in Low-
49
50 607 and Middle-Income Countries : A Systematic Review. 2016;137(2).
51
52
53
54 608 41. Morrow BM, Argent AC, Kling S. Informed consent in paediatric critical care
55
56 609 research--a South African perspective. *BMC Med Ethics*. 2015 Sep;16:62.
57
58
59
60

- 1
2
3 610 42. Swain TR. Clinical trials for children: some concerns. *Indian J Pharmacol* [Internet].
4
5 611 2014;46(2):145–6. Available from:
6
7 612 <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N>
8
9 613 &AN=24741182
- 10
11
12
13 614 43. Ruiz-Casares M. Research ethics in global mental health: Advancing culturally
14
15 615 responsive mental health research. *Transcult Psychiatry*. 2014;51(6):790–805.
- 16
17
18 616 44. Offringa M, Needham AC, Chan WWY. StaR Child Health: Improving global
19
20 617 standards for child health research. *Early Hum Dev* [Internet]. 2013;89(11):861–4.
21
22 618 Available from: <http://dx.doi.org/10.1016/j.earlhumdev.2013.09.011>
- 23
24
25 619 45. Daley TC, Singhal N, Krishnamurthy V. Ethical considerations in conducting
26
27 620 research on autism spectrum disorders in low and middle income countries. *J Autism*
28
29 621 *Dev Disord*. 2013;43(9):2002–14.
- 30
31
32
33 622 46. Denburg AE, Joffe S, Gupta S, Howard SC, Ribeiro RC, Antillon FA, et al. Pediatric
34
35 623 oncology research in low income countries: ethical concepts and challenges. *Pediatr*
36
37 624 *Blood Cancer*. 2012 Apr;58(4):492–7.
- 38
39
40
41 625 47. Mystakidou K, Panagiotou I, Katsaragakis S, Tsilika E, Parpa. Ethical and practical
42
43 626 challenges of implementing informed consent in HIV/AIDS clinical trials in
44
45 627 developing or resource-limited countries. *J Soc Asp HIV/AIDS*. 2009;6(2):46–57.
- 46
47
48 628 48. Embleton L, Ott MA, Wachira J, Naanyu V, Kamanda A, Makori D, et al. Adapting
49
50 629 ethical guidelines for adolescent health research to street-connected children and
51
52 630 youth in low- and middle-income countries: A case study from western Kenya. *BMC*
53
54 631 *Med Ethics*. 2015;

- 1
2
3 632 49. Millum J, Emanuel E. The Ethics of International Research with Abandoned
4
5 633 Children. 2015;35(1):30–7.
6
7
8 634 50. Vreeman R, Kamaara E, Kamanda A, Ayuku D, Nyandiko W, Atwoli L, et al.
9
10 635 Community Perspectives on Research Consent Involving Vulnerable Children in
11
12 636 Western Kenya. *J Empir Res Hum Res Ethics* [Internet]. 2012;7(4):44–55. Available
13
14 637 from: <http://journals.sagepub.com/doi/10.1525/jer.2012.7.4.44>
15
16
17
18 638 51. Tindana P, Bull S, Amenga-Etego L, De Vries J, Aborigo R, Koram K, et al.
19
20 639 Seeking consent to genetic and genomic research in a rural Ghanaian setting: A
21
22 640 qualitative study of the MalariaGEN experience. *BMC Med Ethics* [Internet].
23
24 641 2012;13(1):1. Available from: BMC Medical Ethics
25
26
27
28 642 52. Morris MC, Wilson PT. Medical Device Research in Resource-Poor Settings: A
29
30 643 Pediatric Case Study in Ghana. *IRB Ethics Hum Res*. 2018;36(4):1–7.
31
32
33 644 53. Ward CL, Shaw D, Anane-Sarpong E, Sankoh O, Tanner M, Elger B. The Ethics of
34
35 645 Health Care Delivery in a Pediatric Malaria Vaccine Trial: The Perspectives of
36
37 646 Stakeholders From Ghana and Tanzania. *J Empir Res Hum Res Ethics*.
38
39 647 2018;13(1):26–41.
40
41
42
43 648 54. Devries KM, Child JC, Elbourne D, Naker D, Heise L. “I never expected that it
44
45 649 would happen, coming to ask me such questions”: Ethical aspects of asking children
46
47 650 about violence in resource poor settings. *Trials*. 2015 Nov;16:516.
48
49
50
51 651 55. Oduro AR, Aborigo RA, Amugsi D, Anto F, Anyorigiya T, Atuguba F, et al.
52
53 652 Understanding and retention of the informed consent process among parents in rural
54
55 653 northern Ghana. *BMC Med Ethics*. 2008;9:1–9.
56
57
58
59
60

- 1
2
3 654 56. Krosin MT, Klitzman R, Levin B, Cheng J, Ranney ML. Problems in comprehension
4
5 655 of informed consent in rural and peri-urban Mali, West Africa. *Clin Trials*.
6
7 656 2006;3(3):306–13.
- 8
9
10 657 57. Molyneux CS, Peshu N, Marsh K. Trust and informed consent: Insights from
11
12 658 community members on the Kenyan coast. *Soc Sci Med*. 2005;61(7):1463–73.
- 13
14
15 659 58. Joseph PD, Craig JC, Tong A, Caldwell PHY. Researchers, Regulators, and
16
17 660 Sponsors Views on Pediatric Clinical Trials: A Multinational Study. *Pediatrics*
18
19 661 [Internet]. 2016;138(4):e20161171–e20161171. Available from:
20
21 662 <http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2016-1171>
- 22
23
24
25 663 59. Nakkash R, Makhoul J, Afifi R. Obtaining informed consent: observations from
26
27 664 community research with refugee and impoverished youth. *J Med Ethics*. 2009
28
29 665 Oct;35(10):638–43.
- 30
31
32
33 666 60. Initiative for Vaccine Research of the Department of Vaccines and Biologicals World
34
35 667 Health Organization. Ethical considerations arising from vaccine trials conducted in
36
37 668 paediatric populations with high disease burden in developing countries. In:
38
39 669 WHO/IRV ethics meeting November 26-28, 2002 Accra, Ghana [Internet]. 2002.
40
41 670 Available from: www.who.int/vaccines-documents
- 42
43
44
45
46 671

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



152x85mm (300 x 300 DPI)