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TITLE PAGE

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

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ABSTRACT

Introduction: Conducting research with children in low- and middle-income countries (LMICs) requires consideration of socioeconomic inequalities and cultural and linguistic differences. Our objective was to survey the literature on informed consent in pediatric LMIC research, assessing for practical guidance for culturally- and linguistically-appropriate procedures.

Methods: We conducted a scoping review on informed consent in pediatric LMIC research searching the Pubmed, Web of Science and PsycINFO databases. Eligible articles were published in English, from any date range, of any study design or format.

Results: The search identified 2,027 references, of which 50 were included in the analysis following full-text review. Reviewed guidelines emphasized individual, informed and voluntary consent from parents and caregivers. Reviewed articles provided detailed practical guidance on adapting these guiding principles to LMIC settings, including considerations for community engagement, verbal or other alternative consent procedures for low-literacy settings or less-commonly spoken languages, and guarding against therapeutic misconception by caregivers. There was uncertainty, however, on how to best protect individual autonomy, especially when influenced by gender dynamics, leadership hierarchies, or the social status of researchers themselves. There was, furthermore, limited research discussing the special case of research involving adolescents or of procedures for documenting assent by participating children.

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

INTRODUCTION

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

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

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

speakers of less-common languages, or populations with high levels of illiteracy. Practically, we experienced this recently while designing a clinical trial of a nutrition intervention for indigenous Maya children in rural Guatemala, and our experience navigating consent, literacy, and translingual adaptation in this population prompted our interest in more formally exploring the topic.(6) To this end, here we conduct a scoping review of the existing literature on cultural and contextual considerations for informed consent in the conduct of pediatric research in LMICs. Through this review, we identify evidence for specific culturally- and contextually-sensitive practices, as well as areas where additional research and guideline development is needed.

METHODS

Search and inclusion strategy

To identify articles, we searched the PubMed, Web of Science and PsycINFO databases. We conducted searches using a combination of the following key terms: “pediatric” or “children” or “adolescents”; “research” or “biomedical research”; “consent” or “informed consent” or “ethics”; “developing countries” or “low income countries” or “middle income countries”; “illiteracy”; “culturally competent”. We used no date limits and included all articles published through May 2018. In addition, we visited the websites of international health policy organizations to identify ethics guidelines for the conduct of research in low- and middle-income countries. We also manually reviewed the reference lists of articles identified using the above methods. For this scoping review, of the articles identified above we included for analysis any type of study design or format (original research, commentary,

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

Data extraction and synthesis

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

RESULTS

Results of literature screen

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

was not in English, 7 were not available (abstract nor full text), and 170 abstracts did not meet inclusion criteria. 78 articles were selected for full text review, of which 24 subsequently did not meet inclusion criteria, one was in French, one was a duplicate, and two did not have available full text. Therefore 50 full-text articles were included in this review (Figure 1, Tables 1-2).

Summary of guidelines and commentaries

We selected for review five guidelines that address issues of informed consent in international settings and in research involving children and summarize key recommendations in Table 1. All guidelines emphasize the importance of obtaining individual, informed and voluntary consent for research.(3,4,7–9) Several guidelines suggest modifications appropriate for lower-resource settings, such as obtaining witnessed verbal consent when literacy is a barrier. (7,9) The United States National Bioethics Advisory Commission (NBAC), for example, even acknowledges that oral consent might even be preferable in some circumstances.(8) However, as several commentaries on the guidelines note, there is little specificity on how best operationalize these core principles, such as how to formally document verbal consent.(10,11)

Another important consideration of LMIC research addressed in guidelines is an emphasis on the need to at times obtain consent from community stakeholders and leaders, or other key local decision makers. Nevertheless, all guidelines unanimously assert that community-based consent can never replace individual consent. When local cultural practices around

community-based consent contradict core principles of the international consensus on the informed consent process, such as the need for voluntary individual consent, researchers are advised to search for culturally sensitive ways of providing all information to potential participants without compromising the substantive ethical standard of informed consent, an adaptive process in which local research ethics committees are expected to place a substantial role. (8,10–12)

Finally, with respect to children or adolescents not capable of providing informed consent, in addition to obtaining consent from parents or legal representatives, most guidelines also reinforce the need to obtain assent from the child or adolescent in an age-appropriate way. (3,4,7,9) The CIOMS guidelines on research involving children and adolescents states that as adolescents reach the age of maturity, their agreement to participate may be ethically considered as informed consent. However, if they legally remain minors, researchers are cautioned that consent from a parent is still generally needed, but a list is provided of possible situations when parental consent might be waived, such as with legally emancipated adolescents, or under circumstances where obtaining parental consent is not desirable because of the research topic. (3)

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Table 1 Summary of selected major guidelines, reports and reviews on ethical 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)	• 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	• 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)	• 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	• 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)	• Obtain consent and assent when age-appropriate • Provide age-appropriate, clear, concise, and on-going information for parents and children	• 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		• Develop culturally appropriate ways to disclose information that is necessary for adherence to the ethical

issues in international research(8)		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
European Council and European Parliament Guidelines(9)	• 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	• 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

Thematic summary of research on consent in LMIC pediatric research

Existing published work on informed consent in pediatric research in LMICs consists largely of case studies describing the experience of individual research teams and discussing the challenges and solutions utilized when adapting consent processes to their local context. We summarize several major themes emerging from these studies here and detail key findings from the reviewed articles in Table 2.

Understanding social norms around decision making and protecting individual autonomy

An important principle highlighted in international guidelines on informed consent in LMICs is appropriate and early engagement with existing local leadership structures (such as a council of elders) balanced against respect for the autonomy of individual children or their caregivers.(3,8) In practice, this can be a delicate balance to maintain. Kongsholm and colleagues, for example, describe consent processes in rural Pakistan, where family structures are patriarchal and hierarchical. In this setting, consent procedures involved first seeking consent from an elder, who provided initial consent for the entire family. However, under this approach, the voluntariness of individual participants may be undermined, and it is unclear how best to ensure that individuals still retain an "opt out" mechanism.(13)

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

Adapting consent procedures to low-literate settings

There is strong consensus in international ethics guidelines that written, informed consent is preferred when conducting research. In the case of pediatric research, this again typically involves obtaining written consent from one or both primary caregivers.(4,9,16) However, in many LMIC settings, literacy may be low or a high value may be placed on oral interactions, and lack of alternative consent procedures may violate another core ethics principle, namely the equitable distribution of research benefits and burdens across populations.(3,14,17) Several of the studies we reviewed described these procedures, with verbal consent commonly being obtained, most often in the presence of a literate witness who is able to read available consent documents. (13,14,17,18) In one very thoughtful piece, Kalabuanga and colleagues note, however, that ad hoc witnesses may often impose their views on the consenting caregiver and their child, rather than encourage dialog and act as a safeguard.(18) The authors suggest that these challenges by be mitigated by careful

vetting and training of independent witnesses or, alternatively, but allowing potential consenting caregivers to use a trusted relative or friend as their witness.(18)

Working in indigenous or less-commonly-spoken languages

International ethics guidelines emphasize that research information should be provided to consenting caregivers in a local language understandable to the individual.(7,8,16) However, this is most commonly understood to be a working lingua franca, and the issue of and practical approach to provisioning consent processes in an indigenous language is largely unaddressed in LMICs.(19) This is an important consideration, given that a substantial proportion of the potential pediatric research population in LMICs are from populations that speak indigenous or less-commonly-spoken languages.(20) In an interesting review of lessons learned in a pediatric vaccine trial in West Africa, Martellet and colleagues noted difficulties in preparing consent procedures in some of the less-common language groups included in the trial, where use of the written form was uncommon. They describe alternative procedures, such as the preparation of recordings of consent scripts in local languages and extensive practice sessions with research staff obtaining consent in local languages.(17) Similarly, another vaccine trial in The Gambia described the successful use of audio-visual Speaking Books in local less-common languages to consent caregivers. (21)

Gender dynamics in caregiver consent

Local gender dynamics and decision making procedures when consenting male and female caregivers for research is an important consideration. For example, a female caregiver may be inclined to allow her child to participate, but be unable to do so if her husband or another male authority figure refuses.(13) The opposite may also occur, if a research study is consented by a male figure, but requires significant participatory effort from the primary female for study-related activities, leading the woman to express their refusal through procedural delay or inconsistent participation.(15) Given concerns about gender power imbalance and potential repercussions for consenting female caregivers, some studies discussed working to routinely involve fathers or male authority figures in the consent process for more complex or higher-risk research interventions.(15,22) In one interesting study based in India, Rajaraman and colleagues found that caregivers were more likely to actively participate in the consent process when both were present. They also observed, however, that this factor may have been do the fact that most study staff obtaining consent were male, and they call for more research on how the gender of research staff impacts the consent process.(23)

Disclosing potential benefits and risks of participation in research

Participation in some research studies, particularly those with a controlled design, may not result in direct benefit to participants. Several studies report difficulties explaining to caregivers that medical research procedures may not result in direct benefit to their children. Indeed, therapeutic misconception might be hard to avoid in certain contexts, as it might be affected by factors like educational level and cultural and religious beliefs about

disease.(13,18) However, explicit attention to this dynamic while designing consent procedures may help to ensure caregiver comprehension.(24)

At the same time, care must be given to a culturally-appropriate degree of information disclosure. For example, in several studies, caregivers—especially those of higher socioeconomic or educational status—were more likely to participate when provided with detailed and in-depth information about the study processes and given opportunities to ask questions.(12,22,23,25) At the same time, other case studies point out how over-detailed discussion of study procedures or scientific rationale may provoke unneeded reserve or suspicion where such detailed disclosures by health professionals are not culturally customary.(13)

Finally, in settings where access to healthcare and other important social goods may be limited, even basic diagnostic or ancillary procedures that occur as part of a research study may be better than the local standard of care, leading to an undue inducement for caregivers to enroll their children in research, even after being informed about the experimental nature or studies and the risk-benefit balance.(11,13,18) These considerations highlight the importance of considering the socio-economic and cultural background of study settings well before beginning research and making plans to incorporate appropriate early, equitable benefit-sharing measures when possible.(18)

Adolescents

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)

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

obtaining assent in the research reports we reviewed. However, one interesting qualitative study on parental perceptions of assent in Jordan revealed considerable variability in caregivers' perspectives about at what age assent should be solicited or, even, if assent should in all cases be obtained and dissent respected.(22)

Table 2. Summary of articles selected for inclusion in review. [Insert Table 2 here]

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 were 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.

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

			testing to improve comprehension.

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.

DISCUSSION

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

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

of developing consent procedures that ensure caregivers' comprehension of the potential benefits (or lack thereof) and risks of research procedures for their children.

However, within these four broad thematic areas, we also noted the need for additional careful investigation. In particularly, here is considerable uncertainty on how to ensure the principle of subsequent individual informed consent when community leaders or other authorities are first approached. This is especially the case when gender power imbalance is at play, and female caregivers may be either unempowered to consent or to opt out of a research decision made by a male authority. In addition, the social status of individuals administering or witnessing consent procedures may unduly influence the decision-making of caregivers, and research is needed to better understand and accommodate for the interpersonal dynamics of obtaining consent.

Finally, two thematic topics seem to be particularly underrepresented in the literature on pediatric LMIC research, and more work is urgently needed. First, despite extensive discussions about the difficulties of conducting research with adolescents, we found only few studies with practical discussions or guidance on how to navigate these difficulties. More investigation of the ethical conduct of research with adolescents is needed, with a broader representation of health conditions, research designs, and geographic regions. Second, despite strong representation of the principle of assent in international guidelines on research with children and adolescents, we found little research of cultural and regional differences around notions of assent and virtually no discussion of the mechanics of assessing assent in research studies. Additional research into the topic of assent for research among children in LMICs should be an important priority.

ABBREVIATIONS

IRB: Institutional review board

LMIC: Low and middle-income country

RCT: Randomised clinical trial

STaR: Standards for Research in Child Health

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None.

AUTHOR'S CONTRIBUTIONS

MC designed the search strategy, extracted data from articles, and wrote the first draft of the manuscript. PR conceived the study, reviewed abstracts, and revised the manuscript.

DATA SHARING STATEMENT

Not applicable

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FIGURE LEGENDS

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

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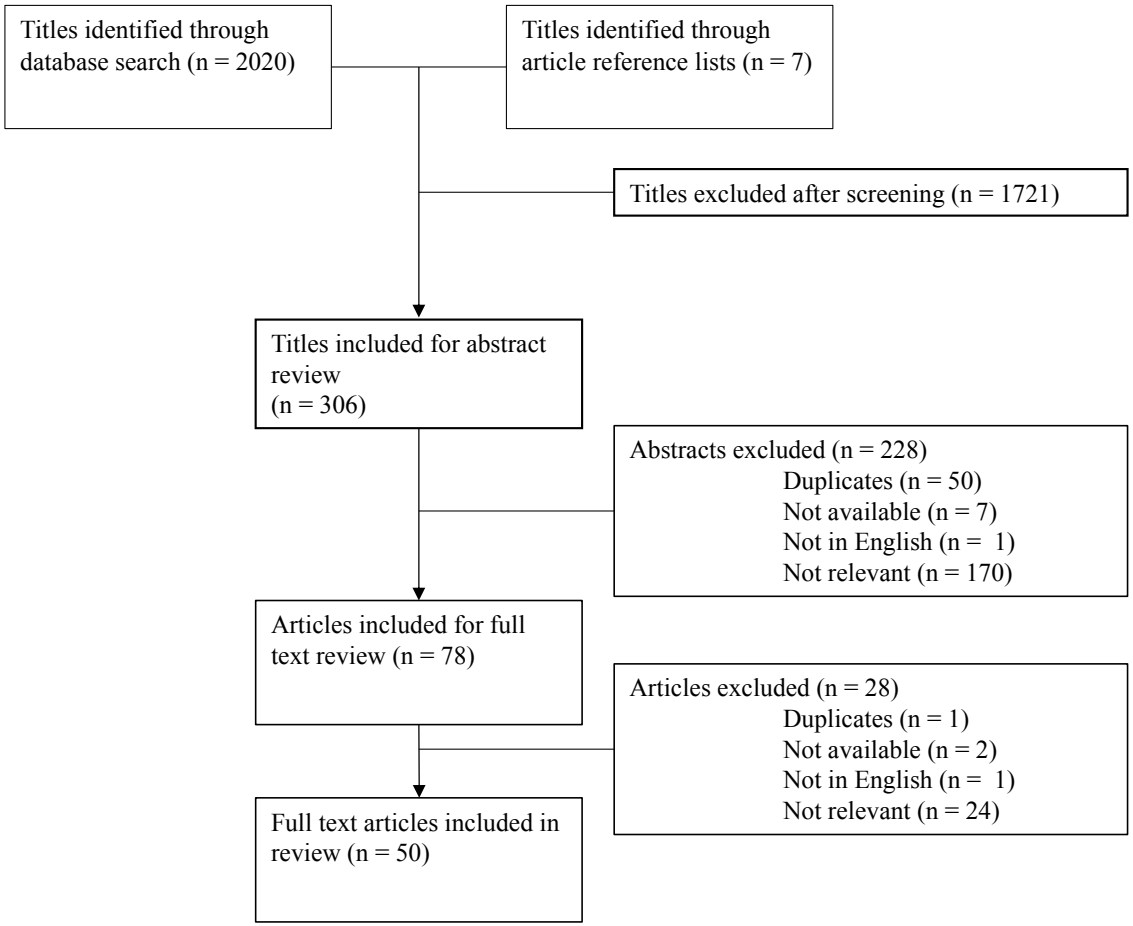
Titles identified through database search (n = 2020)
Titles identified through article reference lists (n = 7)
Titles excluded after screening (n = 1721)
Titles included for abstract review (n = 306)
Abstracts excluded (n = 228)
Duplicates (n = 50)
Not available (n = 7)
Not in English (n = 1)
Not relevant (n = 170)
Articles included for full text review (n = 78)
Articles excluded (n = 28)
Duplicates (n = 1)
Not available (n = 2)
Not in English (n = 1)
Not relevant (n = 24)
Full text articles included in review (n = 50)

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TITLE PAGE

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

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WHAT IS KNOWN ABOUT THIS SUBJECT

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

WHAT THIS STUDY ADDS

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

ABSTRACT

Introduction: Conducting research with children in low- and middle-income countries (LMICs) requires consideration of socioeconomic inequalities and cultural and linguistic differences. Our objective was to survey the literature on informed consent in pediatric LMIC research, assessing for practical guidance for culturally- and linguistically-appropriate procedures.

Methods: We conducted a scoping review on informed consent in pediatric LMIC research searching the Pubmed, Web of Science and PsycINFO databases. Eligible articles were published in English, from any date range, of any study design or format.

Results: The search identified 2,027 references, of which 50 were included in the analysis following full-text review. Reviewed guidelines emphasized individual, informed and voluntary consent from parents and caregivers. Reviewed articles provided detailed practical guidance on adapting these guiding principles to LMIC settings, including considerations for community engagement, verbal or other alternative consent procedures for low-literacy settings or less-commonly spoken languages, and guarding against therapeutic misconception by caregivers. There was uncertainty, however, on how to best protect individual autonomy, especially when influenced by gender dynamics, leadership hierarchies, or the social status of researchers themselves. There was, furthermore, limited research discussing the special case of research involving adolescents or of procedures for documenting assent by participating children.

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

INTRODUCTION

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

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

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

populations, speakers of less-common languages, or populations with high levels of illiteracy. Practically, we experienced this recently while designing a clinical trial of a nutrition intervention for indigenous Maya children in rural Guatemala, and our experience navigating consent, literacy, and translingual adaptation in this population prompted our interest in more formally exploring the topic.(6) To this end, here we conduct a scoping review of the existing literature on cultural and contextual considerations for informed consent in the conduct of pediatric research in LMICs. Through this review, we identify evidence for specific culturally- and contextually-sensitive practices, as well as areas where additional research and guideline development is needed.

METHODS

Search and inclusion strategy

To identify articles, we searched the PubMed, Web of Science and PsycINFO databases. We conducted searches using a combination of the following key terms: “pediatric” or “children” or “adolescents”; “research” or “biomedical research”; “consent” or “informed consent” or “ethics”; “developing countries” or “low income countries” or “middle income countries”; “illiteracy”; “culturally competent”. We used no date limits and included all articles published through May 2018. In addition, we visited the websites of international health policy organizations to identify ethics guidelines for the conduct of research in low- and middle-income countries. We also manually reviewed the reference lists of articles identified using the above methods. For this scoping review, of the articles identified above we included for analysis any type of study design or format (original research, commentary,

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

Data extraction and synthesis

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

RESULTS

Results of literature screen

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

was not in English, 7 were not available (abstract nor full text), and 170 abstracts did not meet inclusion criteria. 78 articles were selected for full text review, of which 24 subsequently did not meet inclusion criteria, one was in French, one was a duplicate, and two did not have available full text. Therefore 50 full-text articles were included in this review (Figure 1, Table 1, Supplementary Table 1). Of the articles excluded at the abstract and full text review stages, the most common reasons for exclusion were: no mention of the informed consent process for research with pediatric or adolescent populations; research not taking place in a low- or middle-income country; articles on pediatric research in low- or middle-income countries that did not discuss the informed consent process

Summary of guidelines and commentaries

We identified seven guidelines that addressed issues of informed consent in international settings and in research involving children in our scoping review. Of these, we selected for detailed review five that were most comprehensive, summarizing key recommendations in Table 1. All guidelines emphasize the importance of obtaining individual, informed and voluntary consent for research.(3,4,7–9) Importantly, however, the guidelines do not necessarily specify in detail how best to operationalize assessment of these core principles. For example, the Declaration of Helsinki comments only that informed consent requires that a subject be adequately informed of the "aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study" (Article 26). (7) Similarly, on

voluntariness, the CIOMS guidelines note only that consent is voluntary if "an individual's decision to participate is free of undue influence" (p. 35). (3)

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

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

Finally, with respect to children or adolescents not capable of providing informed consent, in addition to obtaining consent from parents or legal representatives, most guidelines also reinforce the need to obtain assent from the child or adolescent in an age-appropriate way. (3,4,7,9) The CIOMS guidelines note that assent is "a process...not merely the absence of dissent" and requires "meaningful[l] engage[ment] in the research discussion in accordance with...capacities" (p. 67). (3) They also note that as adolescents reach the age of maturity, their agreement to participate may be ethically considered as informed consent. However, if they legally remain minors, researchers are cautioned that consent from a parent is still generally needed, but a list is provided of possible situations when parental consent might be waived, such as with legally emancipated adolescents, or under circumstances where obtaining parental consent is not desirable because of the research topic. (3)

Table 1 Summary of selected major guidelines, reports and reviews on ethical 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)	• 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	• 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)	• 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	• 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)	• Obtain consent and assent when age-appropriate • Provide age-appropriate, clear, concise, and on-going information for parents and children	• 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		• Develop culturally appropriate ways to disclose information that is necessary for adherence to the ethical

issues in international research(8)		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
European Council and European Parliament Guidelines(9)	• 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	• 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

Thematic summary of research on consent in LMIC pediatric research

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

Understanding social norms around decision making and protecting individual autonomy

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

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

Adapting consent procedures to low-literate settings

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

patients or ancillary hospital staff).(18) Kalabuanga et al. go on to suggest that these challenges may be mitigated by careful vetting and training of independent witnesses or, alternatively, by allowing potential consenting caregivers to use a trusted relative or friend as their witness.(18)

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

Working in indigenous or less-commonly-spoken languages

International ethics guidelines emphasize that research information should be provided to consenting caregivers in a local language understandable to the individual.(7,8,16) However, this is most commonly understood to be a working lingua franca, and the issue of and practical approach to provisioning consent processes in an indigenous language is largely unaddressed in LMICs.(20) This is an important consideration, given that a substantial proportion of the potential pediatric research population in LMICs are from populations that speak indigenous or less-commonly-spoken languages.(21) In an interesting review of lessons learned in a pediatric vaccine trial in West Africa, Martellet and colleagues noted challenges in preparing consent procedures in some of the less-common language groups included in the trial, where use of the written

form was uncommon, where substantial need to rely on metaphor and paraphrase made back-translation difficult, and where written documents where perceived as not being dynamic enough in cultures which valued interactivity and person-to-person exchange. They describe alternative procedures, such as the preparation of recordings of consent scripts in local languages and extensive practice sessions with research staff obtaining consent in local languages.(17) Similarly, another vaccine trial in The Gambia described the successful use of audio-visual Speaking Books in local less-common languages to consent caregivers. (22)

Gender dynamics in caregiver consent

Local gender dynamics and decision making procedures when consenting male and female caregivers for research is an important consideration. For example, when consenting with caregiving couples or within an extended family unit, instances are discussed where a female caregiver wishes to allow her child to participate, but is unable to do so because her husband or another male authority figure refuses.(13) The opposite may also occur, if a research study is consented by a male figure, but requires significant participatory effort from the primary female for study-related activities, leading the woman to express their refusal through procedural delay or inconsistent participation.(15) Given concerns about gender power imbalance and potential repercussions for consenting female caregivers, some studies discussed working to routinely involve fathers or male authority figures in the consent process for more complex or higher-risk research interventions.(15,23) In one interesting study based in India, Rajaraman and colleagues found that caregivers were more likely to actively participate in the consent process when both were present. They also

observed, however, that this factor may have been due the fact that most study staff obtaining consent were male, and they call for more research on how the gender of research staff impacts the consent process.(24)

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

Disclosing potential benefits and risks of participation in research

Participation in some research studies, particularly those with a randomized controlled design or those with differing intervention arms, may not result in direct benefit to all participants. Several studies report difficulties explaining to caregivers that medical research procedures may not result in direct benefit to their children, and in verifying that caregivers comprehended the substance of randomization or control procedures. (25–28) Others noted the need to address issues of information recall and retention, particularly with complex study procedures or consent forms, and to emphasize the right of study withdrawal and the ongoing reaffirmation of consent throughout a study. (26–29) Furthermore, other reports discussed how therapeutic misconception—the perception by research subjects that participation in any component of a multiple-arm, controlled trial, will result in therapeutic

benefits—might be hard to avoid in certain contexts, as it might be affected by factors like educational level and cultural and religious beliefs about disease.(13,18)

At the same time, care must be given to a culturally-appropriate degree of information disclosure. For example, in several studies, caregivers—especially those of higher socioeconomic or educational status—were more likely to participate when provided with detailed and in-depth information about the study processes and given opportunities to ask questions.(12,23,24,30) At the same time, other case studies point out how over-detailed discussion of study procedures or scientific rationale may provoke unneeded reserve or suspicion where such detailed disclosures by health professionals are not culturally customary.(13)

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

Adolescents

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.(31) 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.(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)

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 little explicit discussion or description of procedures for obtaining assent in the research reports we reviewed. (35,36) One interesting qualitative study on parental perceptions of assent in Jordan revealed considerable variability in caregivers' perspectives about at what age assent should be solicited or, even, if assent should in all cases be obtained and dissent respected.(23)

DISCUSSION

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

Through a scoping review of research reports and case studies from LMICs we identified, however, several core areas where existing research reports provided considerable insight and operational guidance which could be used to guide informed consent design processes in additional LMIC settings. These included: (1) *careful consideration of community hierarchy*, where consent for research may first proceed through a council of elders or other authority figure, prior to approaching individual caregivers; (2) *guidance on developing*

verbal consent procedures in settings where caregivers have low literacy levels; (3) and *recognition of the challenges of consent in indigenous or less-commonly spoken languages*, particularly when that language is not commonly written and where alternative procedures, such as audio recordings in the language, must be employed; and (4) *careful consideration of the possibility of therapeutic misconception* and of developing consent procedures that ensure caregivers' comprehension of the potential benefits (or lack thereof) and risks of research procedures for their children.

However, within these four broad thematic areas, we also noted the need for additional careful investigation. In particularly, there is considerable uncertainty on how to ensure the principle of subsequent individual informed consent when community leaders or other authorities are approached first. This is especially the case when gender power imbalance is at play, and female caregivers may be either unempowered to consent or to opt out of a research decision made by a male authority. In addition, the social status of individuals administering or witnessing consent procedures may unduly influence the decision-making of caregivers, and research is needed to better understand and accommodate for the interpersonal dynamics of obtaining consent.

Finally, two thematic topics seem to be particularly underrepresented in the literature on pediatric LMIC research, and more work is urgently needed. First, despite extensive discussions about the difficulties of conducting research with adolescents, we found only few studies with practical discussions or guidance on how to navigate these difficulties.

More investigation of the ethical conduct of research with adolescents is needed, with a broader representation of health conditions, research designs, and geographic regions. Second, despite strong representation of the principle of assent in international guidelines on research with children and adolescents, we found little research of cultural and regional differences around notions of assent and virtually no discussion of the mechanics of assessing assent in research studies. Additional research into the topic of assent for research among children in LMICs should be an important priority.

Our review has two important limitations that must be considered. First, we included only articles published in English in major indexing databases. We believe this approach is justified, given our desire to provide a high-level overview of the topic without focusing specifically on any geographic region. Nevertheless, our review has undoubtedly missed resources in other languages or within the grey literature, which could be taken up in more detailed region-specific work on this topic. Second, given the diversity and heterogeneity of the literature reviewed, it was not possible to detail many of the practical insights and tips given in the individual articles. Nevertheless, given the annotation and thematic organization provided in Supplementary Table 1, we are confident that readers will be able to identify areas of particular interest for more in-depth examination.

ABBREVIATIONS

IRB: Institutional review board

LMIC: Low and middle-income country

RCT: Randomized clinical trial

STaR: Standards for Research in Child Health

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MC designed the search strategy, extracted data from articles, and wrote the first draft of the manuscript. PR conceived the study, reviewed abstracts, and revised the manuscript.

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FIGURE LEGENDS

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

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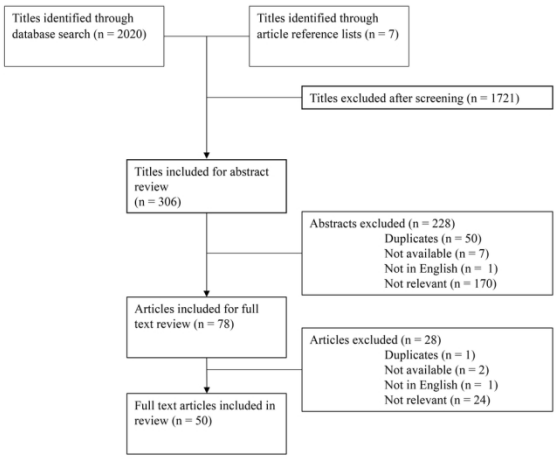

152x85mm (300 x 300 DPI)

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

Reference (Year)	Study Description	Study Location	Major findings
Reviews and Opinion Articles[1]			
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

			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	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 were 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.

[1]Major 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.

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

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TITLE PAGE

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

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WHAT IS KNOWN ABOUT THIS SUBJECT

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

WHAT THIS STUDY ADDS

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

ABSTRACT

Introduction: Conducting research with children in low- and middle-income countries (LMICs) requires consideration of socioeconomic inequalities and cultural and linguistic differences. Our objective was to survey the literature on informed consent in pediatric LMIC research, assessing for practical guidance for culturally- and linguistically-appropriate procedures.

Methods: We conducted a scoping review on informed consent in pediatric LMIC research searching the Pubmed, Web of Science and PsycINFO databases. Eligible articles were published in English, from any date range, of any study design or format.

Results: The search identified 2,027 references, of which 50 were included in the analysis following full-text review. Reviewed guidelines emphasized individual, informed and voluntary consent from parents and caregivers. Reviewed articles provided detailed practical guidance on adapting these guiding principles to LMIC settings, including considerations for community engagement, verbal or other alternative consent procedures for low-literacy settings or less-commonly spoken languages, and guarding against therapeutic misconception by caregivers. There was uncertainty, however, on how to best protect individual autonomy, especially when influenced by gender dynamics, leadership hierarchies, or the social status of researchers themselves. There was, furthermore, limited research discussing the special case of research involving adolescents or of procedures for documenting assent by participating children.

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

INTRODUCTION

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

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

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

illiteracy. Practically, we experienced this recently while designing a clinical trial of a nutrition intervention for indigenous Maya children in rural Guatemala, and our experience navigating consent, literacy, and translingual adaptation in this population prompted our interest in more formally exploring the topic.(6) To this end, here we conduct a scoping review of the existing literature on cultural and contextual considerations for informed consent in the conduct of pediatric research in LMICs. Through this review, we identify evidence for specific culturally- and contextually-sensitive practices, as well as areas where additional research and guideline development is needed.

METHODS

Search and inclusion strategy

To identify articles, we searched the PubMed, Web of Science and PsycINFO databases. We conducted searches using a combination of the following key terms: “pediatric” or “children” or “adolescents”; “research” or “biomedical research”; “consent” or “informed consent” or “ethics”; “developing countries” or “low income countries” or “middle income countries”; “illiteracy”; “culturally competent”. We used no date limits and included all articles published through May 2018. In addition, we visited the websites of international health policy organizations to identify ethics guidelines for the conduct of research in low- and middle-income countries. We also manually reviewed the reference lists of articles identified using the above methods. For this scoping review, of the articles identified above we included for analysis any type of study design or format (original research, commentary, case study, review, expert opinion), which addressed the informed consent process specifically for

pediatric or adolescent populations in low or middle-income countries. Articles not in English were excluded.

Data extraction and synthesis

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

RESULTS

Results of literature screen

A total of 2,027 candidate titles were identified through database searches, supplemented by reference list and website reviews. Of these, 1,721 did not meet eligibility criteria, and 306 were included for abstract review. If the abstract was not available but full text was, the title was included for full text review. After abstract review, 50 duplicates were found, one was not in English, 7 were not available (abstract nor full text), and 170 abstracts did not meet inclusion criteria. 78 articles were selected for full text review, of which 24 subsequently did

not meet inclusion criteria, one was in French, one was a duplicate, and two did not have available full text. Therefore 50 full-text articles were included in this review (Figure 1, Table 1, Supplementary Table 1). Of the articles excluded at the abstract and full text review stages, the most common reasons for exclusion were: no mention of the informed consent process for research with pediatric or adolescent populations; research not taking place in a low- or middle-income country; articles on pediatric research in low- or middle-income countries that did not discuss the informed consent process

Summary of guidelines and commentaries

We identified seven guidelines that addressed issues of informed consent in international settings and in research involving children in our scoping review. Of these, we selected for detailed review five that were most comprehensive, summarizing key recommendations in Table 1. All guidelines emphasize the importance of obtaining individual, informed and voluntary consent for research.(3,4,7–9) Importantly, however, the guidelines do not necessarily specify in detail how best to operationalize assessment of these core principles. For example, the Declaration of Helsinki comments only that informed consent requires that a subject be adequately informed of the "aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study" (Article 26). (7) Similarly, on voluntariness, the CIOMS guidelines note only that consent is voluntary if "an individual's decision to participate is free of undue influence" (p. 35). (3)

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

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

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

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

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)	• 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	• 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)	• 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	• 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)	• Obtain consent and assent when age-appropriate • Provide age-appropriate, clear, concise, and on-going information for parents and children	• 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 issues in international research(8)		• 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
European Council and European Parliament Guidelines(9)	• 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	• 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

Thematic summary of research on consent in LMIC pediatric research

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

[insert Table 2 here]

Table 2 Summary of review and opinion articles on ethical conduct of research in 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.

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 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.

Understanding social norms around decision making and protecting individual autonomy

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

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

[insert Table 3 here]

Table 3 Summary of articles discussing Social Norms, Decision Making, and Autonomy[1]

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.

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

Adapting consent procedures to low-literate settings

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

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

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

[insert Table 4 here]

Table 4 Summary of articles discussing working in low-literate settings, and with 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 were 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.

Working in indigenous or less-commonly-spoken languages

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

interactivity and person-to-person exchange. They describe alternative procedures, such as the preparation of recordings of consent scripts in local languages and extensive practice sessions with research staff obtaining consent in local languages.(17) Similarly, another vaccine trial in The Gambia described the successful use of audio-visual Speaking Books in local less-common languages to consent caregivers. (22)

Gender dynamics in caregiver consent

Local gender dynamics and decision making procedures when consenting male and female caregivers for research is an important consideration (Table 5). For example, when consenting with caregiving couples or within an extended family unit, instances are discussed where a female caregiver wishes to allow her child to participate, but is unable to do so because her husband or another male authority figure refuses.(13) The opposite may also occur, if a research study is consented by a male figure, but requires significant participatory effort from the primary female for study-related activities, leading the woman to express their refusal through procedural delay or inconsistent participation.(15) Given concerns about gender power imbalance and potential repercussions for consenting female caregivers, some studies discussed working to routinely involve fathers or male authority figures in the consent process for more complex or higher-risk research interventions.(15,23) In one interesting study based in India, Rajaraman and colleagues found that caregivers were more likely to actively participate in the consent process when both were present. They also observed, however, that this factor may have been due the fact that most study staff obtaining consent

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

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

[insert Table 5 here]

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.

Disclosing potential benefits and risks of participation in research

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

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

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

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

[insert Table 6 here]

Table 6 Summary of articles discussing 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 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.

Adolescents

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 (Table 7). 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.(31) 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.(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.

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 little explicit discussion or description of procedures for obtaining assent in the research reports we reviewed (Table 8). (35,36) One interesting qualitative study on parental perceptions of assent in Jordan revealed considerable variability in caregivers' perspectives about at what age assent should be solicited or, even, if assent should in all cases be obtained and dissent respected.(23)

[insert Table 8 here]

Table 8 Summary of articles discussing 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.

DISCUSSION

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

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

of therapeutic misconception and of developing consent procedures that ensure caregivers' comprehension of the potential benefits (or lack thereof) and risks of research procedures for their children.

However, within these four broad thematic areas, we also noted the need for additional careful investigation. In particularly, there is considerable uncertainty on how to ensure the principle of subsequent individual informed consent when community leaders or other authorities are approached first. This is especially the case when gender power imbalance is at play, and female caregivers may be either unempowered to consent or to opt out of a research decision made by a male authority. In addition, the social status of individuals administering or witnessing consent procedures may unduly influence the decision-making of caregivers, and research is needed to better understand and accommodate for the interpersonal dynamics of obtaining consent.

Finally, two thematic topics seem to be particularly underrepresented in the literature on pediatric LMIC research, and more work is urgently needed. First, despite extensive discussions about the difficulties of conducting research with adolescents, we found only few studies with practical discussions or guidance on how to navigate these difficulties. More investigation of the ethical conduct of research with adolescents is needed, with a broader representation of health conditions, research designs, and geographic regions. Second, despite strong representation of the principle of assent in international guidelines on research with children and adolescents, we found little research of cultural and regional differences

around notions of assent and virtually no discussion of the mechanics of assessing assent in research studies. Additional research into the topic of assent for research among children in LMICs should be an important priority.

Our review has two important limitations that must be considered. First, we included only articles published in English in major indexing databases. We believe this approach is justified, given our desire to provide a high-level overview of the topic without focusing specifically on any geographic region. Nevertheless, our review has undoubtedly missed resources in other languages or within the grey literature, which could be taken up in more detailed region-specific work on this topic. Second, given the diversity and heterogeneity of the literature reviewed, it was not possible to detail many of the practical insights and tips given in the individual articles. Nevertheless, given the annotation and thematic organization provided in Supplementary Table 1, we are confident that readers will be able to identify areas of particular interest for more in-depth examination.

ABBREVIATIONS

IRB: Institutional review board

LMIC: Low and middle-income country

RCT: Randomized clinical trial

STaR: Standards for Research in Child Health

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None.

AUTHOR'S CONTRIBUTIONS

MC designed the search strategy, extracted data from articles, and wrote the first draft of the manuscript. PR conceived the study, reviewed abstracts, and revised the manuscript.

DATA SHARING STATEMENT

Not applicable

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FIGURE LEGENDS

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

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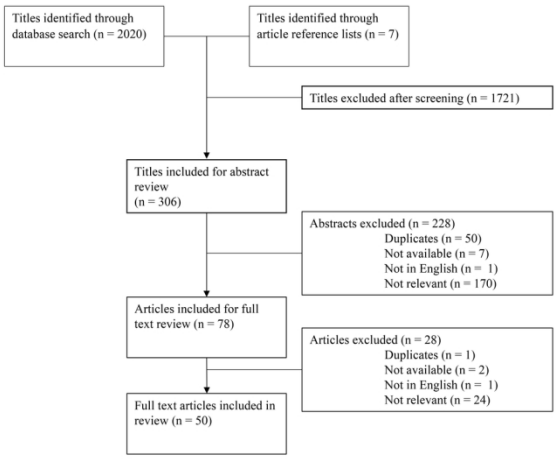

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