Researchers’’, Regulators’’, and Sponsors’ Views on Pediatric Clinical Trials: A Multinational Study

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abstract

BACKGROUND AND OBJECTIVE: The last decade has seen dramatic changes in the regulatory landscape to support more trials involving children, but child-specific challenges and inequitable conduct across income regions persist. The goal of this study was to describe the attitudes and opinions of stakeholders toward trials in children, to inform additional strategies to promote more high-quality, relevant pediatric trials across the globe.

METHODS: Key informant semi-structured interviews were conducted with stakeholders (researchers, regulators, and sponsors) who were purposively sampled from low-to-middle-income countries and high-income countries. The transcripts were thematically analyzed.

RESULTS: Thirty-five stakeholders from 10 countries were interviewed. Five major themes were identified: addressing pervasive inequities (paucity of safety and efficacy data, knowledge disparities, volatile environment, double standards, contextual relevance, market-driven forces, industry sponsorship bias and prohibitive costs); contending with infrastructural barriers (resource constraints, dearth of pediatric trial expertise, and logistical complexities); navigating complex ethical and regulatory frameworks (“draconian” oversight, ambiguous requirements, exploitation, excessive paternalism and precariousness of coercion versus volunteerism); respecting uniqueness of children (pediatric research paradigms, child-appropriate approaches, and family-centered empowerment); and driving evidence-based child health (advocacy, opportunities, treatment access, best practices, and research prioritization).

CONCLUSIONS: Stakeholders acknowledge that changes in the regulatory environment have encouraged more trials in children, but they contend that inequities and political, regulatory, and resource barriers continue to exist. Embedding trials as part of routine clinical care, addressing the unique needs of children, and streamlining regulatory approvals were suggested. Stakeholders recommended increasing international collaboration, establishing centralized trials infrastructure, and aligning research to child health priorities to encourage trials that address global child health care needs.

WHAT’S KNOWN ON THIS SUBJECT: Conducting clinical trials in children is complex because of safety concerns, stringent regulatory requirements, lower prevalence of disease, and lack of commercial interest. Recent changes in the regulatory environment have alleviated these challenges somewhat.

WHAT THIS STUDY ADDS: This article provides stakeholder views on mitigating the inequities by addressing children’s unique needs, integrating trials into clinical care, streamlining regulatory approvals, building infrastructure, relevant pediatric trials.

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Dr Joseph contributed to study conception and design, data acquisition, analysis and interpretation of the data, and drafting and revising the manuscript; and Drs Caldwell, Tong, and Craig contributed to study conception and design, reviewing the collected data, analysis and interpretation of the data, and critical review of the manuscript. All authors approved the final manuscript as submitted.
The last decade has seen major changes in the regulatory framework for clinical trials in children, resulting in substantial incentivization for industry and investigators to rigorously evaluate new therapies through the conduct of trials.1-3 Several pediatric research networks have also been established to support trials in children, with variable success.4,5 Despite these advances, children all too often remain "therapeutic orphans," as the majority of medicines prescribed for this age group have still not been adequately tested for safety and efficacy, and disparities exist compared with adults and according to income regions.1

Trials in children are complex and can be challenging due to the unique requirements of this population, safety concerns, stringent ethical requirements, and the lack of commercial interest.5,7 In low- and middle-income countries (LMICs), there are additional challenges related to poverty, fear of exploitation, and mistrust.8,9 The pharmaceutical industry is perceived as reluctant to conduct trials in children, whereas pediatricians’ concerns regarding risks are seen as barriers.1

The goal of the present study was to describe the attitudes and opinions of researchers, regulators, and sponsors regarding the conduct of clinical trials in children. A comprehensive understanding of their values, beliefs, and experiences across different income contexts could inform local and international strategies to improve the number, quality, and appropriateness of trials conducted in children.

METHODS

The Consolidated Criteria for Reporting Qualitative Research framework was followed for interviews and focus groups.10

Respondent Selection and Practice Setting

Respondents were eligible if they were researchers, regulators, or sponsors involved in trials in children. Consumers (children, families, and the public) were excluded. Respondents were purposively selected to capture a range of age, sex, income settings, and experience in trials. Respondents were recruited via professional networks. A snowball sampling strategy was also used whereby respondents could nominate others who could add a different or important viewpoint. The University of Sydney Ethics Committee approved this study.

Data Collection

The interview guide was based on a systematic review of trials in children and discussion among the study team.1 It focused on the challenges and strategies to improve trials relevant to child health (Supplemental Table 4). From October 2013 to August 2014, the lead author (P.D.J.) conducted face-to-face interviews in offices or meeting rooms or via telephone. Respondent recruitment ceased when theoretical saturation (ie, when little or no new information was being obtained from subsequent interviews) was reached.11,12 We audio-recorded and transcribed all interviews.

Analysis

Transcripts were entered into HyperRESEARCH version 3.5.2 software (ResearchWare Inc, Randolph, MA). Based on grounded theory13 and thematic analysis,12 the lead author (P.D.J.) coded transcripts line-by-line and then translated similar and different concepts into existing or new codes, respectively, as they emerged in the data. Similar concepts were grouped into themes and subthemes, and the coding structure was revised until all concepts relating to barriers and enablers of trials in children were captured. Relationships and patterns between themes were identified to develop a thematic schema. To enhance the comprehensiveness and validity of the thematic framework, the preliminary findings were discussed among the research team (investigator triangulation) and then e-mailed to all respondents, who were given 2 weeks to include additional viewpoints (ie, member checking). Their feedback was coded and incorporated into subsequent revisions of the analytical framework.

RESULTS

Study Respondents

In total, 35 (88%) of the 40 invited stakeholders participated. They were from 10 countries; 20 stakeholders were from high-income countries, and 15 stakeholders were from LMICs (Table 1). Nonparticipation was due to nonavailability or institutional restrictions. The duration of the interview ranged from 20 to 70 minutes. Eight interviews were conducted face-to-face.

Themes

Five major themes were identified: addressing pervasive inequities, contending with infrastructural barriers, navigating complex regulatory and ethical frameworks, respecting uniqueness of children, and driving evidence-based child health. These themes are described with illustrative quotations in Table 2 and Supplemental Table 5. Figure 1 shows the conceptual relationships among themes and subthemes.

Addressing Pervasive Inequities

Pauclity of Safety and Efficacy Data

The growth in the number of trials in diseases specific to children was perceived to be less than expected. Clinicians were concerned that children could potentially be harmed
due to “treatment uncertainties” and “practicing unresearched health care” because trials were still “skewed” with data from the adult population. In particular, respondents felt there was a paucity of safety and efficacy data in diseases with a high burden in resource-poor settings, rare childhood diseases, older off-patent medicines, and younger age groups.

Knowledge Disparities

Researchers believed that they were perceived by some pediatricians, the community, and politicians to be “using” children and were described as “vampires after your blood.” Some respondents believed that parents in the West were “pretty informed and educated,” whereas researchers in LMICs had to contend with language barriers and lower health literacy in parents.

Volatile Environment

The entrenched social disadvantage, local political instability, and corruption in certain LMICs were offered as the main reasons for insecurity and hesitation among local researchers to conduct trials in children. Historical fears were believed to have damaged public trust of trials involving children (eg, the unethical trials conducted during World War II in Germany).

Challenging Double Standards

The “double standard” of the bureaucratic burden and regulatory requirements to conduct trials in children, compared with the ease of using untested interventions in routine clinical care, was questioned. There was controversy regarding the proposal of using placebos or inferior treatments as comparators in trials in LMICs, where the international standard of care was not routinely available. Regulators in the United Kingdom and the United States queried why it was “illegal” to pay children anything beyond reimbursement for trial expenses, whereas in adult trials, it was “fair to pay” for participation.

Ensuring Contextual Relevance

A “disconnect” between the pediatric burden of disease and countries in which trials were conducted was reported by respondents. Researchers believed “data which are not Indigenous” may not be relevant to local settings because of “pharmacogenomic differences” and variability in health care.

Respondents believed industry would “leverage their resources” in trials in which there was greater “financial reward” rather than for “humanitarian reasons.” Clinicians argued that most trials were focused on diseases in adults, driven by political and economic influences, and the regulatory incentives for involving children in trials only helped to “tie the pediatric caboose to the adult marketing train.” They

### TABLE 1 Respondent Characteristics (N = 35)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (71)</td>
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<tr>
<td>Female</td>
<td>10 (28)</td>
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<tr>
<td>Age group, y</td>
<td></td>
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<tr>
<td>&lt;40</td>
<td>5 (14)</td>
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<tr>
<td>40–49</td>
<td>9 (26)</td>
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<tr>
<td>50–59</td>
<td>12 (34)</td>
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<tr>
<td>60–69</td>
<td>9 (26)</td>
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<tr>
<td>Country of practice</td>
<td></td>
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<tr>
<td>High-income countries</td>
<td></td>
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<tr>
<td>Australia</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Canada</td>
<td>5 (14)</td>
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<tr>
<td>Finland</td>
<td>1 (3)</td>
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<tr>
<td>France</td>
<td>1 (3)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>3 (5)</td>
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<tr>
<td>United States</td>
<td>5 (14)</td>
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<tr>
<td>LMICs</td>
<td></td>
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<tr>
<td>India</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Nigeria</td>
<td>4 (11)</td>
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<tr>
<td>Papua New Guinea</td>
<td>1 (3)</td>
</tr>
<tr>
<td>South Africa</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Role</td>
<td></td>
</tr>
<tr>
<td>Researchers/clinicians&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 (50)</td>
</tr>
<tr>
<td>Regulators&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20 (33)</td>
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<tr>
<td>Sponsor&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 (17)</td>
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<tr>
<td>Specialty area&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>General pediatrics</td>
<td>13 (21)</td>
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<tr>
<td>Subspecialty&lt;sup&gt;f&lt;/sup&gt;</td>
<td>46 (72)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5)</td>
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<tr>
<td>Clinical trial experience, y</td>
<td></td>
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<tr>
<td>&lt;10</td>
<td>13 (37)</td>
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<tr>
<td>10–20</td>
<td>11 (31)</td>
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<td>21–30</td>
<td>7 (20)</td>
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<tr>
<td>&gt;30</td>
<td>4 (11)</td>
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<sup>a</sup> Numbers do not equal 35 because multiple categories apply to some individuals.
<sup>b</sup> Researchers: academic, administrator, clinicians/pediatrician, clinical pharmacologist, investigators/researcher, methodologist, networks/working groups, clinical trials center/clinical research facility, and trial coordinators/assistants.
<sup>c</sup> Regulators: institutional review board (bioethicist, ethics committee member, ethical review bodies, ethics subcommittee/scientific advisory committee member), networks/working groups, Data Safety Monitoring Board or Data Monitoring Committee/local safety monitor; regulatory body, policy makers, and research governance.
<sup>d</sup> Sponsors: academic sponsor, charitable organizations, clinical research assistants, government funding body, monitors, pharmaceutical industry, contract research organization, and consultancy work with sponsors.
<sup>e</sup> Number of respondents in subspecialties were as follows: cardiology, n = 1; clinical pharmacology, n = 2; emergency, n = 1; endocrinology, n = 2; immunology and infective disease, n = 8; intensive care, n = 3; hematology, n = 3; neonatology, n = 2; nutrition, n = 1; oncology, n = 8; psychological medicine or mental health, n = 2; renal, n = 1; respiratory, n = 4; and musculoskeletal or rheumatology, n = 1. Other: ethics, n = 1; methodology, n = 2.
Navigating complex regulatory and ethical frameworks

Dearth of pediatric trial

Market-driven forces

Volatile environment

Challenging double standards

Ensuring contextual relevance

Knowledge disparities

Paucity of safety and efficacy data

Addressing pervasive inequities

Table 2

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<td>You have brilliant ideas, but the brilliant ideas at the best they end on the desktop because of the lack of funding. Because...issues relating to children tend to be culturally very last on the priority list. So where we really have the big need is how to get funding for the investigator-initiated studies. (Researcher, IRB, monitor, Nigeria)</td>
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<td>Dearth of pediatric trial expertise</td>
<td>I can't tell you the number of meetings that I have been in where someone said GCP and somebody goes, ‘what’s that?” ‘Good Clinical Practice.’ First of all, we have no real sticks, we have possibly some carrots but we’re sort of neutral on ensuring in a satisfactory fashion that investigators and their staff are qualified and sufficiently maintained skills to carry out trials. (Researcher, IRB, governance, Canada)</td>
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<td>We have some issues such as electricity or power supply which is not very regular, and storage facilities to keep specimens are a challenge because of erratic power supply. And therefore if you are going to conduct clinical trials here, you would need an alternative source of power to ensure that biospecimens and other items are kept properly. (Researcher, Nigeria)</td>
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<td>Dissuaded by prohibitive costs</td>
<td>Investigator-initiated trials were sometimes possible here like the neonatal trials around caffeine for apnea. But they all cost $5 million each to answer 1 question, and so there's no more money in the public arena to sponsor trials that are that expensive. (Researcher, pediatrician, academic, Canada)</td>
</tr>
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<td>Industry sponsorship bias</td>
<td>Within the physician environment, definitely industry-sponsored trials are seen as with a bit of bias and real question as to whether physicians soil themselves by getting involved with industry. (Researcher, IRB, governance, Canada)</td>
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<td>Ensuring contextual relevance</td>
<td>Research in a developing country, it’s like a copy/paste thing from the West...a lot of money goes into it, and we just replicate research with not many really great outcomes. (Researcher, trial coordinator, India)</td>
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<td>Volatile environment</td>
<td>And it has worsened by...the medical profession also becoming extremely defensive, because they don’t want to get into any trouble and bad media publicity if something goes wrong. But this is where actually we really are getting hurt, especially in pediatric research. (IRB, CRO, India)</td>
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<td>Challenging double standards</td>
<td>For a very simple regimen to treat Burkitt’s lymphoma, it was being done in Malawi...the ethics committee in Nigeria refused the protocol. Even though the drugs are cheap and affordable, it was seen as reduced efficacy than the current standard treatment in the country. (Researcher, pediatrician, Nigeria)</td>
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<td>Knowledge disparities</td>
<td>As a doctor, people tell me just do whatever is good for me; he will not be able to understand the meaning of a clinical trial. He will say, ‘are you trying to use me as, a guinea pig or something?’...So the meaning of consent is entirely different for an illiterate patient compared with an Internet-savvy, educated one. (Researcher, trial coordinator, India)</td>
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"Draconian" oversight

Some of the regulations around that are quite stringent and that we can't follow to the letter at the moment because it's just impractical. For instance, it says the Minister has to provide consent for every child that participates in a study. (Researcher, pediatrician, South Africa)

I mean the 17-page sort of consent forms outlining every conceivable risk is counterproductive to good clinical practice, it's counterproductive to good science, it's counterproductive to moving things forward and making things better for everyone. (Researcher, regulator, government sponsor, Australia)

Ambiguous requirements

One area of uncertainty seems to be the definitions of key terms such as minimal risk and minor increase over minimal risk, in the pediatric context. (Regulator, IRB, governance, United States)

There are certain South American countries that just won't allow research with a placebo, and there are countries right next door that do. So it's whatever the local laws and regulations govern. (Researcher, pediatrician, industry sponsor, United States)

Fear of exploiting the vulnerable

In a developing world context, there's a greater potential for exploitation and because in a way they're a vulnerable population, socioeconomically, they're vulnerable, from a point of view of levels and standards of education they're vulnerable, from a point of view of access to care their vulnerable... the reduced capacity for authorities and ethics committee to deal with these complex issues. (Researcher, pediatrician, South Africa)

Excessive paternalism and unwarranted exclusion

If we are convinced of... our basic research that's Phase I, Phase II studies and that we've done this safely, crossed our 't' and dotted our 'i' and you know it's safe. I don't think we need to go adults first and then children... all studies that are safe should be offered to children and adults. This artificial cutoff that we are going to do it in adults first then children should not exist. (Researcher, IRB, regulator, South Africa)

Precariousness of coercion versus volunteerism

They may offer treatment that is otherwise unreachable by the children in this area, too expensive or not present at all. It may bring equipment to the centers such as laboratory, x-ray, and ultrasound whatever is needed for the trial that remains there after the trials. But these are ethically very different questions. Because it is possible that this indirect benefits that benefit the whole health care system... may lead to a situation where children are then allowed to participate in... trials for reasons that are not directly for the benefit of themselves but for the benefit of the society. (Researcher, pediatrician, IRB, Finland)

Respecting uniqueness of children

Regulatory agencies need to move away from a very narrow interpretation of indications in terms of pediatric studies... right now so much of it's still based on the adult indications and the pediatric-intended indications being similar. That's certainly not always the case; for example, sildenafil is used in adults to treat erectile dysfunction and it's used in premature neonates for pulmonary hypertension. Certainly, those 2 indications are very different as are the populations... So we're moving toward an assessment of effect as a way to bridge data between adults and children... And also moving away from trying to prove in some cases that the disease processes are substantially similar;... asthma is asthma, but the disease process is very different. (Researcher, pharmacologist, United States)

But now the trend has been turning. It probably started with the orphan regulations in Europe where it very quickly became clear that there are no way you can make big clinical trials in rare diseases... optimally, pediatric trials should use methods that are designed for small size clinical trials. (Researcher, pediatrician, IRB, Finland)

And it is very dangerous to have a comparator that is an unproven treatment and children are exactly in this position because many of the pediatric treatments even if they are considered current choice of treatment, have not been well documented. (Researcher, pediatrician, IRB, Finland)

Considering child-appropriate approaches

Sometimes we get protocols that are not designed with children in mind so that the assessment periods are too tightly scheduled, or the number of assessments is not appropriate for children. So they've looked at adult studies and tried to just sort of adapt that to children by just scaling down the dose. And they haven't really thought... kids aren't going to come in for that many visits and they've got school and they've got exams. And they've got days where they just don't feel like being poked and prodded and they're just not going to comply. And the protocols are not always written with that flexibility that's required for working with children in mind. (Trial coordinator, trial center, Australia)

Facilitating family-centered empowerment

In the oncology arena, the positive aspects are that the parents are always very enthusiastic and very supportive. So, they see it as an opportunity for their child, and they're very engaged so we don't have problems with compliance and follow-up because the parents want to do the right thing and want to contribute. (Trial coordinator, trial center, Australia)

I think parents, children, and young people need to be at the center of research and that needs to be nurtured. When people are familiar with clinical trials terms, they can be very productive, but unless they're supported, it can be a very bruising journey that wastes a lot of time. So there needs to be specific support for children, parents, and young people that best works with networks. (Researcher, regulator, industry consultant, United Kingdom)

Driving evidence-based child health

Promoting research advocacy

Use all international forum and collaborations to raise awareness, to show success, demonstrate projects that it is feasible and that it is ethical and it is safe for the participant to be in a clinical trial... maybe using international platforms such as WHO, maybe others to engage more children, families, clinicians and researchers across the world. (Researcher, pediatrician, academic, Canada)

Creating and seizing opportunities

The most feasible today would be in the form of building infrastructure where you can have networks with people who are full-time professionals assisting in the local running of the clinical trials. (Researcher, pediatrician, IRB, Finland)

They have been very successful because of a top-down funding model by the NHS (National Health Service) to get the Medicines for Children Research Network going. And they have accomplished a lot of success. (Researcher, pediatrician, academic, Canada)

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**TABLE 2 Continued**

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<tr>
<td>&quot;Draconian&quot; oversight</td>
<td>Some of the regulations around that are quite stringent and that we can't follow to the letter at the moment because it's just impractical. For instance, it says the Minister has to provide consent for every child that participates in a study. (Researcher, pediatrician, South Africa)</td>
</tr>
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<td>I mean the 17-page sort of consent forms outlining every conceivable risk is counterproductive to good clinical practice, it's counterproductive to good science, it's counterproductive to moving things forward and making things better for everyone. (Researcher, regulator, government sponsor, Australia)</td>
</tr>
<tr>
<td>Ambiguous requirements</td>
<td>One area of uncertainty seems to be the definitions of key terms such as minimal risk and minor increase over minimal risk, in the pediatric context. (Regulator, IRB, governance, United States)</td>
</tr>
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<td></td>
<td>There are certain South American countries that just won't allow research with a placebo, and there are countries right next door that do. So it's whatever the local laws and regulations govern. (Researcher, pediatrician, industry sponsor, United States)</td>
</tr>
<tr>
<td>Fear of exploiting the vulnerable</td>
<td>In a developing world context, there's a greater potential for exploitation and because in a way they're a vulnerable population, socioeconomically, they're vulnerable, from a point of view of levels and standards of education they're vulnerable, from a point of view of access to care their vulnerable... the reduced capacity for authorities and ethics committee to deal with these complex issues. (Researcher, pediatrician, South Africa)</td>
</tr>
<tr>
<td>Excessive paternalism and unwarranted exclusion</td>
<td>If we are convinced of... our basic research that's Phase I, Phase II studies and that we've done this safely, crossed our 't' and dotted our 'i' and you know it's safe. I don't think we need to go adults first and then children... all studies that are safe should be offered to children and adults. This artificial cutoff that we are going to do it in adults first then children should not exist. (Researcher, IRB, regulator, South Africa)</td>
</tr>
<tr>
<td>Precariousness of coercion versus volunteerism</td>
<td>They may offer treatment that is otherwise unreachable by the children in this area, too expensive or not present at all. It may bring equipment to the centers such as laboratory, x-ray, and ultrasound whatever is needed for the trial that remains there after the trials. But these are ethically very different questions. Because it is possible that this indirect benefits that benefit the whole health care system... may lead to a situation where children are then allowed to participate in... trials for reasons that are not directly for the benefit of themselves but for the benefit of the society. (Researcher, pediatrician, IRB, Finland)</td>
</tr>
<tr>
<td>Respecting uniqueness of children</td>
<td>Regulatory agencies need to move away from a very narrow interpretation of indications in terms of pediatric studies... right now so much of it's still based on the adult indications and the pediatric-intended indications being similar. That's certainly not always the case; for example, sildenafil is used in adults to treat erectile dysfunction and it's used in premature neonates for pulmonary hypertension. Certainly, those 2 indications are very different as are the populations... So we're moving toward an assessment of effect as a way to bridge data between adults and children... And also moving away from trying to prove in some cases that the disease processes are substantially similar;... asthma is asthma, but the disease process is very different. (Researcher, pharmacologist, United States)</td>
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<td>But now the trend has been turning. It probably started with the orphan regulations in Europe where it very quickly became clear that there are no way you can make big clinical trials in rare diseases... optimally, pediatric trials should use methods that are designed for small size clinical trials. (Researcher, pediatrician, IRB, Finland)</td>
</tr>
<tr>
<td></td>
<td>And it is very dangerous to have a comparator that is an unproven treatment and children are exactly in this position because many of the pediatric treatments even if they are considered current choice of treatment, have not been well documented. (Researcher, pediatrician, IRB, Finland)</td>
</tr>
<tr>
<td>Considering child-appropriate approaches</td>
<td>Sometimes we get protocols that are not designed with children in mind so that the assessment periods are too tightly scheduled, or the number of assessments is not appropriate for children. So they've looked at adult studies and tried to just sort of adapt that to children by just scaling down the dose. And they haven't really thought... kids aren't going to come in for that many visits and they've got school and they've got exams. And they've got days where they just don't feel like being poked and prodded and they're just not going to comply. And the protocols are not always written with that flexibility that's required for working with children in mind. (Trial coordinator, trial center, Australia)</td>
</tr>
<tr>
<td>Facilitating family-centered empowerment</td>
<td>In the oncology arena, the positive aspects are that the parents are always very enthusiastic and very supportive. So, they see it as an opportunity for their child, and they're very engaged so we don't have problems with compliance and follow-up because the parents want to do the right thing and want to contribute. (Trial coordinator, trial center, Australia)</td>
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<td></td>
<td>I think parents, children, and young people need to be at the center of research and that needs to be nurtured. When people are familiar with clinical trials terms, they can be very productive, but unless they're supported, it can be a very bruising journey that wastes a lot of time. So there needs to be specific support for children, parents, and young people that best works with networks. (Researcher, regulator, industry consultant, United Kingdom)</td>
</tr>
<tr>
<td>Driving evidence-based child health</td>
<td>Promoting research advocacy Use all international forum and collaborations to raise awareness, to show success, demonstrate projects that it is feasible and that it is ethical and it is safe for the participant to be in a clinical trial... maybe using international platforms such as WHO, maybe others to engage more children, families, clinicians and researchers across the world. (Researcher, pediatrician, academic, Canada)</td>
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<tr>
<td>Creating and seizing opportunities</td>
<td>The most feasible today would be in the form of building infrastructure where you can have networks with people who are full-time professionals assisting in the local running of the clinical trials. (Researcher, pediatrician, IRB, Finland)</td>
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<td>They have been very successful because of a top-down funding model by the NHS (National Health Service) to get the Medicines for Children Research Network going. And they have accomplished a lot of success. (Researcher, pediatrician, academic, Canada)</td>
</tr>
</tbody>
</table>
Supporting best practice

Up to 80% or 90% of pediatric clinical trials are at an uncertain or high risk of bias when it comes to randomization sequence, allocation concealment, blinding of the intervention of the outcome measurers, attrition, and second outcome reporting. So bias is a big threat to the validity and inefficiency and impact of trials, and so we need to start reducing research waste. (Researcher, pediatrician, academic, Canada)

All research should be demand-driven, by people who live and work in those countries, by Ministries of Health, by institutions of academia or science in those countries. I’ve seen it a lot, but I don’t believe that outside institutions should come and just set up trials with minimal collaboration…there needs to be very good…nontrial evidence, epidemiologic evidence showing the burden of the problem. (Researcher, pediatrician, DSMB, Papua New Guinea)

Improving access to treatment

It …would be unethical not to study the medicines in the children of resource-limited country if they need the medicines and if they are used anyway. (Researcher, pediatrician, IRB, Finland)

If it was performance indicator of a CEO of a hospital or other things, that would be seen it was desirable that people involve in clinical trials. Funding would flow to it in a way that it doesn’t now…it needs to be embedded more at the center of clinical care. (Trial coordinator, IRB, government sponsor, Australia)

Prioritizing research productivity

More trials to do with targeting where the burden of disease is. It’s always a balancing act. Pediatrics has its fair share of rare diseases in terms of genetic disorders and other things that only occur in children. You wouldn’t want to see all the resourcing going toward diseases like diarrhea management, middle ear infection. (Trial coordinator, IRB, government sponsor, Australia)

Pooling of resources, making sure resources are not focused in rich countries. They need to be universally available…Sexy things get the funding…where they can get publicity…there needs to be an appraisal of what research we are doing; what bang for our buck we are getting…We know the burden of disease…we need to prioritize the research in the right way! (Researcher, IRB, regulator, South Africa)

CEO, chief executive officer; CRO, contract research organization; DSMB, Data Safety Monitoring Board; IRB, institutional review board; WHO, World Health Organization.

FIGURE 1
Thematic schema of challenges and enablers of clinical trials in children.
surmised that it had been “a happy marriage between industry and regulators” to conduct trials in children with a large sample size as a “preauthorization marketing tool.”

Industry Sponsorship Bias

Industry-sponsored trials were noted to be almost always multinational and of higher quality because of adherence to regulatory standards for obtaining marketing authorization. In contrast, investigator-initiated trials were deemed to be of “poor quality,” “curiosity-driven,” or for academic promotion. Clinicians suspected that investigators reluctantly participated in industry-sponsored trials so that they could “pay the rent” and subsidize their own research. Industry sponsors believed that the majority of industry “get tainted in that stigma” by the minority of pharmaceutical companies who conduct research unethically. They believed the position “damned if they do and damned if they don’t” involves children from LMICs in trials.

Dissuaded by Prohibitive Costs

The “manifold costs” of regulatory oversight were perceived as a “double-edged sword” for investigators who had to conduct trials “on shoestring budgets or no budgets.” Trials in children were perceived to be a “financial risk” to industry because of the small pool of eligible patients, longer follow-up, and the increasing site costs. Industry sponsors were polarized regarding the perception that they were “shifting” research to the LMICs where it was a “cheaper” option.

Contending With Infrastructural Barriers

Overwhelming Resource Constraints

Researchers stated that “funding was the bane of doing research” in children, as pediatric trial facilities and resources were scarce, especially in disadvantaged settings.

Dearth of Pediatric Trial Expertise

Respondents noted a critical lack of expertise in pediatric trials. Some researchers from LMICs acknowledged that they developed expertise from participating in industry-sponsored trials. Many felt that clinicians required appropriate rewards and “career pathing” to enhance participation in trials.

Traversing Logistical Complexities

All respondents had to confront logistical complexities such as shipping samples overseas. Logistical difficulties were particularly challenging in LMICs. For example, researchers in Nigeria had to contend with electricity disruptions, unreliable telecommunication, and difficulty in following up respondents who frequently relocated.

Navigating Complex Ethical and Regulatory Frameworks

“Dracian” Oversight

Researchers believed that “draconian” ethical and regulatory oversight was a barrier to conducting trials in children. Navigating the long, heterogeneous, and duplicative process of obtaining multiple approvals was considered “cumbersome,” and the informed consent requirements were described as onerous and impractical. Some respondents were frustrated that research funds were wasted on “unreasonable bureaucracy,” while acknowledging that without a “robust governance and safety system we would prejudice our research.”

Ambiguous Requirements

Many felt that the variability in the quality of ethical deliberations and “ambiguous” trial guidelines “drives people crazy” and potentially leads to “unequal protection.”

Fear of Exploiting the Vulnerable

Some respondents believed that children in LMICs were exploited to address the health care needs primarily of wealthy nations. Ethics committee members opposed “exposing children to inappropriate level of research risk absent of any prospective direct benefit” (eg, inserting a central line for placebo administration). The new mandatory requirement of audio-visual consent in India was believed to protect respondents, although some considered this requirement to be excessive and could stigmatize adolescents who preferred to be de-identified.

Excessive Paternalism and Unwarranted Exclusion

Researchers and sponsors believed that parents and regulators had “paternalistic attitudes” and were “overcautious” about including children in trials. However, some argued that excluding children was discriminatory because “the way we should protect children is not from research, but through research.” Researchers reasoned that ethics committees and guidelines were there to protect children from “unreasonable, potential risk.” Some believed that it was easier to justify trialing medicines in neonates, in whom there is limited or no clinical practice evidence, than trialing treatments that are currently used in children without evidence.

Precariousness of Coercion Versus Volunteerism

Researchers were uncertain about the morality surrounding investigator and parent’s inducement to participate in trials, particularly in the context of LMICs. Industry sponsors maintained that the amount of reimbursement could not be universally standardized and should be reflective of the economy, as payment of disproportionately high amounts of reimbursement could unduly influence participation.
Respecting Uniqueness of Children

Embracing Pediatric Research Paradigms

Respondents advocated for stakeholders to “embrace pediatric paradigms” and consider the “uniqueness” of children regarding treatment response, disease pathophysiology, and expression. Clinicians prioritized impact on quality of life and long-term neurocognitive outcomes. Respondents recommended novel, pragmatic trial designs for small populations of rare diseases in children.

Considering Child-appropriate Approaches

Researchers and ethics committee members thought that industry neglected child-specific issues when designing protocols. Respondents proposed that protocols be developed to include child-specific considerations such as microanalysis techniques that require smaller volumes of blood. They recommended a child-friendly research environment with distraction therapies, and using pictures or audio-visual aids and plain language to explain trials. Some suggested that clinical visits or assessments should be scheduled to minimize interference with school attendance.

Facilitating Family-centered Empowerment

Involving families in setting child health care research priorities, as well as the designing and conducting of trials, was proposed by researchers and regulators. The clinical team highlighted that when “recruiting a child, you are recruiting the whole family.” In the United Kingdom, families and children involved in trial networks have lobbied to have trial results provided to respondents.

Driving Evidence-based Child Health

Promoting Research Advocacy

Although “great strides” in benefits of children’s participation in trials was recognized, further behavioral and cultural shifts through a massive awareness campaign was deemed essential. The ethical case that “children deserved evidence-based care,” the economic justification of return on investment by health care cost savings, and involving families to obtain “public acceptance” and policy makers’ support were encouraged.

Creating and Seizing Opportunities

Proponents of trials in children encouraged global “societal commitment” to dedicate funds and attract investment in pediatric trials. Respondents believed that strong networking opportunities contributed to the success of trials in pediatric oncology. Researchers from LMICs welcomed opportunities for participation in international trials. They advocated for research to improve the health system and philanthropic investment to build local trial and health care capacities.

Supporting Best Practice

Respondents supported the development of consensus trial regulations and resources that could be adapted to local contexts. They believed that it would be “utopia” to have 1 “amalgamated” national ethical review process. However, some regarded this scenario as a “double-edged sword” because a central ethical review would eliminate the inherent quality control provided by multiple reviewers. Many encouraged collaboration and sharing of expertise, and they emphasized the need for a centralized trials infrastructure with research “intra-operable tools” to support a range of study designs.

Improving Access to Treatment

Trial participation gave children the opportunity to access new or better treatments that may otherwise be “unreachable,” expensive, or unavailable. Thus, respondents advocated for trials to be embedded in clinical care. They endorsed harmonization and augmentation of regulations and stronger partnerships between researchers, regulators, and industry to support well-designed developmental pipelines for therapeutic agents for children. More efficient dissemination, translation, and implementation of pediatric research into practice and policy were encouraged.

Prioritizing Research Productivity

Multi-stakeholder collaboration to improve trials in child health care globally and reduce research waste was deemed crucial. Prioritization of child health care needs based on analysis of epidemiologic or trial registries data was recommended. Burden of disease, balanced by scientific opportunities in rare diseases, was considered important to justify expenditures in prioritizing funding universally.

DISCUSSION

A broad range of stakeholders involved in the conduct of trials in children recognized that much had been done to promote trial-informed clinical care of children but that large-scale cultural and behavioral changes, coupled with substantial infrastructural enhancement, were still required to promote the conduct of more trials that were relevant and of high quality. They believed that there was still a scarcity of child health care safety and efficacy data, most notably in LMICs, child-specific diseases, neonates, off-patent medicines, and child-appropriate formulations. Challenges and specific pediatric disparities were believed to arise from fears of harming children,
political and economic influences, lack of resources for pediatric trials, and the bureaucratic regulatory framework. Global multi-stakeholder collaboration, integration of trials as part of clinical care, sustainable centralized trials infrastructure, harmonization of regulatory approvals, and alignment of the pediatric research agenda through analysis of trial registries and epidemiologic data were believed to enhance global capacities to conduct pediatric trials.

A recent systematic review of stakeholder views of trials in children in LMICs identified challenges related to social disadvantages, idiosyncratic cultural beliefs, and historical disempowerment, with community engagement as the main enabler.9 In our study, more challenges were identified by respondents in LMICs, where few trials are conducted despite the enormous pediatric disease burden. Some respondents were concerned about safety and exploitation of children, whereas others maintained that trial participation protects children from harm caused by non–evidenced-based health care.14, 15

In addition to the frustration engendered by what was regarded as shortcomings in the technical capacity of ethics committees and ambiguities in the regulatory requirements, researchers in the present study questioned the legitimacy of being explicit about treatment uncertainties and enrolling children in trials as opposed to the ease of giving the same untested treatment in routine clinical practice. Some felt that it was unethical and discriminatory not to involve children in trials. Stakeholders supported harmonizing and expediting ethical review and developing local and international standards. They believed this approach would reduce duplication and improve efficiency of ethical approval.19, 20 Professional stakeholders were polarized regarding the current regulations forbidding payment to children for participation in trials.21

Stakeholders encouraged regulators worldwide to adopt appropriate regulations for the conduct of trials in children. They recognized that market exclusivity incentives supporting patent protection were not designed to meet the current needs of children, and this observation was corroborated in a recent examination of drugs granted exclusivity.22 Stakeholders endorsed improved regulations and incentives addressing child-specific therapeutic needs, off-patent medicines, and rare childhood diseases.23, 24 To accommodate the low disease prevalence in children, innovative and optimum methods were suggested.25– 27

Amalgamated government and philanthropic investments with strengthened multi-stakeholder partnership were regarded as necessary to improve drug development for pediatric use. Stakeholders supported multicenter collaborative trials and open disclosure of trial results through registries to reduce research waste and increase clinical benefit. Investment in a global governance framework of registries was encouraged to assist expedient availability, translation, and implementation of trial results.28 Incorporating analysis of epidemiologic and registries data to inform clinical research needs in children was supported, and integrating trials as part of routine clinical care was considered essential to bring interventions to the bedside in a sustainable manner.

Greater investment in training and resources is urgently required to help progress investigator-initiated trials to the regulatory standards that are required to inform labeling changes of medicines for use in children. Guidance and standards to improve pediatric trial design, conduct, and reporting are recognized as vital, with some initiatives underway.4, 29, 30 Establishing networks to collaborate and support trials was deemed essential by stakeholders. Investing in a centralized trial infrastructure with sustainable funding that could support different studies was considered crucial to promote more high-quality trials in children. This infrastructure has been shown to be beneficial, as illustrated in the highly successful UK Medicines for Children Research Network.31

Our international study highlights a wide spectrum of opinions of pediatric trial experts and decision-makers across different income and health care settings. We applied member checking to ensure that the analysis reflected the range and depth of the data collected. Our study outlines those recommendations that will be of interest to all stakeholders, including policy makers, to enable more high-quality trials primarily by making more explicit and informed decisions concerning child health research priorities (Table 3). However, there are some potential limitations. The transferability of the findings to countries that were not included in our study is uncertain. We recommend extending similar research to other countries that have different health systems, regulations, culture, and resources.

CONCLUSIONS

Stakeholders acknowledge that changes in the regulatory environment have encouraged
Enhance regulatory frameworks:  
- Improve pediatric regulations and incentives to encourage trials in child-specific diseases, including trials of off-patent medicines (eg, Pediatric Trials Network initiatives).
- Establish a global-level pediatric medicines regulatory framework under the leadership of the World Health Organization to regulate and harmonize country of trials conduct, transferability of results, availability of medicines, and improve medicine access and reimbursement strategies (eg, TransCelerate initiative).
- Create an international network of regulators to manage the regulatory requirements and provide support for less-experienced regulators.
- Develop a log of trials to prevent duplication and identify gaps (eg, enprEMA, Medicines for Children Research Network, Global Research in Pediatrics initiatives).

Mitigate disparities in LMICs:  
- Invest in sustainable centralized trial infrastructure, including dedicated management team of a statistician, research nurse, data manager, and pharmacist to support investigators.
- Establish networks with sustainable funding to collaborate and support trials in children, especially nonindustry-sponsored trials (eg, Medicines for Children Research Network).
- Develop standards and guidance on trial design, conduct, and reporting (eg, valid child health outcomes including child-reported outcomes), explicit definitions (eg, minimal risk, adequate sample size), selection of appropriate comparators, reduction of risk of bias (eg, StaR Child Health, Toronto Outcomes Research in Child Health, Enhancing Research Impact in Child Health, Standard Protocol Items for Randomized Trials–Children, Consolidated Standards of Reporting Trials–Children).
- Invest in training and standards for data monitoring committees.
- Implement programs to audit the conduct of trials at sites.
- Increase research and development investment to encourage trials in LMICs.
- Build expertise in LMICs by encouraging research collaborations with investigators from high-income countries.
- Share trial resources of high-income countries for adaptation to local contexts.
- Advocate for philanthropic investment to build local trial and health care capacity.
- Encourage operational research (advanced analytical techniques) on improving practices in these difficult contexts.
- Invest in prevention and curative health services and research to address some of the neglected health burdens.
- Promote health and education of the community.
- Encourage sponsor provision of ongoing supportive medical care posttrial and ancillary care to siblings and other family members.

Improve evidence-base practice:  
- Encourage multicenter collaborative trials to reduce research waste.
- Develop good referral network among pediatric clinicians to enhance recruitment.
- Conduct trials of more economically feasible treatment modalities for LMICs, where appropriate.
- Promote ongoing supplies of successful interventions to participants, while expediting regulatory approvals of pediatric labeling.
- Invest in developing formulation of medicines appropriate for children in all income regions (eg, suspensions).
- Review medicine reimbursement strategies to improve access of medicines addressing pediatric needs.
- Embed clinical research as part of routine clinical care and in disease-specific registries (eg, Key Performance Indicator of organization to involve children in trials).
- Invest in a governance framework of registries to address the evidence gaps in children and monitor expedient availability of trial results.
- Invest in funding for translation and implementation of effective interventions.

Embrace child-appropriate approaches:  
- Design protocols around pediatric needs with consultation and partnering with the academic, practicing community, and families (eg, United Kingdom, Young Peoples Advisory Group, International Children’s Advisory Network).
- Develop guidelines to engage children and parents in setting priorities, designing and conducting trials (eg, feasibility and selection of patient-reported outcomes, review of consent forms, scheduling appointments).
- Adopt child-appropriate strategies such as reducing pain and discomfort of painful invasive procedures (eg, distraction techniques such as DVDs).
- Develop alternative robust strategies to monitor compliance in children (eg, devices that can monitor use).
- Further research to develop guidelines on adequate pediatric decision-making (assent).
- Further research regarding payment to children for participating in optional research that does not offer direct benefit for the child.
- Provide patient-specific results sheet to families and children who participated.

### TABLE 3 Implications for Practice and Policy to Address Barriers and Inequities

<table>
<thead>
<tr>
<th>Key Issues</th>
<th>Recommendations or Suggested Research and Policy Priorities (Examples and Initiatives Underway)</th>
</tr>
</thead>
</table>
| Advocate for trials in children | • Campaign for children’s participation in trials, using both ethical and economic justification strategies  
  • Analyze health, epidemiologic, and registries data to inform clinical research needs in children  
  • Align the academic, pharmaceutical sponsor, and policy maker’s agendas to prioritize research in response to child health needs through a multinational consortium  
  • Invest and direct prioritization of trials in children from government  
  • Incentivize trials of off-patent medicines (eg, priority list of off-patent medicines developed by the US Pediatric Trials Network)  
  • Improve initiatives to study rare diseases (eg, FDA priority review voucher, International Rare Diseases Research Consortium)  
  • Encourage philanthropic approaches to conduct high-quality research that changes pediatric labeling  
  • Provide better incentives to encourage clinicians’ participation and enthusiasm |
| Strengthen and develop pediatric trial capacity | • Invest in sustainable centralized trial infrastructure, including dedicated management team of a statistician, research nurse, data manager, and pharmacist to support investigators  
  • Establish networks with sustainable funding to collaborate and support trials in children, especially nonindustry-sponsored trials (eg, Medicines for Children Research Network)  
  • Develop standards and guidance on trial design, conduct, and reporting (eg, valid child health outcomes including child-reported outcomes), explicit definitions (eg, minimal risk, adequate sample size), selection of appropriate comparators, reduction of risk of bias (eg, StaR Child Health, Toronto Outcomes Research in Child Health, Enhancing Research Impact in Child Health, Standard Protocol Items for Randomized Trials–Children, Consolidated Standards of Reporting Trials–Children)  
  • Invest in training and standards for data monitoring committees  
  • Implement programs to audit the conduct of trials at sites  
  • Increase research and development investment to encourage trials in LMICs  
  • Build expertise in LMICs by encouraging research collaborations with investigators from high-income countries  
  • Share trial resources of high-income countries for adaptation to local contexts  
  • Advocate for philanthropic investment to build local trial and health care capacity  
  • Encourage operational research (advanced analytical techniques) on improving practices in these difficult contexts  
  • Invest in prevention and curative health services and research to address some of the neglected health burdens  
  • Promote health and education of the community  
  • Encourage sponsor provision of ongoing supportive medical care posttrial and ancillary care to siblings and other family members |
| Mitigate disparities in LMICs | • Adopt pediatric regulations and incentives globally to encourage pharmaceutical industry to trial medicines in children (eg, the US and European Union regulations)  
  • Improve pediatric regulations and incentives to encourage trials in child-specific diseases, including trials of off-patent medicines (eg, Pediatric Trials Network initiatives)  
  • Establish a global-level pediatric medicines regulatory framework under the leadership of the World Health Organization to regulate and harmonize country of trials conduct, transferability of results, availability of medicines, and improve medicine access and reimbursement strategies (eg, TransCelerate initiative)  
  • Create an international network of regulators to manage the regulatory requirements and provide support for less-experienced regulators  
  • Develop a log of trials to prevent duplication and identify gaps (eg, enprEMA, Medicines for Children Research Network, Global Research in Pediatrics initiatives)  
  • Provide better incentives to encourage clinicians’ participation and enthusiasm |
| Enhance regulatory frameworks | • Encourage multicenter collaborative trials to reduce research waste  
  • Develop good referral network among pediatric clinicians to enhance recruitment  
  • Conduct trials of more economically feasible treatment modalities for LMICs, where appropriate  
  • Promote ongoing supplies of successful interventions to participants, while expediting regulatory approvals of pediatric labeling  
  • Invest in developing formulation of medicines appropriate for children in all income regions (eg, suspensions)  
  • Review medicine reimbursement strategies to improve access of medicines addressing pediatric needs  
  • Embed clinical research as part of routine clinical care and in disease-specific registries (eg, Key Performance Indicator of organization to involve children in trials)  
  • Invest in a governance framework of registries to address the evidence gaps in children and monitor expedient availability of trial results  
  • Invest in funding for translation and implementation of effective interventions  
  • Design protocols around pediatric needs with consultation and partnering with the academic, practicing community, and families (eg, United Kingdom, Young Peoples Advisory Group, International Children’s Advisory Network)  
  • Develop guidelines to engage children and parents in setting priorities, designing and conducting trials (eg, feasibility and selection of patient-reported outcomes, review of consent forms, scheduling appointments)  
  • Adopt child-appropriate strategies such as reducing pain and discomfort of painful invasive procedures (eg, distraction techniques such as DVDs)  
  • Develop alternative robust strategies to monitor compliance in children (eg, devices that can monitor use)  
  • Further research to develop guidelines on adequate pediatric decision-making (assent)  
  • Further research regarding payment to children for participating in optional research that does not offer direct benefit for the child  
  • Provide patient-specific results sheet to families and children who participated |
more trials in children to be undertaken, but they contend that inequities and political, regulatory, and resource barriers still exist. Embracing unique pediatric needs and creating a culture of embedding trials as part of routine clinical care are recommended. International collaboration, sustainable pediatric clinical trials infrastructure, development of pediatric trial expertise, and alignment of research to child health care priorities are suggested to encourage more high-quality, appropriate trials that address the health care needs of children globally.

ACKNOWLEDGMENTS

The authors thank the stakeholders who shared their perspectives in the study.

ABBREVIATION

LMICs: low- and middle-income countries

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Researchers', Regulators', and Sponsors' Views on Pediatric Clinical Trials: A Multinational Study
Pathma D. Joseph, Jonathan C. Craig, Allison Tong and Patrina H.Y. Caldwell
Pediatrics 2016;138; DOI: 10.1542/peds.2016-1171 originally published online September 30, 2016;

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Pathma D. Joseph, Jonathan C. Craig, Allison Tong and Patrina H.Y. Caldwell
Pediatrics 2016;138;
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