

Clinical Trials in Global Health 2



Strengthening the paediatric clinical trial ecosystem to better inform policy and programmes

James A Berkley, Judd L Walson, Glenda Gray, Fiona Russell, Zulfiqar Bhutta, Per Ashorn, Shane A Norris, Ebunoluwa A Adejuyigbe, Rebecca Grais, Bernhards Ogutu, Jun Zhang, Guillermo L Chantada, Sharon Nachman, Edward Kija, Fyezah Jehan, Carlo Giaquinto, Nigel C Rollins*, Martina Penazzato*



The first WHO Global Clinical Trials Forum was convened in November, 2023 to develop a shared vision of an effective global clinical trial infrastructure. The Paediatric Clinical Trials Working Group was formed to provide perspectives, identify challenges, and propose solutions to strengthen the paediatric clinical trials ecosystem. Participants represented paediatric disciplines, including infectious diseases, nutrition, neonatology, pharmacology, oncology, neurodevelopment, public health, and policy. Childhood diseases have profound lifelong effects on health, livelihoods, and societies. Investment in early childhood results in highly cost-effective changes to lifelong health, productivity, and human capital returns. Yet, there remain substantial gaps in knowledge on the efficacy and safety of many paediatric interventions, which represents a failure to establish shared priorities and alignment across governments, researchers, communities, and funders. Children are frequently marginalised from clinical trials, which is an issue of equity. Challenges include mismatched priorities and funding, risk adversity, poor design, power imbalances, and inadequate infrastructure. Solutions include aligning on and tracking local and global child health priorities against funding and supporting regional consortia to pool resources for larger, more consequential trials. We propose actions and responsibilities for global, regional, and national institutions for prioritisation, coordination, enabling paediatric trials consortia, funding, and tracking progress.

Introduction

Global child survival has improved considerably over the past four decades. However, progress is not evenly distributed, and declining mortality rates for those younger than 5 years have levelled off since 2015 despite increased access to evidence-based interventions (figure 1). Neonatal mortality has declined more slowly and now makes up half of all mortality for those younger than 5 years. Global financing for child health interventions, such as vaccinations, nutritional support, and universal health coverage has shrunk in the wake of the COVID-19 pandemic, the global cost of living crisis, and competing priorities of multiple ongoing humanitarian emergencies. As such, the UN Secretary-General António Guterres suggested that the world is “woefully off-track” to achieve the Sustainable Development Goals by the 2030 deadline.²

Neonates, infants, children, and adolescents differ from each other and from adults with different physiologies manifested in the pace and trajectories of immune, brain, and other organ growth and development. Hence, the causes, burden, and course of disease differ between these age groups. The consequences of disease, impaired growth, malnutrition, and adverse development during childhood have profound lifelong effects on future health, livelihoods, and societies,³ further exacerbating inequities.^{4,5}

James Heckman, Nobel prize winner for economics, showed decades ago that investments to give children the best start in life to reach their full developmental potential are greatly outweighed by the productivity and human capital returns across the life course, and of greatest

relevance to the world’s lowest-income nations.⁶ Although this return on investment is clear, there is a cognitive dissonance between the acknowledged importance of children for our shared future and the actual attention, investment, and priority given to children, including in research. Since the start of the Millennium Development Goals, the importance of evidence-informed strategies has been highlighted, for example, in the Bellagio Child Survival *Lancet* series paper in 2003.⁷ However, the full potential of these approaches has not yet been achieved.^{8,9}

High-quality controlled clinical trials, defined as prospectively assigning individuals to one or more interventions to evaluate health outcomes, are key tools to generate robust evidence to drive policy, guidelines, investment, and practice. Of all trials registered on the International Clinical Trials Registry Platform between 2000 and 2023, only 10% included children. Among those that were uniquely paediatric trials, only 9% were conducted in low-income and middle-income countries (LMICs), 1% in low-income countries (figures 2, 3), and few focused on the highest mortality period at birth and in infancy. These simple statistics show a stark mismatch between disease burden and research activity.⁹ Consequently, for the next 5–10 years, as clinical trials are reviewed to inform updated guidelines, we will continue to face substantial gaps in knowledge on the efficacy and safety of commonly used interventions, including antibiotics, fluids, nutritional products, oxygen, and vaccines. Malnutrition is a major contribution to up to half of childhood mortality, but there is a dearth of evidence on the pathophysiological mechanisms and

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*Joint last authors

Clinical Research Department, KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya (Prof J A Berkley FMedSci); Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK (Prof J A Berkley); Department of International Health and Medicine (Infectious Disease) and Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA (Prof J L Walson MD); South African Medical Research Council, Tygerberg, Cape Town, South Africa (Prof G Gray FCPaed); Murdoch Children’s Research Institute, University of Melbourne, Melbourne, VIC, Australia (Prof F Russell PhD); Institute for Global Health and Development (Prof Z Bhutta PhD), and Department of Paediatrics and Child Health (Prof F Jehan FCPS), The Aga Khan University, Karachi, Pakistan; Centre for Global Child Health, Hospital for Sick Children, Toronto, ON, Canada (Prof Z Bhutta); Center for Child, Adolescent and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland (Prof P Ashorn PhD); Department of Paediatrics, Tampere University Hospital, Tampere, Finland (Prof P Ashorn); SAMRC Developmental Pathways for Health Research Unit, University of the Witwatersrand, Johannesburg, South Africa

Key messages

How do we measure progress?

- Goals and metrics are needed to track progress—with funding to do so—including annual reporting as a specified responsibility
- Regular reports on trials involving children as a proportion of all registered trials from international and regional bodies, such as WHO, are required
- Reports on the proportion of registered and published paediatric trials meeting maturity framework criteria, including specific assessment for paediatric clinical trials capacity from international and regional bodies, such as WHO central and regional offices, are needed
- Published child health research priorities should be agreed among a broad set of stakeholders (ie, by national governments and regional bodies, including WHO and UNICEF regional offices)
- Paediatric trial ethics and practice standards should be set out in published child health-specific good clinical practice and research ethics training packages that are endorsed and used (ie, by WHO, national research institutions, or national ethical review boards)
- The presence of funded regional consortia within high burden areas with demonstrable capacity are needed to address priority questions (ie, from funders and national and regional bodies, including WHO regional offices)
- Regular reports of government co-funding and ongoing research in relation to national priorities (ie, from national governments, research institutions, and ethical review boards) should be provided
- Priority should be given to create leadership roles (besides first and last authorships) in the highest burden regions (ie, by national research institutions and funders)
- Annual reports of total funding for paediatric trials should be aligned with national and regional research priorities (ie, by funders)
- Funding calls should be made for child health research priority settings and quality criteria should be defined by funders

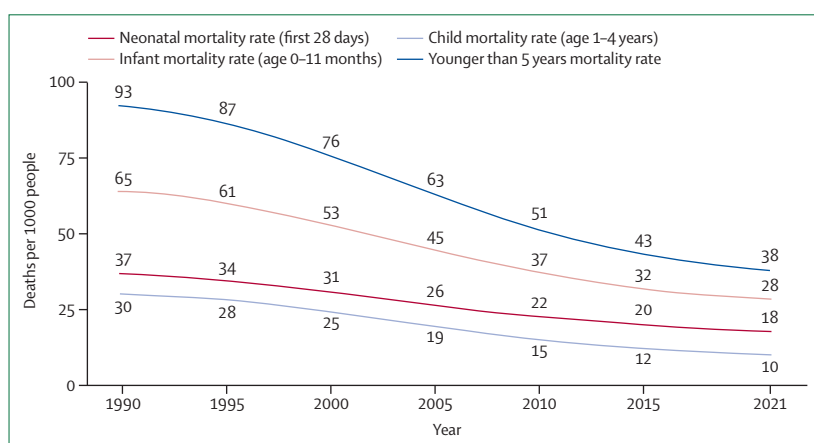


Figure 1: Global trend in neonatal and childhood deaths from 1990 to 2021

Figure was created based on WHO and UNICEF data.¹

(Prof S A Norris PhD); School of Human Development and Health, University of Southampton, Southampton, UK (Prof S A Norris); Department of Paediatrics, Obafemi Awolowo University, Ile-Ife, Osun, Nigeria (E A Adejuyigbe PhD); Pasteur Network, Paris, France

clinical research and trials on prevention and treatment for these children.¹¹

We are similarly disadvantaged by inadequate evidence on haemoglobinopathies, cancer, developmental and behavioural conditions, and rare and orphan diseases; on diagnostic tools; on preventive interventions; and on how care should be delivered, such as for newborns or risk-based approaches. Consequently, infant and child survival,

growth, and development will suffer. For the global child health research community, these knowledge gaps represent a failure to establish shared priorities that reflect disease burdens and efficiently coordinate and align across governments, communities, international agencies, researchers, and funders. Altering the status quo will require considerable redirection in multiple sectors.

Some barriers to high-quality research are common to all health topics, although disproportionately affecting low-income and lower-middle-income countries. These barriers include unstable or poorly targeted funding, resource and training limitations, increased burden of health care at the expense of clinical research, the absence of public trust of science, and power imbalances between low-income and high-income settings. Barriers specific to research involving children include complexity due to specific ethical challenges arising from their susceptibility and lack of agency leading to risk aversion and unnecessarily restrictive ethics or regulatory oversight; a higher prevalence of acute versus chronic illnesses; and insufficient previous data on safety, dosing, and metabolism, thus a lack of suitable paediatric drug formulations.¹² Collectively, these barriers result in greater time and costs of paediatric research, yet children have the right to be included in research that will generate evidence and improve their outcomes.

There are important examples where the paediatric research and policy communities have come together to generate substantial practice changes. With malaria, for example, international and academic-public-private partnership efforts have resulted in long-term scientific and funding commitment to create and evaluate effective vaccines and test therapeutics and chemoprophylaxis for children, infants, and pregnant women. With HIV, antiretrovirals to prevent vertical transmission, clarity on breastfeeding, co-trimoxazole prophylaxis, and timely antiretroviral therapy, including novel and effective generic paediatric formulations, have led to substantial reductions in the rate of HIV vertical transmission and mortality. Encouragingly, in the last 20 years, paediatric trials have started to broaden and include a focus on parental support, nutrition, development, and adolescent sexual and reproductive health.¹³

Notwithstanding these successes, a change of course is urgently needed, including innovative partnerships and multidisciplinary and coordinated approaches to effectively tackle ongoing major child health problems and emerging threats. This approach should encompass prioritisation and the specific research questions being asked, the ethical and regulatory frameworks for paediatric trials, the ability of trials to influence policy and guidelines and to register new drugs, adequate sustained funding commensurate with generating definitive evidence to inform policy, and adequate local research capacity and leadership in the highest disease burden settings, including in the context of humanitarian settings and

polycrises. There is a need for coordination and alignment cuts across all these domains.

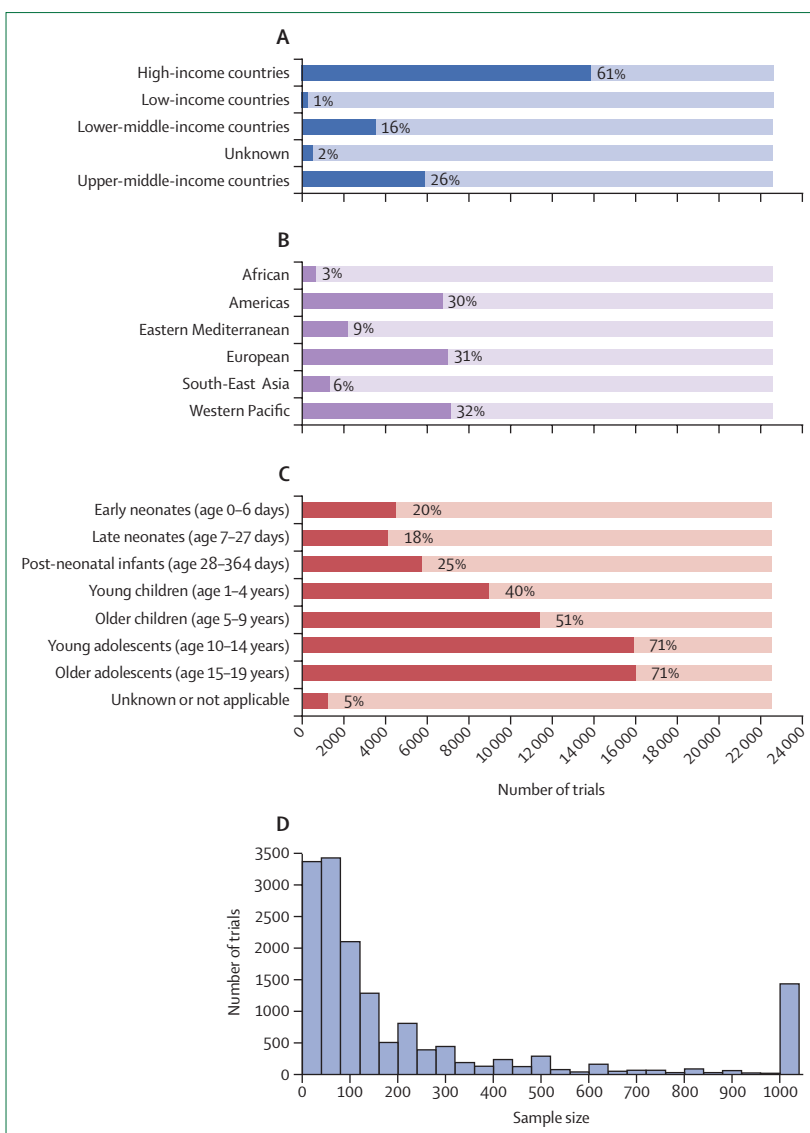
Ethics and regulation of paediatric trials

The under-representation of children in research reflects perspectives among funders, regulatory agencies, pharmaceutical companies, and some researchers that are often incorrect and fundamentally unjust, including excessive risk adversity, short-sighted perceptions of children's value in society, and failure to recognise the childhood foundations of healthy lifelong trajectories. The absence of effective and efficient regulatory pathways shifts risks to clinicians who, in the absence of robust guidance and policies, are often obliged to provide interventions off-label outside the controlled context of clinical trials.

Although national regulatory bodies are ultimately responsible for ensuring safety, to accelerate evidence generation, improved efficiency in national and regional regulatory processes is needed by implementing collaborative approaches and reliance mechanisms. Agreement on local and regional health priorities, including with communities, to link health issues with equity is anticipated to ease discussions between the diverse stakeholders in paediatric trials.¹⁴ Developing systems for expanding research ethics literacy, consensus, trust, and awareness of paediatric research and the need to improve child health include two-way dialogue with parents, communities, clinicians, and national governments. Implementing regional and national action plans for training and accreditation—and paediatric-specific versions of good clinical practice—research ethics training made mandatory for staff working on research involving children will help ensure better standards.

In some settings, it is essential to clarify the role of children of different ages in assent and consent processes, including emancipated minors, such as adolescent girls with a child of their own. It is also important to establish awareness among patients, clinicians, researchers, and regulatory boards on the physiological effects of blood volumes typically taken in clinical trials and the rationale for current recommendations. Furthermore, it is important to have agreed collaborative policies on standards of care in paediatric trials, which provide protection for trial participants while ensuring results are applicable within the realistic level of care that is typically available.

Ethics and regulatory bodies require adequate funding and skills, including specific ethics of paediatric research, established mechanisms for protecting children in trials, and access to statistical expertise in innovative trial designs and biostatistics to avoid the approval of poorly designed or underpowered studies. Establishing national and regional paediatric research priorities will enable ethics and regulatory bodies to provide reduced-cost and expedited reviews of trials that directly address agreed national and regional priority questions. Where phase 3



Fundación Pérez-Scremini,
Montevideo, Uruguay
(Prof G L Chantada); Division of
Pediatric Infectious Disease,
Renaissance School of
Medicine, SUNY Stony Brook,
Stony Brook, NY, USA
(Prof S Nachman MD);
Department of Paediatrics and
Child Health, Muhimbili
University of Health and Allied
Sciences, Dar es Salaam,
Tanzania (E Kija MD);
Department of Woman's and
Child's Health, University of
Padova, Padova, Italy
(Prof C Giaquinto PhD);
Department of Maternal,
Newborn, Child and Adolescent
Health and Ageing
(N C Rollins MD), and
Department of Research for
Health, Science Division
(M Penazzato PhD), WHO,
Geneva, Switzerland

Correspondence to:
Prof James A Berkley, Clinical
Research Department, KEMRI/
Wellcome Trust Research
Programme, Kilifi, Kenya
jberkley@kemri-wellcome.org

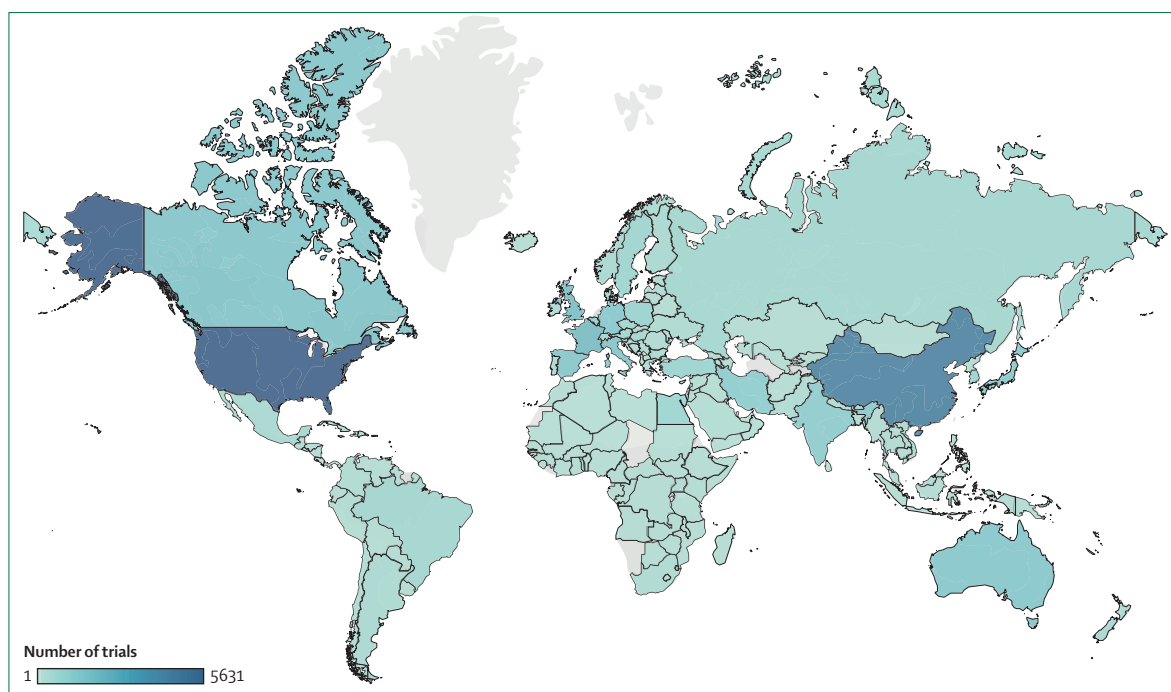


Figure 3: Registered paediatric clinical trials by country (2020–23)

Trials by country, enrolling children, that are registered on the International Clinical Trials Registry Platform¹⁰ between 2020 and 2023.

continues to raise controversy.¹⁴ A common concern is not providing active treatment to an unwell child. Here, clarity and consensus about the current standard of care is needed between investigators, ethical review boards, and regulatory bodies. Where there is no drug with established efficacy, a placebo can be considered. However, there can be difficulties where there is established use in children despite the absence of trial evidence. For example, the use of paracetamol in febrile children is well established. In this situation where there is biological plausibility that a commonly used agent could be harmful, we believe the use of placebos to improve the paediatric evidence base can be warranted. An example is the use of paracetamol in malaria.¹⁷ Safety is paramount in this context and close monitoring or other proactive trial design features are usually needed. A further concern around the use of placebos is the potential for placebo responses to differ between younger and older children, adolescents, and adults.¹⁸

The views of parents are important and less often considered and could vary between and within populations. There is a lack of published data on this topic from high-income countries¹⁹ and more studies in LMICs are needed. Parents should be provided with adequate information and rationale that a trial is using a placebo before seeking consent, allowing them to decline. Reporting of trials involving placebos or standard of care is variable in quality, and new guidance—ie, SPIRIT-Children, and CONSORT-Children—has recently been developed.²⁰

Enabling the paediatric research environment

In many low-resource settings where human resources are restricted and health systems are fragile, the pressures of service delivery limit the opportunity for high-quality research. It is however, precisely in such LMIC settings that the need for quality research is paramount, as suggested by former Indian Prime Minister Jawaharlal Nehru: “It is science alone that can solve the problems of hunger and poverty, of insanitation and literacy, of superstition and deadening custom and tradition, of vast resources running to waste, of a rich country inhabited by starving people...The future belongs to science and to those who make friends with science.”²¹

Governments and funders recognise that research is required to improve child health outcomes. However, there is a disconnect between this acknowledgment and health system learning approaches that ensure that the new data generated from research are translated into policy and practice. This translation can happen via partnerships between researchers, policy makers, and national programmes,^{8,22,23} although it requires investment to develop trained professionals with skills in trials, data science, epidemiology, clinical and public health, social sciences, and knowledge translation strategies.

To elevate paediatric research and strengthen capacity, we believe there is a need to establish and fund regional consortia and networks around priority questions. This process requires bringing together individuals, regional and local centres of excellence, and for the community to share ideas, develop hypotheses, and provide access to

essential knowledge for paediatric research conduct (ie, statistics and trial design, ethics, high-quality multicentre trial conduct, monitoring, research management, communication, and dissemination expertise). Furthermore, it is essential to develop capability in more complex and implementation science trial design and methodologies and their use for paediatric trials.

Long-term, always on, always busy⁸ paediatric trial consortia provide sufficient critical mass for emerging investigators to be continually exposed to high-quality science, mentorship, and constructive feedback at the development, proposal, and protocol stages. Consortia also provide geographical representativeness and understanding of local health systems and how interventions can be implemented within health programmes. In some cases, in the lead-up to a trial, a consortium needs to collect harmonised data on the presentation and burden of disease and treatment.²⁴ Research should also be considered essential by clinical paediatrics and subspecialty hospital departments' senior leadership to avoid separation between clinical service and academic paediatricians.

Achieving quality in paediatric trials

Quality issues in trials are a major barrier to progress. Paediatric trials are often too small to reach statistically precise conclusions, commonly have short follow-up, or have design features that are irreproducible to lead to future interventions.²⁵ Less than 40% of clinical trials in children from 1996 to 2002 had a sample size of more than 100 (figure 2). High rates of loss to follow-up are common, resulting in considerable inclusion bias that is often not addressed in analysis since participants that are most difficult to trace commonly have had poorer outcomes than those retained.²⁶ Paediatric loss to follow-up might be more driven by investigator expectations rather than the actual potential for participant tracing. Research on the abandonment of treatment (which is a major event in malnutrition) in chronic diseases (eg, HIV or paediatric tumours) and its clinical and socioeconomic determinants is crucial.

To avoid wastage of resources, researchers, regulators, and funders should question whether the proposed work provides sufficient information value. Funders should ask themselves how they can support robust designs, appropriately skilled staffing, staff and participant retention, and community engagement. A shared vision between funders, researchers, communities, and other stakeholders of where the trial lies within a broader (funded) plan or sequence of trials, rather than regarding each trial as an isolated event, can help avoid wastage. For preparedness in meeting emerging threats, it would be ideal to make available teams that are ready and preprepared trials to be executed at short notice.

Efficiency might be increased by adaptive designs, such as multi-comparison or multi-stage trials with appropriate statistical methods. These designs can be especially

helpful when there is more than one potential treatment option. Other efficient new trial designs are based on generating a ranking efficacy of several potential interventions rather than a traditional one-to-one or one-to-many comparison.²⁷ Such approaches could be valuable where there are doubts over the efficacy of the current standard of care, or when the standard of care stems from high-income settings that might not be applicable or have the same efficacy in low-resource settings. Additional innovative methods include nesting regulatory trials into strategic trials, using real-world data or synthetic data in simulated trials to complement randomised trials,¹⁶ and family-centred trial designs going beyond only a child's clinical needs.²⁸

Trial quality might also be augmented by developing and implementing training with certification for paediatric research manuscript reviewers to harmonise standards in recognising high-quality trials and highlighting inferior quality, such as good clinical practice and research ethics training for trialists. The annual corpus of published paediatric trials should be assessed using trial maturity framework criteria.^{29,30}

Funding paediatric trials

There is no doubt that funding for paediatric trials is far lower than the proportional burden of mortality, lifelong consequences of childhood illness, and loss of economic potential. Funding-related challenges identified by the Paediatric Clinical Trials Working Group include difficulty in retaining skilled staff between funding cycles, a lack of longer-term commitment, shifting priorities, the burden of reporting, and excessive paperwork at the initial proposal stage that could be replaced with a more straightforward concept statement. Funders should consider funding consortia of excellence rather than only centres or individuals of excellence. Enabling the intellectual centre of gravity in high-burden, low-resource regions will help overcome resource, skill, and power inequalities. While few will disagree with the principle, change requires commitment by funders to meaningfully build capacity alongside the research and support job security for skilled staff, enabling institutions to bridge key staff between grants and allowing local career development opportunities. Mobilising core government funding is also crucial for ensuring local ownership, addressing priorities, and translation into policy via a learning health systems approach.²³ Funding of potential trials that appear as simple technical solutions should be regarded cautiously and matched by funding research to address underlying problems driving poor child health.

Redirection is needed away from smaller inconsequential trials and those outside the context of a development pathway. At earlier stages, smaller proof-of-principle, safety, dose finding, and proxy outcome trials are necessary and need to be well designed. The predominance of small trials in child health partly highlights that many promising ideas prove unsuccessful,

but also design or funding limitations, or that smaller investigator-led trials lack a plan for further developing the results. It is essential that early-phase trials are funded with commitment to support the next phase should they prove successful.

Smaller funders might consider establishing collaborations with larger funders to provide proportionately matched funding to support trials in priority areas. The private sector could also contribute to priority research via financial and technical support for global consortia and access arrangements. With appropriate due diligence, coordinated funding could be committed to a programme of work rather than individual trials, as some funders are already doing.

Prioritisation of paediatric trials

Currently, paediatric trials are prioritised by different stakeholders in various ways. International academic and policy maker groups commonly use approaches such as the Child Health and Nutrition Research Initiative.³¹ However, the voices of communities, national governments, local stakeholders, and funders are frequently under-represented in such exercises. Emerging threats, climate change, antimicrobial resistance, and the opportunities offered by scientific discoveries, such as from omics technology, are increasingly funded. However, research to improve healthy practices, such as breastfeeding or parenting for early childhood development, or delivery strategy, such as towards more child-centred care, is less commonly undertaken. Paradoxically, governments and communities in low-resource settings, typically have a more restricted voice than external donors and researchers in shaping which child health topic, strategy, or intervention proposals are developed or funded. As a result, national priorities and researchers' specific areas of expertise are commonly adapted to fit the funder's priorities, rather than vice versa.

An improved evidence base and research prioritisation requires data on the burden of disease, short-term and long-term outcomes, and on the population groups most affected. Global-scale modelling typically lacks local resolution and might be based on imprecise or inaccurate health data and interpolated estimates. However, local capacity for aetiological surveillance is often insufficient in high child mortality settings, and reliably estimating deaths attributable to a pathogen is challenging in the best of circumstances, and could vary by geographical setting.

A crucial step for trial prioritisation is funding calls for regional and national institutions to establish disease burdens and work with governments and other stakeholders to prioritise questions that trials have to address in the next 5–10 years. Such priorities should be communicated to funders and published as position statements, which researchers and applicants for funding or ethical approval can refer to. However, it is also important that shared prioritisation does not inhibit

creative and disruptive thinking. Research on interventions that are practical now within current health infrastructure can be aligned to high-quality evidence generation over a defined time period.

Coordination

Going forward, success will require funding and willingness to pursue shared goals and to achieve this, vastly increased engagement, coordination, and alignment between researchers in different disciplines, communities, governments, international agencies, and funders is needed. Our vision is that such alignment includes at a national level, consensus between government, regulators, and investigators on priority research questions and gaps in guidelines that are in urgent need of trials for their population. Internationally, alignment would be shown by collaborative networks of investigators tackling shared questions on a scale large enough to generate robust, generalisable evidence, ethical review boards cooperating and delegating approval to each other, and funders responding to these regional priorities and potentially including co-funding with governments.

Addressing power imbalances, particularly those stemming from donor-driven agendas and the predominance of researchers from the Global North (ie, higher-income countries), is crucial. Enhancing, and monitoring the involvement of community members, patient advocacy groups, clinicians, and national governments is essential. The voices of patients and communities were not represented in the Paediatric Working Group. Although efforts in this direction are under way,^{32,33} there is a considerable need to reinforce research literacy within communities and clinical organisations, and for governments to facilitate connections and create wider open public discussions on issues, such as ethics in child health research.

Clarity over responsibilities is essential. WHO and other international and regional agencies (eg, Africa Centres for Disease Control and Prevention) in partnership with governments and national research institutions should play a greater role in coordination to convene stakeholders and mobilise funding in the public and private sectors for paediatric research prioritisation. This coordination involves mapping child disease burdens and gaps in policies and services. These agencies should assist the development of consortia, mechanisms to expand reach and enhance quality, and help leverage funding. There is a need to facilitate and publish online national, regional, and global directories of upcoming and ongoing child health trials and national governments and research institutions should map these against their priorities annually, with published reports. Lastly, a key coordination role of international, regional, and national bodies is to translate research into policy and guidelines more efficiently. Web-based technology now enables so-called living guidelines rather than wholesale guideline revisions on a 5-year to 10-year timescale.

	Rationale	Outcome
WHO convened or endorsed process to facilitate coordination and alignment between key stakeholders (ie, researchers, community, national authorities, ethics and regulatory bodies, and funders)	Continued high mortality in low-resource settings; continued major evidence gaps to improve interventions and their delivery; failure to conduct high-quality research in low-resource settings	Coordinated process leading to a substantial investment over a defined time horizon to a restricted set of research priorities that can address gaps in survival, health, and development via implementation of research at country level
Enhancing regulation and ethics in paediatric trials	Ongoing risk adversity; lack of recognition of harms to children when trials in crucial health topics are not conducted; limited paediatric ethics literacy among institutional review boards, policy makers, and the community	Published regional and national action plans for paediatric ethics training and accreditation; paediatric-specific versions of good clinical practice and research ethics training providing a common set of standards; annual publication of the number and proportion of trials being undertaken in children at national, regional, and global levels
Prioritisation process and agreement on five major evidence gaps with broad set of stakeholders (ie, community, national authorities, researchers, and programme implementers, etc)	Child health needs are not currently matched by evidence from clinical trials; priorities are often driven by funders and researchers from higher-income countries; an absence of mechanisms and funding to establish local priorities	Five research priorities identified with potential for high impact on survival and improved health and development among infants, children, and adolescents living in settings with low resources or who have polycrises; published mechanisms for balancing different regional and global priorities
Establish research consortia and collaborations to tackle priority research questions, including capacity development with a coordinated and high-quality approach	Skill and power inequalities within research communities (ie, higher-income vs lower-income countries); priority research not implemented; research capacity for future	Dedicated research consortia that are funded and can ensure high-quality evidence generated in a timely manner
Funders to commit to mechanisms to support coordination, collaboration, and capacity, including pooled resources with accountability	Fragmentation of resources and research agenda without relevant inputs	Pooled funding from multiple stakeholders (ie, public and private sector) to support prioritised research; ensuring community engagement and capacity building within budgets; supporting staff career development and staff retention; not only providing per participant costs to research institutions in resource poor settings; publishing as a requirement regardless of trial results
Policies and activities enabling the research environment	Existing or perceived barriers impede the timeliness and quality of priority research, including an absence of a local critical mass of high-quality research, gaps between clinical and academic staff, scarce training opportunities, and the costs and reliability of laboratories, internet, importation, and sample shipment	Alignment of ethical and regulatory principles in support of rapid implementation of prioritised research
Build the environment for knowledge translation to communities and policy, including capacity for future research	To anticipate and accelerate communication of study findings and their implications for policy and practice	Efficient dissemination of study findings and translation into community practice and policy change and practice at global and national levels; government involvement and funding of research; learning health system approaches in knowledge translation; establish capacity incrementally for future research

Table: Priority actions to strengthen the regulatory and academic environment for paediatric trials

Priority actions

The Working Group identified seven priority actions (table). These actions can be achieved with funded annual meetings convened by WHO and its regional offices; engagement with funders, national governments, research institutions, and ethical review boards; template development and create expectations to provide annual online reporting of funding and activity on clinical trials in children in relation to established local priorities.

Conclusion

Strong health, economic, and equity considerations underpin the need for extraordinary commitment, cooperation, investment, quality, and capacity development to create a step-change in interventional research for infants, children, and adolescents. As such, donors and researchers will need to align with the priorities of local communities and national governments with

stronger coordination and clear mechanisms and responsibilities for evidence-based research prioritisation. Unprecedented research collaboration with sustained funding in high-burden countries can address barriers to conducting locally conceived and led trials. Substantially raising expectations and performance regarding the quality of all paediatric trials is overdue and we need to strategically rebalance ethical perceptions between the individual risks associated with children participating in research and insufficient paediatric research to optimise care. Children represent our shared futures; unless there is an urgent and deliberate step-change, individuals and countries will continue to fail to reach their health and economic potential.

Contributors

All authors participated in the Paediatric Working Group and inputted ideas before the WHO Global Clinical Trials Forum and contributed to the discussion following the forum. The manuscript was conceived by

MP and NCR. The first draft and subsequent revisions were written by JAB. All authors advised on the content and critically reviewed the manuscript.

Declaration of interests

We declare no competing interests.

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