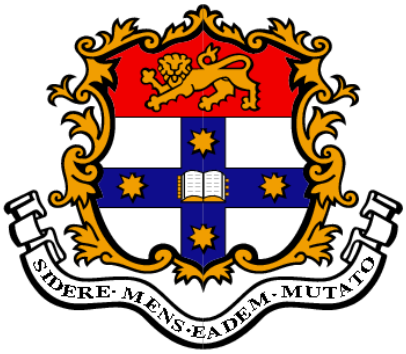
THE UNIVERSITY OF
SYDNEY

Clinical trials in children: Equity, quality and relevance

Destiny Pathma Joseph

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy



Discipline of Paediatrics and Child Health

Faculty of Medicine

University of Sydney

2015

Declaration

This thesis is submitted to the University of Sydney in fulfilment of the requirements for the degree of Doctor of Philosophy.

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Signature: DP Joseph Date: 4 December 2015

Author's Contribution

The work presented in this thesis has been carried out by the author under the supervision of Associate Professor Patrina HY Caldwell, Discipline of Paediatrics and Child Health, University of Sydney and Professor Jonathan C Craig, School of Public Health, University of Sydney.

The author planned the research, designed the studies, obtained ethics approval, collected, managed and analysed the data, interpreted results, drafted and revised the manuscripts for submission to peer-reviewed journals, and wrote and compiled this thesis.

Ethical clearance

The study presented in Chapter 5 was approved by the Human Research Ethics Committees at The University of Sydney, The Royal Children's Hospital Melbourne, Monash Children's Hospital, Women's and Children's Health Network, and The Princess Margaret Hospital.

The study presented in Chapter 6 was approved by the Human Research Ethics Committee at The University of Sydney.

All study participants gave written informed consent for participation in the study.

Abstract

Background

Safety and efficacy data on many medicines used in children are surprisingly scarce. As a result, children are sometimes given ineffective medicines or medicines with unknown harmful side effects. Better and more relevant clinical trials in children are needed to increase our knowledge of the effects of medicines and to prevent the delayed or non-use of beneficial therapies. Clinical trials provide reliable evidence of treatment effects because they perform controlled testing of interventions on human subjects. Trials in children are more challenging to conduct than trials in adults because of the paucity of funding, unique needs of children and particular ethical and safety concerns. Although current initiatives and regulations are improving the number and quality of trials in children, there are still deficiencies that need to be addressed to radically accelerate equitable access to evidence-based therapies in children.

This thesis is one of the first major attempts to comprehensively look at the equity, quality and relevance of clinical trials in children to inform better evidence-based child healthcare and outcomes worldwide. There is a growing recognition that more, better, and more relevant trials need to be conducted in children to drive improvements in child health. To enhance treatment, healthcare and outcomes in children requires us to understand the current context of trials in children, the challenges, disparities and strategies that could inform improvements. We hypothesised that there may be a poor match between the health problems that children face and the trials that are being conducted. Clinical trials are necessary to address unmet therapeutic needs and the disease burden of children globally. However, few trials are conducted in the LMICs where the majority of the global burden of disease resides. We, thus aimed to describe stakeholder beliefs and experiences of

conducting trials in children in LMICs to inform strategies for improving the number and relevance of trials in LMICs.

Empiric studies of published trials involving children have shown methodological flaws and high risk of bias but it is unclear if this reflects editorial processes or true problems in design and conduct. We aimed to ascertain the completeness of the reporting of key domains in the conduct of clinical trials involving children by evaluating the protocols of pharmacological interventions for trials submitted to the Human Research Ethics Committees (HRECs) of Children's Hospitals in Australia. 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. We conducted a study to describe the attitudes and opinions of stakeholders towards trials in children, to inform additional strategies to promote more high-quality, relevant trials in children across the globe.

Methods

A number of different methods were used which best suited the thesis research questions. All trials on the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) registered from 2005 to 2013 were reviewed. The disease-specific focus of registered clinical trials for children by income region was compared to the global burden of disease for 2011 using WHO disability-adjusted life-year (DALY) data. We conducted a systematic review of qualitative studies of stakeholders' perspectives on conducting clinical trials among children in LMICs to inform strategies for more, better trials relevant to child health in LMICs. In the study checking for completion of the trial protocols, Ethics Offices in all Australian paediatric hospitals were invited to participate. De-identified trial protocols submitted for review in 2012 were evaluated using checklists based on CONSORT (CONsolidated Standards of Reporting Trials), the Cochrane risk of bias tool and Good

Clinical Practice guidelines. The international study of key informant semi-structured interviews were conducted with stakeholders (researchers, regulators and sponsors) purposively sampled from LMICs and high-income countries. The transcripts were thematically analysed.

Findings

The analyses of the trials on the WHO ICTRP showed that children account for 25% of the global disease burden, but represent only 15% (29 899/203 726) of registered trials. Although the number of trials in children registered annually has increased over time (from 3174 in 2005 to 3392 in 2013), the proportion of trials involving children has decreased (from 18% to 13%). Despite 98% of the paediatric illness burden being in LMIC, only 22% of all trials in child health are conducted in those countries. There was moderate correlation between the number of trials and the burden of each disease within each region (Spearman's correlation r=0.6, P=0.007 and r=0.55, P=0.015 in low-middle and high-income regions, respectively). There were mismatches of trials focus compared with disease burden. For example, respiratory diseases and neoplasms were over-represented and congenital and neonatal conditions were under-represented.

The analyses of registered trials identified the inequities of trials in children. This was particularly prevalent in LMICs and we explored the contributory factors further by conducting a systematic review of stakeholder's views of trials in children in LMICs. In this systematic review, 39 studies involving 3110 participants (children [n=290], parents or caregivers [n=1609], community representatives [n=621], clinical or research team [n=376], regulators [n=18] and sponsors [n=15]) across 22 countries were included. We identified five themes: *centrality of community engagement* (mobilising community, representatives pivotal role, managing expectations, retaining involvement); *cognisance of vulnerability and*

poverty (therapeutic opportunity, medical mistrust); *contending with power differentials* (exploitation, stigmatisation, disempowerment); *translating to local context* (cultural beliefs, impoverishment constraints, ethical pluralism) and *advocating fair distribution of benefits* (healthcare, sponsor obligation, collateral community benefits).

Our narrative review of the literature on clinical trials in children showed that the study design of trials in children is complex and the protocol of trials therefore requires careful planning. In our assessment of completion of scientific components of paediatric trial protocols, four hospitals participated and 69 trials were included. Four of 8 hospitals agreed to participate and 69 protocols were analysed. The domains most frequently reported were clustered around the background and trial plan (planned interventions for each group (99%), specific objectives (97%), and scientific background (96%)). Domains that were reported least frequently were clustered around the statistical analysis plan (66%), the justification for a new trial based upon a systematic review of the published literature (48%), and child-specific domains (48%).

The interviews of the multinational stakeholders explored more in-depth the challenges identified in the narrative and systematic reviews, the analysis of registered trials and the completion of reporting domains in paediatric trial protocols. In the interview study, 35 stakeholders from 10 countries participated. We identified five major themes: *addressing pervasive inequities* (paucity of safety and efficacy data, knowledge disparities, volatile environment, double-standards, contextual relevance, market-driven forces, industry sponsorship bias, prohibitive costs); *contending with infrastructural barriers* (resource constraints, dearth of paediatric trial expertise, logistical complexities); *navigating complex ethical and regulatory frameworks* ("draconian" oversight, ambiguous requirements, exploitation, excessive paternalism and unwarranted exclusion, precariousness of coercion

vs. volunteerism); *respecting uniqueness of children* (paediatric research paradigms, child-appropriate approaches, family-centred empowerment); and *driving evidence-based child health* (advocacy, opportunities, treatment access, best practices, research prioritisation).

Conclusions

Overall, children continue to be under-represented in trials, particularly children from LMICs where disease burden is greatest. Trial activity correlates moderately with disease burden among the world's children. Redressing these disparities requires prioritisation of child healthcare needs. Stakeholders believe that conducting trials in children in LMICs is complex due to social disadvantages, economic scarcity, idiosyncratic cultural beliefs and historical disempowerment which contribute to inequity, mistrust and fears of exploitation. They suggested effective community engagement in recruiting, building research capacity and designing trials that are pragmatic, ethical and relevant to the healthcare needs of children in LMICs to help improve equity and health outcomes of this vulnerable population.

The design of trials in children across all income settings could be enhanced. In the study evaluating the completeness of reporting in protocols we found that protocols of clinical trials involving children assessed by Ethics Committees are generally comprehensive, but many key domains in trial design and conduct are not reported. There is widespread recognition of how problems in the design and conduct of clinical trials may lead to misleading conclusions. Stakeholders acknowledged that changes in the regulatory environment have encouraged more trials in children, but they contended that inequities, 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. Increasing international collaboration, establishing sustainable

centralised trials infrastructure, and aligning research to child health priorities were proposed to encourage more high-quality trials that address global child healthcare needs.

Acknowledgements

I give thanks to my Lord Jesus Christ who has given me the grace, strength and joy to embark and complete this enriching PhD journey. This PhD thesis is dedicated to our precious children, the "therapeutic orphans" who deserve better evidence-informed healthcare.

"Lack of research, poor research, and poorly reported research are violations of children's human rights." Richard Horton

Heartfelt thanks to both A/Professor Patrina Caldwell and Professor Jonathan Craig who have shepherded, motivated, and supported my development as a researcher. Patrina, your expertise, commitment and enthusiasm has made this a truly rewarding experience. Jonathan, you empowered me with your excellent research standards, insight and leadership.

I wholeheartedly thank all my friends, colleagues and co-authors. Thanks to my friends at The Centre for Kidney Research for warmly welcoming me into this collegial environment and generously sharing your ideas, wisdom and humour. In particular, I wish to thank A/Professor Allison Tong who introduced me to qualitative research and was ever willing to share her knowledge and resources. The support of my colleagues at The Discipline of Paediatrics and Child Health and The Pharmacy Department at The Children's Hospital at Westmead is greatly appreciated. I acknowledge and thank the co-authors and stakeholder participants for their contributions.

This research was funded by the National Health and Medical Research Postgraduate PhD scholarship.

Thank you to my dear husband, Christopher and my beloved parents for your encouragement and covering me with your love and prayers. Sincere thanks to all my family and friends especially in Australia and South Africa, who have been part of this PhD journey and for spurring me to the finish.

Table of Contents

List of Figures

List of Tables

Publications arising out of this thesis

This thesis is presented for examination as a "Thesis Containing Published Work." Chapter 2 has been published in a peer-reviewed journal, Chapter 4 has been accepted for publication, Chapter 3 has been submitted to a peer-reviewed medical journal and Chapters 5 and 6 are being finalised for submission. The candidate is the principal author of each of these papers.

Chapter 2

Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. *Br J Clin Pharmacol*. 2015;79:357-369.

Chapter 3

Joseph PD, Caldwell PHY, Barnes EH, Craig JC. Disease burden - research match? Registered trials in child health from low-middle and high-income countries. (Submitted and under review).

Chapter 4

Joseph PD, Craig JC, Tong A, Caldwell PHY. Stakeholder Views of Clinical Trials in Low- and Middle-Income Countries: A Systematic Review. *Pediatrics* (accepted November 2015).

Chapter 5

Joseph PD, Caldwell PHY, Barnes EH, Hynes K, Choong C, Turner S, Vosk C, White J, Richichi K, Craig JC. Completeness of Protocols of Clinical Trials in Children Submitted to Ethics Committees. (To be submitted).

Chapter 6

Joseph PD, Craig JC, Tong A, Caldwell PHY. Researchers', regulators' and sponsors' views on trials in children: a multinational study. (To be submitted).

Presentations arising out of this thesis

1. **Joseph DP**, Caldwell PHY and Craig JC. Disease burden - research match? Registered trials in child health from low-middle and high-income countries. Oral presentation. Australian Clinical Trials Alliance (ACTA) 2015 International Clinical Trials Symposium, Sydney, Australia 7-10 October 2015.
2. **Joseph DP,** Caldwell PHY, Tong A, Hanson CS and Craig JC. Stakeholder perspectives on conducting clinical trials in children in low-and middle-income countries: systematic review and thematic synthesis of qualitative research. Moderated oral and poster presentation. Australian Clinical Trials Alliance (ACTA) 2015 International Clinical Trials Symposium, Sydney, Australia 7-10 October 2015.
3. **Joseph DP**, Caldwell PHY, Tong A and Craig JC. Perspectives of professional stakeholders on clinical trials in children: an international, semi-structured interview study. Poster presentation. Australian Clinical Trials Alliance (ACTA) 2015 International Clinical Trials Symposium, Sydney, Australia, 7-10 October 2015.
4. **Joseph DP**, Caldwell PHY. Clinical trials in children in resource-limited countries. Poster presentation. Medicines Management 2014, the 40th Society of Hospital Pharmacists of Australia (SHPA) National Conference, Darwin, Australia, 11-14 September 2014.
5. **Joseph DP**, Caldwell PHY, Tong A and Craig JC. International stakeholder experiences and perspectives of paediatric clinical trials. Poster presentation. Medicines Management 2014, the 40th Society of Hospital Pharmacists of Australia (SHPA) National Conference, Darwin, Australia, 11-14 September 2014.
6. **Joseph DP**, Caldwell PHY, Tong A and Craig JC. Stakeholder experiences and perspectives of clinical trials in children. Oral presentation. Discipline of Paediatrics and Child Health, Annual Post-graduate Seminar, Sydney, Australia, 15 August 2014.

7. **Joseph DP**, Caldwell PHY. The way forward in multi-centre research approval. Oral presentation: 39th Society of Hospital Pharmacists of Australia (SHPA) National Medicine Management Conference, Cairns, Australia, 19-22 September 2013.
8. **Joseph DP**, Caldwell PHY. Paediatric clinical trials in the Australian context. Oral presentation: 39th Society of Hospital Pharmacists of Australia (SHPA) National Medicine Management Conference, Cairns, Australia, 19-22 September 2013.
9. **Joseph DP**, Caldwell PHY and Craig JC. Registered paediatric trials worldwide: frequency, location and focus. Poster presentation. Cochrane Colloquium, Quebec City, Canada, 19-23 September 2013. (Presenter: Patrina HY Caldwell).
10. **Joseph DP**, Caldwell PHY, Tong A and Craig JC. A review of paediatric clinical trials of medicinal products. Poster presentation. International Congress of Pediatrics 2013 (ICP), The 27th Congress of International Pediatric Association, Melbourne, Australia, 24-29 August 2013.
11. **Joseph DP**, Caldwell PHY and Craig JC. Registered paediatric Clinical trials: A global context. Poster presentation. International Congress of Pediatrics 2013 (ICP), The 27th Congress of International Pediatric Association, Melbourne, Australia, 24-29 August 2013.
12. **Joseph DP**, Caldwell PHY and Craig JC. Applications for ethics approval of pharmaceutical trials among paediatric hospitals in Australia. Oral presentation. Discipline of Paediatrics and Child Health, Annual Post-Graduate seminar, Sydney, Australia, 2 August 2013.
13. **Joseph DP**, Caldwell PHY and Craig JC. Paediatric Clinical Trials-Where are we today. Oral presentation. The Children's Hospital at Westmead, Grand Rounds Research Symposium, Sydney, Australia, 23 August 2012.
14. **Joseph DP**, Caldwell PHY and Craig JC. The scope of clinical trials of medicinal products in children. Oral presentation. Discipline of Paediatrics and Child Health, Annual Post-Graduate seminar, Sydney, Australia, 10 August 2012.

15. **Joseph DP**. Paediatric clinical trials - A context and the opportunity for Australia. Oral presentation, invited speaker. Australian Research Collaboration Service (ARCS) Scientific Congress, Sydney, Australia, 6 June 2012.

16. **Joseph DP.** Caldwell PHY and Craig JC. Global Perspective of registered trials in children. Oral presentation. Paediatric Seminar Medicines Management 2011, the 37th Society of Hospital Pharmacists of Australia (SHPA) National Conference, Hobart, Australia,10-13 November 2011.

17. **Joseph DP.** Caldwell PHY and Craig JC. Comparison of disease burden and health priorities in paediatric clinical trials conducted globally. Oral presentation. Discipline of Paediatrics and Child Health, Annual Post-Graduate seminar, Sydney, Australia, 12 August 2011.

List of abbreviations

ADR	Adverse Drug Reaction
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EMA	European Medicines Agency
ENRICH	Enhancing Research Impact in Child Health
EU	European Union
FDA	Food and Drug Administration
GRIP	Global Research in Paediatrics
HREC	Human Research Ethics Committees
ICAN	International Children's Advisory Network
ICTRP	International Clinical Trials Registry Portal
IRB	Institutional Review Board
IRDiRC	International Rare Diseases Research Consortium
LMICs	Low-and middle-income countries
MCRN	Medicines for Children Research Network
MIYCRN	Maternal Infant Youth and Child Research Network
PTN	Pediatric Trial Network
SPIRIT	Standard Protocol Items for Randomized Trials
USA	United States of America
WHO	World Health organisation
YPAG	Young People's Advisory Group

Chapter 1

Introduction and overview of chapters

Chapter 1: Introduction and overview of the thesis

1.1 Background and rationale

Improving child health is a global concern. There are several contributory factors to child mortality including lack of access to healthcare and medicines, multiple social determinants as well as a scarcity of evidence to support safe and effective prescribing. Reliable evidence of treatment effects is essential to inform child healthcare and can be obtained from clinical trials by rigorous controlled testing of interventions. There is a need to evaluate the issues and challenges of performing clinical trials in children to help inform strategies for better evidence-informed care and outcomes in children. Children have unique therapeutic needs as they are developmentally and physiologically different from adults. They can also respond differently to medicines, which have the potential to impact their growth and maturation and affect them psychosocially. Many medicines prescribed for children have not been adequately evaluated for safety, dosing, efficacy and administration [1-3]. This can present challenges with medicine licensing, labelling and access in children. It is often necessary to prescribe medicines off-licence (not licensed with the regulatory authority) and off-label (not a labeled indication), which can risk exposing children to unintended adverse reactions or suboptimal therapies [4, 5]. It is essential for children to participate in clinical trials to enable the development of empirically-verified, age-specific therapies and interventions [6]. Data from trials in children would therefore support licensing, labelling and access of medicines in the paediatric population.

The dearth of paediatric trials denies children equitable access to evidence-based healthcare. This scarcity of appropriate testing of medicines in children is due to multiple factors, which require further in-depth exploration to inform improvements. Paediatric trials have novel

complexities due to the safety concerns of testing medicines in children, ethical considerations such as informed consent, lower prevalence of disease, the need to test different age groups, the possibility of late adverse effects, the requirement for tailored study designs and the need for child-appropriate medicine formulations [4, 7]. Historically, clinical trials have focused on adults where there is a higher burden of illness and greater returns on investment [7]. Fewer trials in children is also related to the lack of economic incentives for the pharmaceutical industry to conduct trials of medicines in children as this market is not likely to compensate for the arduous and expensive drug development phases. Obtaining data on the current status of trials in children in comparison to adults and the paediatric disease burden is useful information for regulators, policy-makers and funding bodies in charge of allocating research funds aligned to health priorities.

About 85% of research is estimated to lead to waste, due to inappropriate research questions, poor study designs and lack of transparency and completeness of reporting and implementation of findings [8]. There are reports that published paediatric trials are judged to be poorly designed with a high risk of bias which could threaten the internal validity of trial results, with possible consequences of harming children and overestimating trial effects [9, 10]. It is also important to ascertain if the weak evidence-base in child healthcare is due to the scarcity of robust safety and efficacy data which can be improved by clinically-relevant trials, or if it is related to the design, conduct and reporting of trials. If it is related to the trial, this will warrant the development of guidance and standards to support the training and education of all paediatric trial stakeholders. To increase the value of research and reduce research waste, new interventions should be of value in a wide population group where burden of disease is greatest. Global investments in health research and development indicate inequitable access with only 10% of funds spent in low- and middle-income countries (LMICs) [11]. There are concerns that there is a critical lack of evidence-based child

healthcare in LMICs magnified by the scarcity of resources [12, 13]. A comparison of clinical trials in children conducted in the LMICs and high-income countries with the paediatric disease burden will help determine if they are matched to inform the child health research agenda locally and worldwide.

The last decade has seen clinical trials in children undergoing an evolution with heightened awareness and advocacy that children are not little adults and require high-quality evidence to support clinical care [14]. The need for timely medicinal product development in children has been identified internationally by health care providers, researchers, professional and regulatory authorities and the public with some legislation and initiatives underway to improve trials in children. The impact of these initiatives to support trials in children and the success and challenges need investigation. Children are our future and have a right to evidence-informed healthcare. Improving evidence-based child healthcare through clinical trials is "everybody's business" and is an important topic for further research [15].

1.2 Objectives

The issues of equity, quality and relevance of trials in child health in the current context are not clear. This theme of the thesis is very broad, thus selected components of the entire topic mainly focussing on the current status, challenges, gaps and enablers of clinical trials in children were chosen to be explored. The objectives of this thesis were to gather evidence to clarify some of the unresolved issues of equity, quality and relevance to inform improvements of clinical trials in children. The aims of this thesis were to:

1.2.1 Provide a comprehensive narrative overview of what is written in the literature about clinical trials of medicinal products in children over the last decade.

1.2.2 Compare registered trials in children to the paediatric disease burden of the LMICs and high-income countries.

1.2.3 Describe stakeholder beliefs and experiences of conducting trials in children in LMICs to inform strategies for improving the number and relevance of trials in LMICs.

1.2.4 Evaluate the completeness of protocols of paediatric trials of pharmacological interventions submitted to the HRECs among Australian Children's Hospitals, and to identify areas for improvement.

1.2.5 Describe the attitudes and opinions of multinational researchers, regulators and sponsors of trials in children that could inform local and international strategies to improve trials in children.

1.3 Overview of chapters

This thesis comprises 7 chapters (Figure 1.1) including this introduction chapter. Five papers will be presented that use quantitative and qualitative research methods to explore different aspects of equity, quality of trial design, conduct and reporting and appropriateness of the trials in addressing global paediatric disease burden and child health priorities. The contents of Chapter 2 are published and chapter 4 is accepted for publication. Chapter 3 is submitted for publication and Chapters 5 and 6 are to be submitted.

Chapter 2 is a systematic literature search of MEDLINE and Embase databases of pharmaceutical intervention trials in children as a topic. The search was conducted over the last decade to capture the major changes and developments with regard to clinical trials in children during this period. The search strategy appears in Appendix A1. This comprehensive narrative review describes the dearth of safety and efficacy evidence in children and the urgency to conduct more, high-quality trials of relevance to child healthcare. It also discusses

the importance of strong advocacy to increase paediatric evidence-based care and initiatives such as paediatric legislation, incentives and paediatric research networks. Study design and conduct issues in children such as pharmacokinetic studies, trial registration and publication, small sizes for paediatric studies, attitudes to children's participation in trials and appropriate medicine formulations for children are also described. The ethical issues in children such as informed consent and assent and payment for participation are included.

Each of these original research presented in Chapters 3 to 6 contribute new understanding to the overarching theme of the thesis of equity quality and relevance of clinical trials in children.

In Chapter 3, findings related to equity in Chapter 2 are built upon and the relevance of paediatric trials to disease burden is also examined. The registered clinical trials in children on the World Health Organisation (WHO) International Clinical Trials Registry Platform were reviewed. The disease-specific focus of registered clinical trials for children was compared to the global burden of disease by LMICs and high-income countries to determine whether these were matched. The WHO disability-adjusted life-year (DALY) was used to estimate the burden of disease or health in children. The number of trials in children was compared with those in adults.

Chapter 4 continues the theme of equity and relevance of trials in children, but also examines issues related to quality of trials in children in LMICs. This is a systematic review of qualitative studies of children's, parents', researchers', regulators', sponsors' and the public's perspectives on conducting clinical trials among children in LMICs to inform strategies for more, better trials relevant to child health in LMICs. Findings were analysed using thematic synthesis, which inductively generated new analytical themes from the findings of the

included primary studies.

In Chapter 5, we build on the theme of the quality of trials in children from Chapters 2 and 4. We evaluated the completeness of reporting of the scientific components of protocols of trials in children submitted to Ethics Committees of Australia Children's Hospitals to identify gaps that could be improved. De-identified data on the protocols for trial characteristics and completion of scientific domains related to the background, rationale, objective(s), design, methodology, statistical considerations, organisation of a trial and risk of bias were extracted using a consolidated checklist to identify areas for improvement.

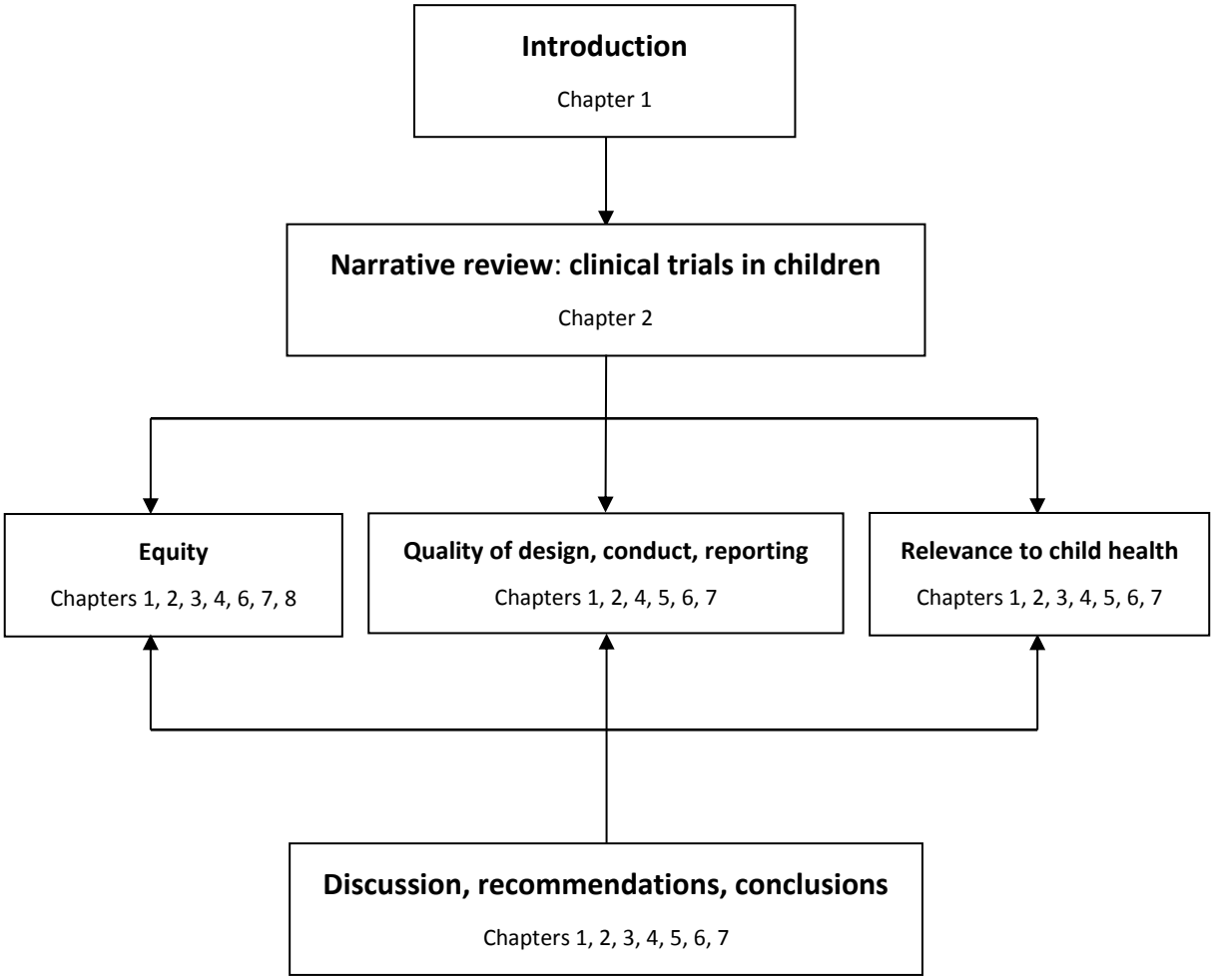
Chapter 6 builds on Chapters 2, 3, 4, 5 looking at equity, quality and relevance of paediatric trials. It is a multinational qualitative study where key informant researchers, regulators and sponsors of trials in children were interviewed to elicit their attitudes and opinions on challenges and enablers of trials in children. Grounded theory and thematic analysis was used to group similar concepts into themes and subthemes relating to barriers and enablers of trials in children in the current clinical trials landscape. Relationships and patterns between themes were identified to develop a thematic schema encompassing the key findings.

Chapter 7 concludes this thesis with a summary of the main findings, strengths and potential limitations, implications for clinical practice and policy making, and future research related to the equity, quality and relevance of trials in children.

Rationale for subsequent chapters: Chapter 2 is an extensive review of clinical trials in children. Chapter 3 then focuses on registered trials in children by analysing trials on the WHO portal by income regions. In Chapter 4 we further explored issues surrounding conducting trials in LMICs by a systematic analysis of published literature of qualitative

studies looking at trials in children in LMICs. Chapter 5 is an analysis of the scientific components of trial protocols submitted to Ethics Committees. Chapter 6 explored the viewpoints of stakeholders by a qualitative analysis of perspectives from stakeholders obtained through interviews. Chapter 7 is the discussion and conclusion of the overarching theme of the thesis: equity, quality and relevance of clinical trials in children.

Figure 1.1 Overview of chapters



1.4 References

1. Choonara I, Sammons H. Paediatric clinical pharmacology in the UK. Arch Dis Child. 2014;99(12):1143-6.
2. Giacoia GP, Taylor-Zapata P, Zajicek A. Drug studies in newborns: a therapeutic imperative. Clin Perinatol. 2012;39(1):11-23.
3. Tishler CL, Reiss NS. Psychotropic drugs and paediatrics: a critical need for more clinical trials. J Med Ethics. 2012;38(4):250-2.
4. Contopoulos-Ioannidis DG, Baltogianni MS, Loannidis JPA. Comparative Effectiveness of Medical Interventions in Adults Versus Children. Journal of Pediatrics. 2010;157(2):322-30.
5. Noah B. Just a Spoonful of Sugar: Drug Safety for Pediatric Populations. The Journal of Law, Medicine & Ethics. 2009;37(2):280.
6. World Health Organisation. WHO International Clinical Trials Registry Portal (ICTRP) Available at: http://www.who.int/ictrp/en/. Accessed 18 November 2015.
7. Caldwell PHY, Murphy SB, Butow PN, Craig JC. Clinical trials in children. The Lancet. 2004;364(9436):803-11.
8. Consensus statement on mandatory registration of clinical trials. J Pediatr Surg. 2007;42(4):601-2.
9. Crocetti MT, Amin DD, Scherer R. Assessment of risk of bias among pediatric randomized controlled trials. Pediatrics. 2010;126(2):298-305.
10. Sinha YK, Craig JC, Sureshkumar P, Hayen A, Brien JAE. Risk of Bias in Randomized Trials of Pharmacological Interventions in Children and Adults. Journal of Pediatrics. 2014;165(2):367-U206.
11. Edwards D, Matlin SA, Eide M, Young AJ, Regmi S, Ardal C, Guzman J, Terry RF, Røttingen JA, Viergever RF. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet. 2013;382(9900):1286-307.
12. Hoppu K, Sri Ranganathan S, Dodoo AN. Realities of paediatric pharmacotherapy in the developing world. Arch Dis Child. 2011;96(8):764-8.
13. MacLeod SM, Knoppert DC, Stanton-Jean M, Avard D. Pediatric clinical drug trials in low-income countries: key ethical issues. Paediatr Drugs. 2015;17(1):83-90.
14. Klassen TP, Hartling L, Craig JC, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS medicine. 2008;5(8):e172.
15. Shirkey HC. Therapeutic orphans--everybody's business. Ann Pharmacother. 2006;40(6):1174.

Chapter 2

Literature review: clinical trials in children

Chapter 2: Literature review - clinical trials in children

2.1 Abstract

Safety and efficacy data on many medicines used in children are surprisingly scarce. As a result children are sometimes given ineffective medicines or medicines with unknown harmful side effects. Better and more relevant clinical trials in children are needed to increase our knowledge of the effects of medicines and to prevent the delayed or non-use of beneficial therapies. Clinical trials provide reliable evidence of treatment effects by rigorous controlled testing of interventions on human subjects. Paediatric trials are more challenging to conduct than trials in adults because of the paucity of funding, uniqueness of children and particular ethical concerns. Although current regulations and initiatives are improving the scope, quantity and quality of trials in children, there are still deficiencies that need to be addressed to radically accelerate equitable access to evidence-based therapies in children.

2.2 Imperative to conduct trials in children

Since the acknowledgement of children as "therapeutic or pharmaceutical orphans" in the 1960s [1-3] there has been a worldwide recognition of the need to conduct trials of medicines used in children as a mechanism to improve the health of children [4-7]. Significant advances in child health have resulted from the conduct of paediatric trials. Well-known trials of polio vaccines and the subsequent rapid translation into practice were instrumental in the successful and almost complete eradication of polio [8, 9]. Recent advances in multicentre cancer trials in children have increased childhood cancer 5-year survival from 28% in the late 1960s to 79% by 2005 [10-13]. Regrettably, these stories of remarkable benefits cannot be extended to many other childhood conditions [14] because of the dearth of relevant trials.

Prescribing in children is often based on extrapolation from trials in adults due to the lack of paediatric data. Children are not "little adults," but are a heterogeneous group, ranging from preterm neonates to post-pubertal adolescents [15-17]. Their disease presentation may have a different natural history than adults and they may also suffer from diseases which do not occur in adults [18-20]. Children have complex physiological, developmental, psychological and pharmacological characteristics that vary from adults and these features are also different across the newborn to adolescent age range [21]. They may metabolise certain medicines differently from adults resulting in sub-optimal therapy, unexpected responses, adverse drug reactions and toxicity which may affect development and future reproductive capacity [22-24].

Relying on adult safety and efficacy data when prescribing in children can have unpredictable and tragic effects [4, 17, 25]. For example, faster metabolism of cyclosporin in children could lead to sub-therapeutic levels because of under-dosing [26]. Prescribing tetracycline in children during the period of mineralisation of developing teeth results in severe enamel dysplasia [27]. Children may experience paradoxical hyperactivity with phenobarbital which is not experienced in adults due to differences in pharmacodynamics [26]. In neonates, because of the immaturity of the liver, reduced medicine clearance resulted in the Gray baby syndrome with chloramphenicol [28, 29]; hepatotoxicity, hypotension, renal failure and death with the solvent propylene glycol which was in E-Ferol® [30] and "gasping syndrome" from metabolic acidosis with formulations containing benzyl alcohol [15]. Thalidomide, was used for morning sickness in pregnant women with devastating effects on foetal development, resulting in thousands of children being born with phocomelia [31].

More trials are needed, especially in areas of high clinical need. A study in 2007 showed that the number of randomised controlled trials in adults published in five high-impact general

medical journals has nearly doubled over 20 years, while the number of paediatric trials has not increased [32]. Despite about 27% of the world's population being children [33], paediatric trials constitute only 16.7% of the total number of trials registered on the World Health Organisation (WHO) portal [34]. In a study of trials registered on clinicaltrials.gov on selected medical conditions, only 12% were paediatric trials although children contributed to almost 60% of the total disease burden [35]. The WHO Global Burden of Disease study in 2002 estimated 11.4 million deaths in children under 10 years of age with 91% of these in children less than 5 years [36]. Fewer trials are conducted in younger children where it is most needed [37]. Only 7% (42) of all paediatric trials published in 2007 were in neonates [38, 39]. There are a disproportionately small number of trials in children in low-income countries [40, 41]. Over 89% of children live in low and lower-middle income countries, but only about a quarter of the 604 trials of medicinal products in children published in 2007 were conducted in these countries [38].

The pharmaceutical industry funds a greater proportion of trials in adults (65%) than children [35, 42]. Industry may be reluctant to conduct trials in children due to decreased commercial interest, increased cost and greater risk of liability [20, 43-45]. The more restrictive regulatory oversight for paediatric trials [23, 46] which includes the recommendation for provision of medicines post-trial to participants where there is proven therapeutic benefit [47, 48], may further discourage industry from conducting trials in children. Funding for paediatric trials therefore often rely on non-profit organisations, which has limited funding. The government favours trials in adults because of political and economic pressures [17, 35].

2.3 Study design and conduct of paediatric trials

There are special considerations when designing any of the four phases of clinical trials in children [49, 50]. Phase I trials, which test the safety and pharmacokinetics of a new

intervention for the first time, are discouraged in children due to the unknown effects of the intervention [51, 52]. However, Phase I trials are more acceptable in children with severe or life-threatening conditions where there are no proven treatment or when standard therapies have failed [51, 52]. Phase I trials can only occur when there are appropriate pre-clinical safety and efficacy data available from animal studies, modelling or other predictive studies [53]. Phase II trials, which study the safety and efficacy of the intervention [51], are sometimes conducted in children. Generally, medicinal products testing in children are deferred until the trials reach phase III which evaluate efficacy, acceptability and adverse effects [54]. Although the intent of the deferral is to protect children from exposure to unnecessary harms, it also means a delay to the access of children to potentially useful medications [54]. Phase III trials (randomised controlled trials) compare the investigational intervention with standard therapy, another effective therapy or placebo to estimate unbiased treatment effects [54-56]. Control groups and placebos are used when there are no established alternative therapies [54, 57-59]. Phase IV post marketing trials are infrequently conducted in children. However, the Food and Drug Administration (FDA) Paediatric Research Equity Act (PREA) require paediatric trials of marketed medicines [60].

2.3.1 Pharmacokinetic studies

Pharmacokinetic studies (which generally occur in Phase I) are important in the different paediatric age ranges. Challenges with pharmacokinetic studies include the lack of expertise in paediatric population pharmacokinetic or pharmacodynamic analysis; problems associated with the number, volume and timing of sampling; and the absence of sensitive micro-analytical techniques to accurately determine the drug concentration of very small volume specimens [61]. If the disease progression is similar between children and adults, an initial dose extrapolated from adult data may be adequate, followed by pharmacokinetic studies to determine the most appropriate paediatric dose [62]. Another approach is to conduct single

dose paediatric studies in the different age groups if medicines are known to have linear pharmacokinetics in adults [63]. In paediatric pharmacokinetic studies, innovative trial design techniques for reducing the number and volume of samples required are sometimes used. These techniques use sparse and scavenged pharmacokinetic samples with population pharmacokinetic methods using non-linear mixed effects [61, 63]. Opportunistic trials, which collect pharmacokinetic samples from children receiving treatment as part of routine clinical care, is another low-risk and high-yield design that is efficient and acceptable to parents and ethics committees [61]. Pharmacogenomic methods are also being developed for investigating drug disposition, efficacy and safety [46].

2.3.2 Trial registration and publication

Public registration of clinical trials is especially important to protect participants from unnecessary, duplicative studies, to improve transparency and overcome publication and selective outcome reporting bias [37, 64-66]. Prospective registration of trials is strongly advocated internationally by regulatory authorities, ethics committees and journals as a condition of publication [67]. However, a review of published paediatric randomised controlled trials showed that some were poorly reported [42] and had incomplete reporting of adverse drug reactions [68]. Disappointingly, a considerable number of paediatric trials that were conducted as a result of the paediatric exclusivity legislations were not published [69]. For paediatric trial results to be translated into clinical practice, prompt and accessible publication of unbiased results including negative results helps to improve public trust and confidence in paediatric research [70-72].

2.3.3 Small trials sizes for paediatrics

The recruitment of children in trials is more difficult than for adults [45, 47] because of the lower burden of disease in children [46, 73, 74]. Most paediatric trials have small sample

sizes [35, 38, 41] with only 38% of 736 paediatric trials published from 1996 to 2002 having a sample of more than 100 [40]. The small sample size, heterogeneity of response of children to treatments and rarity of certain important outcomes contribute to the problem of inadequate power [75]. Underpowered trials may provide inconclusive results and fail to detect modest but clinically relevant outcomes including adverse effects [17, 21, 54, 71]. This may waste resources and the efforts of children's participation in trials [76]. To address the small sample sizes in children, there have been major achievements in developing statistical methods and collaborative specialist multinational groups and paediatric clinical trials networks that pool their data and resources [77-82].

2.3.4 Attitudes to participation in trials

There has been a general reluctance about involving children in trials particularly by parents and doctors because of fears of harming children by exposing them to uncertain treatment effects [45, 72, 83]. In particular, parents were anxious about their child being treated as a "guinea pig" and were concerned that investigators may have conflicting interests and do not have their child's health as a priority [45, 84]. However, in a neonatal study, 75% of parents believed that their doctor would not approach them to do research if it might place babies in real danger and 50% reported that they trusted their doctor and would agree to participate in a trial if suggested by their doctor [85]. Practitioners interviewed in a study in 2011 were apprehensive and averse to recruiting children for trials due to the trial burdens which included the overwhelming amount of information they had to provide to the families [72]. Assisting practitioners to understand families' perceptions of trials and providing 'moral' support may improve recruitment of children [72]. In contrast, parents who reported a positive recruitment experience, viewed participation in a trial as an "exciting" opportunity, felt a sense of comfort and safety, acknowledged the value of research and desired to be informed about a trial if their child was eligible [72]. Other positive aspects of parents' experiences

include the altruistic desire to help future children, the opportunity to access new therapies, increased access to health care professionals and medical information, better medical care for their child, meeting other parents in a similar situation, and feeling a sense of hope when no other effective therapies are available [72-74, 86, 87]. The high level of threat and need for hope may account for the generally high rates of recruitment to neonatology and childhood cancer trials [83]. There are also perceived benefits for children participating in trials. Children often enjoy being part of a trial, interacting with other participants, being able to contribute to helping other children and are empowered about their treatment [84].

There has been some work on developing strategies to aid parents in the decision making process for trial participation [88]. Some strategies include improving the readability of the consent [89]. Masty et al conceptualised a "goodness-of-fit" approach to informed consent for paediatric trials that encouraged investigators to create consent procedures that took into account the research context, the child's cognitive and emotional maturity, and the family system [90]. The James Lind Library has been created to help the public understand that trials are fair tests of treatments in health care [91].

The use of placebo is poorly understood by parents who do not understand the rationale for using placebo to determine whether the intervention is effective or necessary. Parents fear assignment of their child to the placebo arm or to the treatment arm which is later proven to be less effective [45, 92, 93]. This concern may be compensated for by providing the proven effective treatment to all participants at the conclusion of the study. Alternative randomisation methods should also be considered which may be more acceptable to parents. In a conventionally randomised trial, parents' views were evenly divided on accepting the controversial Zelen randomisation where randomisation occurs prior to discussion with the family and only if the child is allocated the experimental treatment arm is consent sought [94].

In a survey investigating different types of consent to hypothetical neonatal resuscitation trials, parents wished to be responsible for making the informed decisions and were more comfortable with prospective consent than deferrals, waivers or 'opt-out' options [95].

The burdens of trial participation for children are different to adults, for example, children's aversion to needles makes obtaining blood samples challenging. To address this burden and protect children from unnecessary testing, the volume of blood sampling generally allowed in paediatric trials is less than 3% of the estimated circulating blood volume over a 2 to 8 week period [20, 96, 97]. Alternative appropriate sampling techniques, for example, finger or heel pricks or salivary samples may be preferred as it minimizes discomfort for children [15, 20, 96, 97]. There is a strong advocacy that paediatric trials requires the same dedicated time and attention to educate families and participants, ensuring appropriate child friendly environment and adapting treatments to their special needs that is generally accepted as routine clinical care [98, 99]. The use of pragmatic trials where there are no additional burdens of testing and monitoring beyond the requirements of routine clinical care [37-40] may also alleviate some of these concerns, including the use of placebos [55]. Participation may also be improved by having trained investigators who understand the complexities of conducting trials in children, appropriate facilities that meet the needs of children and a designated trials coordinator to facilitate recruitment and trial conduct [45, 93, 100]. Increasingly the importance of engaging children and families in the recruitment, consent and design of trials has also been recognised [99].

2.3.5 Appropriate medicine formulations in trials

The development of appropriate formulations for children has been slow. This may be due to historical disasters such as the formulation of sulphanilamide as an elixir which used diethylene glycol without animal toxicity testing resulting in poisoning and deaths in the

1930s [101, 102]. Consequently, risk averse companies may be reluctant to develop paediatric formulations due to the potential harmful effects of excipients used in the products and the low market share of these products. To encourage the pharmaceutical industry to develop paediatric appropriate formulations, the 2003 FDA Best Pharmaceuticals for Children Act (BPCA) [103] and European Union Paediatric regulations was endorsed.

Administration of medicines in children is complex and the trial design needs to consider the child's developmental abilities and the medicine's acceptability and tolerability as this will impact on compliance. Children are fearful of injectable medicines and if an alternative route of administration is not available, the provision of local anesthetic gels or patches will decrease discomfort. The requirements of child friendly formulations may differ in resource limited settings where there may be a lack of refrigeration facilities which may impact on the stability and efficacy of the medicine [104]. When there is a lack of paediatric appropriate formulations, the use of adult dose forms such as tablets and capsules can be problematic for younger children who cannot swallow tablets as crushing tablets or opening capsules and dispersing in liquids may compromise the palatability and bioavailability of the medicine and affect the trial results [96]. The inclusion of extemporaneous preparation guidelines in paediatric trials which use solid oral dosage forms, will improve the accuracy and reproducibility of the preparation [73]. Skin patches or flexible oral solid dosage forms such as dispersible tablets or powders, melts (wafers, sublingual) and sprinkles may be more suitable across various settings [102].

2.3.6 Outcome measures

As children grow and mature through the developmental stages, it may not be suitable to use the same outcome measures when comparing children of different ages and stages [16]. Some outcomes such as pain, nausea, dizziness, level of sedation or visual and auditory responses

[42] are difficult to measure and report in young children. When designing how to measure these outcomes, researchers need to consider using age-appropriate tools such as the face pain scale [57, 105]. Because of differences in body composition in different age groups, pharmacokinetic studies have sometimes resulted in incomplete and incorrect conclusions [96]. Trials that include different paediatric ages may need appropriate dose adjustments by weight or body surface area [96, 106]. Researchers are increasingly recognising the importance of qualitative outcome measures that are relevant to the child and family, including the impact of the illness and treatment on the quality of life [16]. When measuring quality of life outcomes, consideration needs to be given about whether to use proxy response by parents or reporting by the child or both [107], as these may differ. Involving parents and children in the selection of outcome measures that are important to them is recommended [16, 21].

2.4 Ethics of paediatric clinical trials

There is a dilemma in finding a balance between the obligation to conduct trials to protect children from the risk of using untested medicines and to protect children against unknown risks and harms which may occur with trial participation [27, 39, 108, 109]. The ethical principles of respect for persons, beneficence, non-maleficence and justice in trials involving children are the same as adults. There are additional ethical challenges because children lack the capacity to understand the risks involved in trials and depend upon adults to make decisions for them [110]. In a review of 739 paediatric trials from 1996 to 2002, 523 (71%) reported adverse drug reactions, but only 13 (2%) of the trials had safety monitoring committees [4]. Since then, trial governance are becoming more stringent with a requirement for an independent safety monitoring board with paediatric expertise, who can appreciate the uniqueness and unpredictability of responses in children [76, 111]. Long-term follow up in children is particularly important as many adverse effects may present later in life [17, 44].

2.4.1 Informed consent and assent

Informed consent for participation in paediatric trials is more complex than adult studies because consent is by proxy from the parents or guardian, who have a duty to protect the child's welfare [112]. Parents are uncomfortable with this responsibility because they are making a decision for their child [87]. Mason and Allmark propose that parents' consent in trials is vital to socially recognise parental roles, but does not offer added protection for neonates to that provided by appropriate research ethics, safety monitoring and governance procedures and parents' knowledge of these measures would improve decision making [113]. A review by Shilling and Young indicated that parents are keen to take responsibility for the decision to enrol their child in a trial, but are also fearful of making the 'wrong' decision' [83]. They also reported that individual parent's understanding of the threat of the child's condition and the trial risks depends on their personal values and experiences, their child's medical condition and the type of the trial [83]. Suggestions to address some of these parental concerns identified in this review include positive interactions at recruitment with the flexibility to tailor discussions to the needs and circumstance of individual parents [83]. The study by Woolfall et al in 2013 suggest that the investigating team involved in recruitment need to be aware of parents' priorities and the sorts of misunderstandings that can arise with parents [86]. A goodness-of-fit approach is described by Masty and Fisher whereby consent procedures are tailored to the research, the cognitive and emotional maturity of the child, the family system, the participants' priorities and well-being and are focussed on the issues that are of concern to potential participants and helping them achieve understanding of a trial [90]. To improve recruitment of children, the study by Woolfall et al also recommended providing tailored trial information on aspects that parents considered important in making a decision for their child participating in a trial [86]. Also providing information about the trial not only to parents but also to children in an age-appropriate method to improve comprehension, show respect, preserve trust and enable cooperation [98, 114]. The most frequently cited

suggestions from interviews and focus groups for improving informed consent related to allowing parents more time to make their decision, the amount and type of information provided, organisation of the consent meeting, communication style, and providing additional materials [115]. Although consent by parents or guardians is a legal requirement for trials, the autonomy of children should be respected and investigators need to also include them in decision making as much as they are capable [27, 87, 116]. Children's dissent should also be respected, particularly if their dissent is different from their usual response to the same procedure in normal clinical care.

2.4.2 Payment for participation

Although it is common practice to compensate trial participants for travel, parking, meal allowance and accommodation [54], payments for participation in trials is more controversial in children [117]. The types of payment can be in the form of *reimbursement* for direct trial-related expenses, *compensation* for the time and inconvenience of trial participation, *appreciation* after participation to thank them for their involvement and *incentives* to reward enrolment above actual out-of-pocket expenses [112, 117]. While the European Union (EU) advocates banning of all incentive payments to children [118], this is common practice in the United States (US) where almost 25% of paediatric trials offer payment [117]. The ethical concern about large incentive payments is that it might entice and distort the judgement and decision of the parent or child about the risks of trial participation [112, 118]. However, non-payment for direct expenses and inconvenience of trial participation may create unnecessary financial obstacles for participation and risks hindering essential paediatric research [45, 117-119]. The ethics committees, investigators and sponsors need to ensure that payment for trial participation of children is fair by keeping payments reasonable [98, 120].

2.5 Advocacy for trials

The 1989 'Convention on the Rights of the Child' 'recognise the right of the child to the enjoyment of the highest attainable standard of health' [121]. This includes the right to have research evidence for treatments commonly used in children. It is a reasonable requirement for the developmental pipeline of new interventions to include children in trials when use in children is anticipated [54, 122]. Several rigorous guidelines including the Belmont Report [123], Declaration of Ottawa on Child Health [124], Declaration of Helsinki and International Conference on Harmonisation (ICH) E11 [15, 125] address the need for paediatric trials and protection of the rights and welfare of children. Many countries have also developed their own regulations, guidelines and standards for the inclusion of children in trials [22, 54, 57, 126-128].

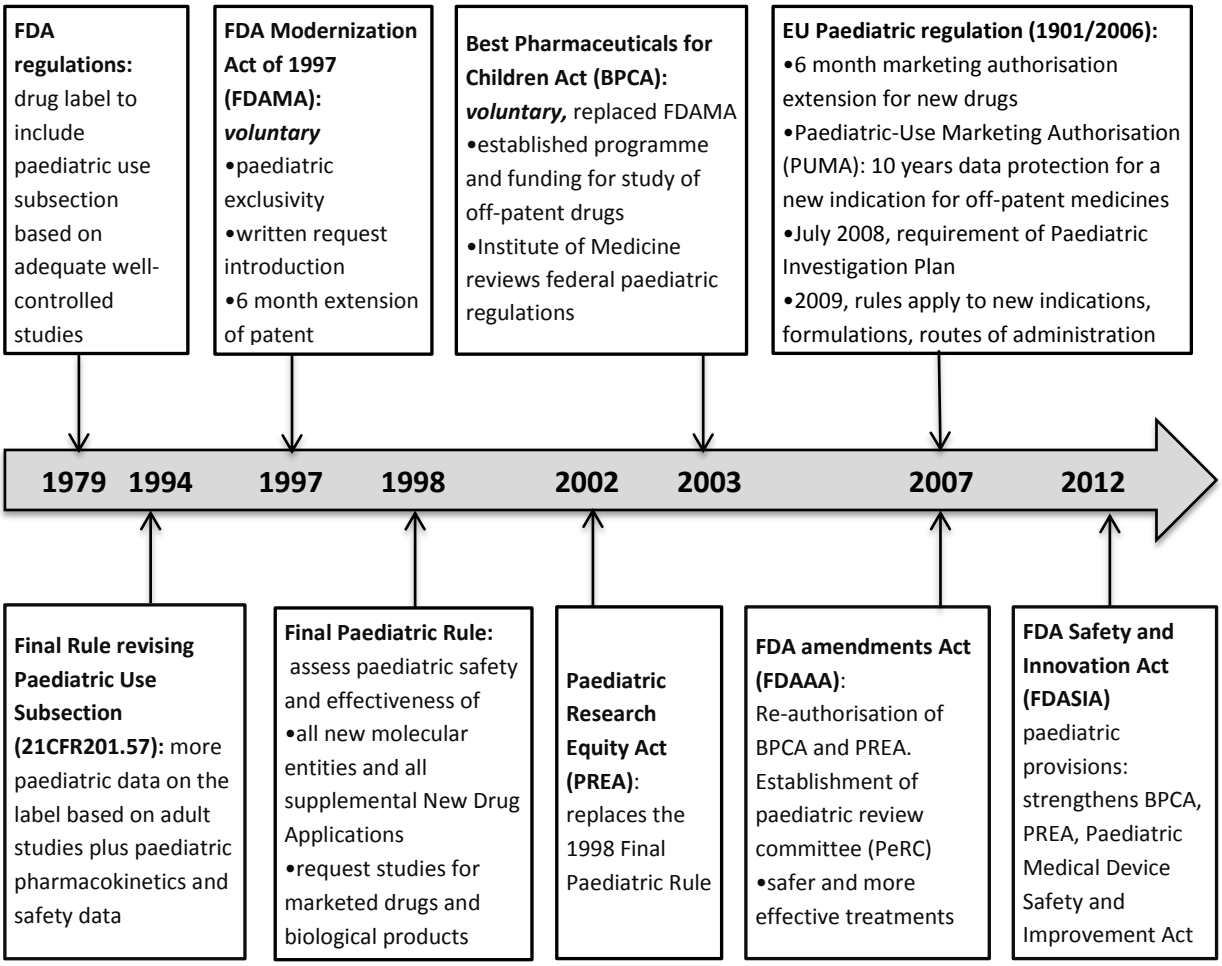
2.5.1 Paediatric legislations

Most medicines used by children internationally are unlicensed or off-label, with no randomised controlled trial data in more than 50% of interventions used in children as compared to adults [44, 71, 129-131]. The US was the first to initiate legislative changes in 1997 to encourage more trials in children to improve the evidence-base for medicines in children [28, 51], followed by the EU in 2007 [7, 132-135] (Figure 2.1). Their expectations were for the pharmaceutical industry to evaluate the safety and efficacy of medicines used by children in all appropriate paediatric age groups, to ensure that product labels contain the known paediatric data, to develop paediatric appropriate formulations and to provide a Paediatric Investigation Plan for testing in children at the time of medicine application submission [122]. Both regulations have mandatory requirements with an incentive of a six-month extension of patent protection to encourage the pharmaceutical industry to conduct paediatric trials. These incentives resulted in an increase in the number of paediatric trials [136-138]. By March 2008, more than 49,000 children were enrolled in trials and the FDA

had granted exclusivity to 150 medicines and granted requests for 842 studies which were mostly for new indications of existing medicines [134]. The FDA "New Paediatric Labelling Information Database" provides information of new paediatric trials that resulted in new or enhanced safety data in children [137, 139]. In a retrospective analysis of the applications for Paediatric Investigation Plan and Waivers submitted to the European Medicines Agency (EMA), from 2007 to 2009, there has only been a slight increase in the proportion of paediatric trials from 8.2% of all trials in 2007 to 9.4% in 2009 [140]. The main therapeutic areas of applications were endocrinology (13.4%), oncology (11%), infectious diseases (10.8%) and cardiovascular diseases (7.1%) [140]. This pattern reflected the commercial interest of the pharmaceutical industry to evaluate medicines with a high market value and which are commonly prescribed in adults rather than addressing the priority health needs of children [140, 141]. Many frequently prescribed, essential medicines that are off-patent and have a small market-share in children have yet to be investigated [39, 142, 143]. This is because incentives for the development of off-patent medicines in both the US and EU is small and voluntary and public funding is inadequate [142].

The pharmaceutical industry does not appear to be interested in transferring the benefits of approved paediatric appropriate medicines in the US and EU to other countries. This may be due to the lack of economic incentives and the high costs associated with amending the labels of existing medicines with new paediatric data or registering new medicines. Therefore, there needs to be an efficient, harmonised process globally through collaboration of government, pharmaceutical industry and the medical community to ensure that the development of paediatric medicine is optimally aligned with priority healthcare needs [45, 142]. Canada and Japan has implemented modest paediatric regulation reforms [142]. Other countries need to adopt regulations and incentives for promoting paediatric medicines research with sustained government and societal support.

Figure 2.1 Timeline of paediatric regulations in the US and EU



2.5.2 International paediatric trials initiatives

Global priorities of the WHO Millennium Development Goals include the 'Make medicines child size' initiative and the World Health Assembly “Better Medicines for Children" Resolution WHA60.20 in 2007 to improve knowledge, access, research and development of paediatric medicines [144, 145]. Another WHO initiative is the Paediatric medicines Regulator's Network (PmRN) which involves National Medicines Regulatory Authorities (NMRAs) which aims to harmonise the regulation of manufacture, license and research of medicines for children [144].

International paediatric trial networks have been established in many countries to address some of the challenges by improving the infrastructure and research capacity. The US and EU created networks with specialised expertise in conducting trials in children and have dedicated funding for paediatric research and training [142]. The US National Institute of Child Health and Human Development (NICHD) Pediatric Trial Network (PTN) was launched in September 2010 with US $95 million for 7 years to conduct paediatric trials on off-patent medicines [146]. This network provides an appropriate environment for performing safe and effective trials in children as recommended by the Best Pharmaceuticals for Children Act (BPCA) drug development program in a variety of therapeutic areas [146]. In 2012, the network in collaboration with the FDA has commenced paediatric studies on 30 drugs [147].

The Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)] was established in March 2011 in collaboration with research networks, investigators and centres with recognised expertise in conducting paediatric trials [148]. This network is working towards developing the necessary competences and avoiding unnecessary duplication of paediatric studies; educating parents or carers and children about trials and encouraging their participation; raising awareness among healthcare professionals of the necessity for trials in children of all ages, supporting their involvement in such studies and engaging in dialogue with ethics committees on paediatric trials issues [148]. The National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) in the UK was established in 2005. This network has been more successful because of funding from the government [99]. The Standards for Research in (StaR) Child Health is an international initiative founded in 2009 to improve the quality of the design, conduct, and reporting of paediatric trials by promoting the use of internationally developed research standards to enhance their reliability and relevance [5, 149-151].

Professional bodies and research organisations internationally have also recognised the imperative to conduct paediatric trials. These include the International Pediatric Association (IPA) [152], the American National Institute of Health (NIH) [153, 154] and Academy of Paediatrics (AAP) [54], the UK Medical Research Council (MRC) [155] and Royal College of Paediatrics and Child Health (RCPCH) [156] and the European Agency for the Evaluation of Medicinal Products (EMEA) [125].

International collaborative disease specific groups have been formed to address the logistical and methodological difficulties in conducting trials of diseases with a low prevalence [80]. Examples of successful disease specific groups include the Children's Oncology Group (COG) [77], Paediatric Rheumatology International Trials Organisation (PRINTO) [79] and Paediatric European Network for the Treatment of AIDS (PENTA) [81]. As a result of collaboration, the Children's Oncology Group has developed a research culture in the participating institutions which accepts protocol-driven trials as part of standard care [13]. It has also facilitated rigorous protocol development and review, centralisation of pathology review, central database and safety monitoring of toxicity and response, internal auditing to ensure compliance to Good Clinical Practice and involvement of established investigators with oncology paediatric expertise [45, 157]. The Paediatric Rheumatology International Trials Organisation (PRINTO) has a Scientific Advisory Council, International and National Coordinating Centres to facilitate logistics and scientific elements of multicenter, multinational studies [80]. PRINTO's achievements include developing standardised treatment outcome measures, training young researchers, access to network facilities for the conduct trials and establishing a website for families to access health information [80]. All these global initiatives can be adopted by other disease specific groups to support the collaborative efforts to increase the number of clinically relevant paediatric trials.

2.6 The way forward

Although progress has been slow, paediatric clinical trials has undergone a renaissance with international recognition of the importance of trials in children. However, there continues to be deficiencies including inadequate funding and conflicts of interest with trials still being driven by financial and political incentives. Health policy makers need to consider the needs of children by setting priorities, developing infrastructure and providing sufficient funding [158] that is sustainable to accelerate the progress of equitable healthcare. The future health of children hinges on the success of paediatric trials. Greater advocacy and collaboration between all major stakeholders including regulatory authorities, pharmaceutical industries, scientific community, clinicians and the public at national and international level is crucial to this success. Investment into better evidence-based treatments for our children is an investment into a better future for all.

2.7 References

1. Wilson JT. An Update on the Therapeutic Orphan. Pediatrics. 1999;104(Supplement 3):585-90.
2. Shirkey H. Therapeutic orphans. J Pediatr. 1968;72(1):119-20.
3. Shirkey H. Editorial Comment: Therapeutic Orphans. J Pediatr. 1999;104:583-4.
4. Sammons H, Gray C, Hudson H, Cherrill J, Choonara I. Safety in paediatric clinical trials – a 7-year review. Acta Pædiatrica. 2008;97:474-7.
5. Klassen TP, Hartling L, Hamm M, van der Lee JH, Ursum J, Offringa M. StaR Child Health: an initiative for RCTs in children. The Lancet. 2009;374(9698):1310-2.
6. Smyth RL. Making a difference: the clinical research programme for children. Archives of Disease in Childhood. 2007;92(10):835-7.
7. Schreiner MS. Paediatric clinical trials: redressing the imbalance. Nat Rev Drug Discov. 2003;2(12):949-61.
8. Dawson L. The Salk Polio Vaccine Trial of 1954: risks, randomization and public involvement in research. Clin. 2004;1(1):122-30.
9. Juskewitch JE, Tapia CJ, Windebank AJ. Lessons from the Salk Polio Vaccine: Methods for and Risks of Rapid Translation. Clinical and Translational Science. 2010;3(4):182-5.
10. Macy ME, Sawczyn KK, Garrington TP, Graham DK, Gore L. Pediatric developmental therapies: interesting new drugs now in early-stage clinical trials. Curr Oncol Rep. 2008;10(6):477-90.
11. Pritchard-Jones K, Europe S. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. Eur J Cancer. 2008;44(15):2106-11.
12. Stiller CA, Kroll ME, Pritchard-Jones K. Population survival from childhood cancer in Britain during 1978–2005 by eras of entry to clinical trials. Annals of Oncology. 2012;23: 1-6.
13. UK Cancer Research. Childhood cancer survival statistics.Section updated 14/11/11 Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/childhoodcancer/survival/.Accessed 5 August 2013.
14. Martinez-Castaldi C, Silverstein M, Bauchner H. Child versus adult research: the gap in high-quality study design. Pediatrics. 2008;122(1):52-7. Epub 2008/07/04.
15. Foex BA. The ethics of clinical trials. Anaesthesia and Intensive Care Medicine. 2009;10(2):98-101.
16. Sinha I, Jones L, Smyth RL, Williamson PR. A Systematic Review of Studies That Aim to Determine Which Outcomes to Measure in Clinical Trials in Children. PLoS Med. 2008;5(4):e96.
17. Klassen TP, Hartling L, Craig JC, Offringa M. Children Are Not Just Small Adults: The Urgent Need for High-Quality Trial Evidence in Children. PLoS Med. 2008;5(8):e172.
18. Saint Raymond A, Brasseur D. Development of medicines for children in Europe: ethical implications. Paediatr Respir Rev. 2005;6(1):45-51.

19. Amann JP, Dulac O. Trials in children. Epilepsy Res. 2001;45(1-3):133-6; discussion 7-40.

20. Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. Br J Clin Pharmacol. 2000;49(2):93-7.

21. Rocchi F, Tomasi P. The development of medicines for children. Part of a series on Pediatric Pharmacology, guest edited by Gianvincenzo Zuccotti, Emilio Clementi, and Massimo Molteni. Pharmacol Res. 2011;64(3):169-75.

22. Canadian Paediatric Society. Drug investigation for Canadian children: The role of the Canadian Paediatric Society. Review. 2003 Apr. Report No.: 1205-7088 Contract No.: 4.

23. Contopoulos-Ioannidis DG, Baltogianni MS, Loannidis JPA. Comparative Effectiveness of Medical Interventions in Adults Versus Children. J Pediatr. 2010;157(2):322-30.

24. Noah B. Just a Spoonful of Sugar: Drug Safety for Pediatric Populations. The Journal of Law, Medicine & Ethics. 2009;37(2):280.

25. Pandolfini C, Bonati M, Sammons HM. Registration of trials in children: update of current international initiatives. Archives of Disease in Childhood. 2009;94(9):717-9.

26. Institute of medicines of the national academies: Committee on Clinical Research Involving Children. The Ethical Conduct of Clinical Research Involving Children: The national academies press 500 fifth street, NW Washington DC 20001; 2004.

27. Ackerman TF. The ethics of drug research in children. Paediatr Drugs. 2001;3(1):29-41.

28. Christensen ML, Helms RA, Chesney RW. Is Pediatric Labeling Really Necessary? Pediatrics. 1999;104(Supplement 3):593-7.

29. Burns LE, Hodgman JE, Cass AB. Fatal Circulatory Collapse in Premature Infants Receiving Chloramphenicol. New England Journal of Medicine. 1959;261(26):1318-21.

30. Balistreri WF, Farrell MK, Bove KE. Lessons From the E-Ferol Tragedy. Pediatrics. 1986;78(3):503-6.

31. Curran WJ. The Thalidomide Tragedy in Germany: The End of a Historic Medicolegal Trial. New England Journal of Medicine. 1971;284(9):481-2.

32. Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985-2004. Journal of clinical epidemiology. 2007;60(2):118-23. Epub 2007/01/09.

33. The World Bank. Population ages 0-14 (% of total), The United Nations Population Division's World Population Prospects 2011 http://data.worldbank.org/indicator/SP.POP.0014.TO.ZS/countries/1W?display=default. Accessed 30 May 2013.

34. Joseph DP, Caldwell PHY, Craig JC. Registered paediatric clinical trials: a global context. Poster presentation International Congress of Pediatrics 2013 (ICP), The 27th Congress of International Pediatric Association 24-29 August 2013 Melbourne, Australia 2013.

35. Bourgeois FT, Murthy S, Pinto C, Olson KL, Ioannidis JP, Mandl KD. Pediatric versus adult drug trials for conditions with high pediatric disease burden. Pediatrics. 2012;130(2):285-92. Epub 2012/07/25.

36. Mathers C. Chapter 2 Global Burden of Disease Among Women, Children, and Adolescents. In: Maternal and Child Health, ed Ehiri JE. Springer Science,Business Media, LLC 2009, 19-42.

37. Hoppu K. Can we get the necessary clinical trials in children and avoid the unnecessary ones? Eur J Clin Pharmacol. 2009;65(8):747-8.

38. Aripin KNBN, Choonara I, Sammons HM. A systematic review of paediatric randomised controlled drug trials published in 2007. Archives of Disease in Childhood. 2010;95(6):469-73.

39. Salazar JC. Pediatric clinical trial experience: government, child, parent and physician's perspective. Pediatr Infect Dis J. 2003;22(12):1124-7.

40. Sammons HM, Choonara I. Clinical trials of medication in children 1996-2002. Eur J of Clin Pharmacol. 2005;61:165-7.

41. Aripin KNBN, Choonara I, Sammons HM. Published pediatric randomized drug trials in developing countries, 1996-2002. Pediatric Drugs. 2010;12(2):99-103.

42. Thomson D, Hartling L, Cohen E, Vandermeer B, Tjosvold L, Klassen TP. Controlled Trials in Children: Quantity, Methodological Quality and Descriptive Characteristics of Pediatric Controlled Trials Published 1948-2006. PLoS ONE. 2010;5(9):e13106.

43. Karlberg JPE. Clinical Trials in paediatrics. In: Machin D, Day S,Green S, eds. Textbook in Clinical Trials. Chichester: John Wiley and Sons, Ltd.pp 701–10.2006.

44. Hill P. Off licence and off label prescribing in children: litigation fears for physicians. Arch Dis Child. 2005;90(Suppl I):i17-i8.

45. Caldwell PHY, Murphy SB, Butow PN, Craig JC. Clinical trials in children. The Lancet. 2004;364(9436):803-11.

46. Krekels EHJ, van den Anker JN, Baiardi P, Cella M, Cheng KY, Gibb DM, Green H, Iolascon A, Jacqz-Aigrain EM, Knibbe CAJ, Santen GWE, van Schaik RHN, Tibboel D, Della Pasqua OE. Pharmacogenetics and paediatric drug development: issues and consequences to labelling and dosing recommendations. Expert Opin Pharmacother. 2007;8(12):1787-99.

47. Lim A, Cranswick N. Clinical Trials, Ethical Issues and Patient Recruitment: An Australian Perspective. Paediatric and Perinatal Drug Therapy. 2003;5(4):183-7.

48. Cohen ERM, O'Neill JM, Joffres M, Upshur REG, Mills E. Reporting of informed consent, standard of care and post-trial obligations in global randomized intervention trials: a systematic survey of registered trials. Developing World Bioeth. 2009;9(2):74-80.

49. National Institute of Health. Glossary of terms for human subjects protection and inclusion issues. 2001. Available at: http://grants.nih.gov/grants/peer/tree_glossary.pdf.Accessed 4 August 2013.

50. Australian Government National Health and Medical Research Council and Department of Industry, innovation, Science, Research and Tertiary education. Australian Clinical Trials.Phases of clinical trials. Available at: http://www.australianclinicaltrials.gov.au/node/5. Accessed 5 August 2013.

51. US Food and Drug Administration (FDA). Title 21--Food and drugs. Chapter 1--Food and Drug administration, Department of health and human services.Subchapter C-Drugs: General, Code of Federal Regulations, Volume 4, Revised as of 1 April 2011. Available at:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57. Accessed 10 May 2013.

52. Aleksa K, Koren G. Ethical issues in including pediatric cancer patients in drug development trials. Paediatr Drugs. 2002;4(4):257-65.

53. Bellanti F, Della Pasqua O. Modelling and simulation as research tools in paediatric drug development. Eur J Clin Pharmacol. 2011;67 Suppl 1:75-86.

54. Shaddy RE, Denne SC, The Committee on Drugs and Committee on Pediatric Research. Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. Pediatrics. 2010;125:850.

55. Henschel AD, Rothenberger LG, Boos J. Randomized clinical trials in children-ethical and methodological issues. Curr Pharm Des. 2010;16(22):2407-15.

56. Zhang B, Schmidt B. Do we measure the right end points? A systematic review of primary outcomes in recent neonatal randomized clinical trials. J Pediatr. 2001;138(1):76-80.

57. European Medicines Agency (EMA). Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. Recommendations of the ad hoc group for the development of implementing Guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.2008 ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf. Accessed 5 August 2013.

58. Flynn JT. Ethics of placebo use in pediatric clinical trials: the case of antihypertensive drug studies. Hypertension. 2003;42(5):865-9.

59. Fost N. Ethical issues in research and innovative therapy in children with mood disorders. Biol Psychiatry. 2001;49(12):1015-22.

60. US Food and Drug Administration. Postmarketing Requirements and Commitments: Frequently Asked Questions (FAQ).Updated:02/08/2012. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm#q15. Accessed 18 August 2013.

61. Matthew M Laughon, Daniel K Benjamin Jr, Edmund V Capparelli, Gregory L Kearns, Katherine Berezny, Ian M Paul, Kelly Wade, Jeff Barrett, Phillip Brian Smith a, Cohen-Wolkowiez M. Innovative clinical trial design for pediatric therapeutics. Expert Rev Clin Pharmacol 2011 September;4(5):643–52.

62. Johnson TN. Modelling approaches to dose estimation in children. Br J Clin Pharmacol. 2005;59(6):663-9.

63. European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP). Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population.Doc. Ref. EMEA/CHMP/EWP/147013/2004.Corrigendum. London, 28 June 2006

64. Viergever Roderik F, Ghersi Davina. The Quality of Registration of Clinical Trials. PLoS ONE. 2011; 6 (2):1-8.

65. South African Cochrane Centre. Pan African clinical trials registry (PACTR): http://www.pactr.org. Accessed 9 April 2013.

66. Thomas-Urban KB, Joergensen M, Lynch G, Rubison M, Porter BD, Sayers J, Tesch C. Clinical trial disclosure: Global overview and implications of new laws and guidelines. Drug Information Journal. 2010;44(3):213-25.

67. International Committee of Medical Journal Editors. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. The New England Journal of Medicine 2004;351(12):1250-1.

68. de Vries TW, van Roon EN. Low quality of reporting adverse drug reactions in paediatric randomised controlled trials. Archives of Disease in Childhood. 2010;95(12):1023-6.

69. Benjamin DK, Smith P, Murphy M, Roberts R, Mathis L, Avant D, Califf RM, Li JS. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. JAMA. 2006;296(10):1266-73.

70. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet Oncol. 2009 Jul 4.;374(9683):86-9.

71. Cramer K, Wiebe N, Moyer V, Hartling L, Williams K, Swingler G, Klassen TP. Children in reviews: methodological issues in child-relevant evidence syntheses. BMC Pediatr. 2005;5:38. Epub 2005/09/24.

72. Young B, Shilling V, Hickey H, Sowden E, Smyth R, Williamson P. What parents think about being approached about children's trials, how this differs from what practitioners expect, and what this tells us about enhancing recruitment. Oral presentation: Clinical trials methodology conference 2011, Bristol UK 4-5 October 2011. Trials. 2011;12(Suppl 1):A116.

73. Morales-Olivas FJ, Morales-Carpi C. Clinical trials in children. Rev Recent Clin Trials. 2006;1(3):251-8.

74. Deal G, Nikitin N. European and non-European paediatric clinical trials. Regulatory Rapportteur. 2009;6(5):4-7.

75. Foster BJ, Warady BA. Clinical research in pediatric nephrology: challenges, and strategies to address them. Jn, J. 2009;22(6):685-93.

76. Bavdekar SB. Pediatric clinical trials. Perspectives in Clinical Research. 2013;4(1):89-99.

77. The Children's Oncology Group (COG). Available at: http://www.childrensoncologygroup.org/. Accessed 2 August 2013.

78. Children's Cancer and Leukaemia Group (CCLG). Available at: http://www.cclg.org.uk/. Accessed 2 August 2013.

79. Paediatric Rheumatology International Trials Organisation (PRINTO). Available at: http://www.printo.it/. Accessed 3 August 2013.

80. Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). Archives of Disease in Childhood. 2011;96(6):596-601.

81. Paediatric European Network for the Treatment of AIDS (PENTA). Available at: http://www.pentatrials.org/network.htm. Accessed 5 August 2013.

82. Paediatric Emergency Care Applied Research Network (PECARN). Available at: http://www.pecarn.org/. Accessed 1 August 2013.

83. Shilling V, Young B. How do parents experience being asked to enter a child in a randomised controlled trial? BMC Medical Ethics. 2009;10(1):1.

84. Martin K. Current issues in paediatric clinical trials. Meeting Report. Association of the British Pharmaceutical Industry. 2005. Available at: www.abpi.org.uk. Accessed 3 October 2013.

85. Singhal N, Oberle K, Burgess E, Huber-Okrainec J. Parents' perceptions of research with newborns J Perinatol 2002;22(1):57-63.

86. Woolfall K, Shilling V, Hickey H, Smyth RL, Sowden E, Williamson PR, Young B. Parents' Agendas in Paediatric Clinical Trial Recruitment Are Different from Researchers' and Often Remain Unvoiced: A Qualitative Study. PLoS ONE. 2013;8(7):e67352.

87. Caldwell PHY, Butow PN, Craig JC. Parents' attitudes to randomised controlled trials involving children J Pediatr. 2003;145(555-60).

88. Caldwell PHY, Hamilton S, Tan A, Craig JC. Strategies for Increasing Recruitment to Randomised Controlled Trials: Systematic Review. PLoS Med. 2010;7(11):1-16.

89. Tarnowski KJ, Allen DM, Mayhall C, Kelly PA. Readability of pediatric biomedical research informed consent forms. Pediatrics 2007;119(4):849-59.

90. Masty J, Fisher C. A Goodness-of-Fit Approach to Informed Consent for Pediatric Intervention Research. Ethics & Behavior. 2008;18(2-3):139-60.

91. Why fair tests are needed. Available at: http://www.jameslindlibrary.org/essays/fair_tests/why-fair-tests-are-needed.html. Accessed 2 November 2013.

92. Allmark P, Spedding M. Clinical trials in neonates: ethical issues. Semin Fetal Neonatal Med. 2007;12(4):318 - 23.

93. Caldwell P, Butow P, Craig J. Parents' attitudes to children's participation in randomized controlled trials. Jl of Pediatr. 2003;142(5):554 - 9.

94. Snowdon C, Elbourne D, Garcia J. Zelen randomization: attitudes of parents participating in a neonatal clinical trial. Control Clin Trials. 1999;20(2):149 - 71.

95. Culbert A, Davis DJ. Parental preferences for neonatal resuscitation research consent: a pilot study. J Med Ethics. 2005;31(12):721-6.

96. Abdel-Rahman SM, Reed MD, Wells TG, Kearns GL. Considerations in the rational design and conduct of phase I/II pediatric clinical trials: avoiding the problems and pitfalls. Clin Pharmacol Ther. 2007;81(4):483-94.

97. de Wildt SN, Ito S, Koren G. Challenges for drug studies in children: CYP3A phenotyping as example. Drug Discov Today. 2009;14(1-2):6-15.

98. Caldwell PHY, Dans L, de Vries MC, Newman BA Hons J, Sammons H, Spriggs M, Tambe P, Van't Hoff W, Woolfall K, Young B, Offringa M. Standard 1: Consent and Recruitment. Pediatrics. 2012;129(Supplement 3):S118-S23.

99. NHS National Institute for Health Research. Medicines for Children Research Network Available at: http://www.mcrn.org.uk/. Accessed 12 April 2012.

100. Caldwell PHY, Butow PN, Craig JC. Paediatricians' attitudes to randomised controlled trials involving children. J Pediatr. 2002;141:798–803.

101. Wax PM. Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act. Annals of Internal Medicine. 1995;122(6):456-61.

102. Ernest TB, Elder DP, Martini LG, Roberts M, Ford JL. Developing paediatric medicines: identifying the needs and recognizing the challenges. J Pharm Pharmacol. 2007;59(8):1043-55.

103. US Food and Drug Administration (FDA). FDA Amendments Act of 2007 (FDAAA), Title IV: Pediatric Research Equity Act of 2007 (PREA) and Title V: Best Pharmaceuticals for Children Act of 2007 (BPCA). September 27, 2007 (Public Law No. 110-85). Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm. Accessed 25 January 2013.

104. World Health Organization. Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. Geneva: WHO, 2008. http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_ reportDEC2008.pdf. Accessed 12 August 2013.

105. von Baeyer CL. Children's self-reports of pain intensity: Scale selection, limitations and interpretation. Pain Research & Management:The Journal of the Canadian Pain Society. 2006;11(3):157-62.

106. Ligi I, Boubred F, Grandvuillemin I, Simeoni U. Clinical research in newborn infants: difficulties and specificity. Eur J Clin Pharmacol. 2011;67 Suppl 1:29-32.

107. Abbott J, Gee L. Quality of life in children and adolescents with cystic fibrosis: implications for optimizing treatments and clinical trial design. Paediatr Drugs. 2003;5(1):41-56.

108. O'Lonergan TA, Milgrom H. Ethical considerations in research involving children. Curr Allergy Asthma Rep. 2005;5(6):451-8.

109. Ross LF, Newburger JW, Sanders SP. Ethical issues in pediatric trials. Am Heart J. 2001;142(2):233-6.

110. Dixon-Woods M, Ashcroft R, Jackson C, Tobin M, Kivits J, Burton P, Samani N. Beyond "misunderstanding": written information and decisions about taking part in a genetic epidemiology study. Soc Sci Med. 2007;65(11):2212 - 22.

111. Hirtz DG, Gilbert PR, Terrill CM, Buckman SY. Clinical trials in children--How are they implemented? Pediatr Neurol. 2006;34(6):436-8.

112. Spriggs M, Caldwell P. The ethics of paediatric research. Journal of Paediatrics and Child Health. 2011;47:664–7.

113. Mason SA, Allmark PJ. Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study. Lancet. 2000;356(9247):2045 - 51.

114. World Medical Association. Declaration of Helsinki,2008. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed 9 February 2013.

115. Eder M, Yamokoski A, Wittmann P, Kodish E. Improving informed consent: suggestions from parents of children with leukemia. Pediatrics. 2007;119(4):e849 - 59.

116. Davidson AJ, O'Brien M. Ethics and medical research in children. Paediatr Anaesth. 2009;19(10):994-1004.

117. Wendler D, Rackoff JE, Emanuel EJ, Grady C. The ethics of paying for children's participation in research. The Journal of Pediatrics. 2002;141(2):166-71.

118. Dobson R. Lump sums for children taking part in research may distort parents' judgment. BMJ. 2002;325(7368):796.

119. Tishler CL, Reiss NS. Pediatric drug-trial recruitment: enticement without coercion. Pediatrics. 2011;127(5):949-54.

120. Glasser S, Howard G. Clinical trial design issues: at least 10 things you should look for in clinical trials. J Clin Pharmacol 2006; 46:1106–15.

121. United Nations General Assembly. "Convention on the Rights of the Child" Part 1, Article1, A/RES/44/25, 61st plenary meeting, 20 November 1989. Available at: http://www.un.org/documents/ga/res/44/a44r025.htm. Accessed 4 April 2013.

122. Tassinari MS, editor. Pediatric Regulations in the US and Europe.United States FDA Office of New Drugs, ODAC Pediatric Subcommittee. November 2010. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM236390.pdf. Accessed 1 July 2013.

123. Office of the Secretary: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report:Ethical Principles and Guidelines for the Protection of Human Subjects of Research. 18 April 1979 Available at: http://science.education.nih.gov/supplements/nih9/bioethics/guide/teacher/Mod5_Belmont.pdf. Accessed 9 July 2013.

124. World Medical Association I. WMA Declaration of Ottawa on Child Health. Available at: http://www.wma.net/en/30publications/10policies/c4/. Accessed 3 August 2013.

125. The European Agency for the Evaluation of Medicinal Products (EMA). Evaluation of Medicines for Human use. ICH Topic E11 Clinical Investigation of Medicinal Products in the Paediatric Population. CPMP/ICH/2711/99. 2000:1-12.

126. US Food and Drug Administration (FDA). Fact Sheet: Pediatric provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA).07092012. Available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm311038.htm. Accessed 6 July 2013.

127. US Food and Drug Administration. Running clinical trials.Additional Protections for Children. Last update 08/05/2010. Available at: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm119111.htm. Accessed 31 July 2013.

128. National Health and Medical Research Council. Clinical trials. http://www.nhmrc.gov.au/health-ethics/human-research-ethics/clinical-trials. Accessed 10 August 2013.

129. Smit-Marshall P. Pediatric Clinical trials: A Worldview. Applied Clinical Trials. January 2010;19:32-7.

130. Smyth AR, Barbato A, Beydon N, Bisgaard H, de Boeck K, Brand P, Bush A, Fauroux B, de Jongste J, Korppi M, O'Callaghan C, Pijnenburg M, Ratjen F, Southern K, Spencer D, Thomson A, Vyas H, Warris A, Merkus PJ. Respiratory medicines for children: current evidence, unlicensed use and research priorities. Eur Respir J. 2010;35(2):247-65.

131. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, van

den Anker J. Survey of unlicenced and off label drug use in paediatric wards in European countries. BMJ. 2000;320:79-82.

132. Permanand G, Mossialos E, McKee M. The EU's new paediatric medicines legislation: serving children's needs? Archives of Disease in Childhood. 2007;92(9):808-11.

133. Sammons H. Ethical issues of clinical trials in children: a European perspective. Archives of Disease in Childhood. 2009;94(6):474-7.

134. Greener M. Bitter medicine.New regulations aim to address the dearth of clinical safety trials for drugs used in children. EMBO Rep. 2008;9(6):505-8.

135. European Medicines Agency (EMA). Paediatric Regulation. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp. Accessed 5 August 2013.

136. Li J, Eisenstein E, Grabowski H, Reid E, Mangum B, Schulman K, Goldsmith J, Murphy MD, Califf R, Benjamin D. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program: JAMA February 7, 2007;297(5):480-488; 2007.

137. US Food and Drug Administration (FDA). New Pediatric Labeling Information Database. Available at: http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase. Accessed 22 May and 19 July 2013.

138. WHO and StaR Child Health. Report of the WHO and StaR Child Health Paediatric Trials in Developing Countries Meeting: Use of Standards in Paediatric Clinical Trials in Developing Countries Meeting. Available at: http://www.who.int/childmedicines/progress/Amsterdam_Meeting.pdf. Accessed 5 May 2013. Amsterdam, The Netherlands: 28 October 2009.

139. US Food and Drug Administration. Database Is One-Stop Resource on Kids' Medications. Available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm305040.htm?source=govdelivery. Accessed 30 May 2012.

140. Olski TM, Lampus SF, Gherarducci G , Saint Raymond A. Three years of paediatric regulation in the European Union. Eur J Clin Pharmacol. 2011 Mar;67(3):245-52.

141. Boots I, Sukhai RN, Klein RH, Holl RA, Wit JM, Cohen AF, Burggraaf J. Stimulation programs for pediatric drug research--do children really benefit? Eur J Pediatr. 2007;166(8):849-55. Epub 2007/01/18.

142. Hoppu K, Anabwani G, Garcia-Bournissen F, Gazarian M, Kearns G, Nakamura H, Peterson R, Sri Ranganathan S, Wildt S. The status of paediatric medicines initiatives around the world—what has happened and what has not? Eur J Clin Pharmacol. 2012;68(1):1-10.

143. Flynn JT. Successes and shortcomings of the Food and Drug Modernization Act. Am J Hypertens. 2003;16(10):889-91.

144. World Health Organisation (WHO). Essential Medicines for children. Available at: http://www.who.int/childmedicines/. Accessed 12 April 2013.

145. World Health Organisation. Medicines for children: Resources, progress reports and scientific publications: Medicines: medicines for children.Fact sheet N°34, 1June 2010. Available at: http://www.who.int/mediacentre/factsheets/fs341/en/index.html.Accessed 9 April 2013.

146. Duke translational Medicine Institute. Pediatric Trials Network funded with $95M NIH grant, has FDA approval to study 4 drugs, now enrolling. https://www.dtmi.duke.edu/news-publications/news/dtmi-news-archives/putting-an-end-to-2018ballpark-dosing2019-in-children. Accessed 20 October 2013.

147. Benjamin D. Clinical Trials Approach and the Pediatric Trials Network. American Society for Clinical Pharmacology and Therapeutics (ASCPT) conference, 12-17 March, 2012: Available at https://pediatrictrialsorg/background/ptn-news-papers/ptn-presentations/. Accessed 20 October 2013.

148. European Medicines Agency (EMA). Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). Available at http://www.ema.europa.edu/ema/index.jsp?curl=pages/partners_and_networks/general_content_000303.jsp&mid=WC0b01ac05801df74a. Accessed 12 April 2012.

149. Star Child Health. Standards for Research in Child Health. Available at:http://ifsrc.org/. Accessed 30 July 2013.

150. Frakking FNJ, Van der Lee JH, Klassen JH, Offringa M, for the StaR-Child Health Group. Report: Survey of current guidance for Child health clinical trials The star child health project: standards for research with Children. 2009 Available at: http://www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf. Accessed 5 August 2013.

151. Hartling L, Wittmeier KDM, Caldwell P, van der Lee H, Klassen TP, Craig JC, Offringa M, for the StaR Child Health Group. StaR Child Health: Developing Evidence-Based Guidance for the Design, Conduct, and Reporting of Pediatric Trials. Pediatrics. 2012;129(Supplement 3):S112-S7.

152. International Pediatric Association. IPA Statement on Equity and Quality Healthcare for Children of the World.Fifty-seventh Session of the WHO Regional Committee for the Western Pacific Auckland, New Zealand, 18 –22nd September 2006.Agenda Item 7: Report of the Regional Director. Available at: http://www.ipa-world.org/uploadedbyfck/WSO_0001.pdf. Accessed 3 August 2013.

153. National Institutes of Health. NIH policy and guidelines on the inclusion of children as participants in Research involving human subjects. 6 March1998. Available at: http://grants.nih.gov/grants/guide/notice-files/not98-024.html. Accessed 10 August 2013.

154. National Institute of Health (NIH) and Child Development (NICHD). Clinical Trials & Clinical Research. Available at:www.nichd.nih.gov/health/clinicalresearch/. Accessed 5 July 2013.

155. UK Medical Research Council. MRC Ethics guide. Medical Research involving children. 2004. Available at: http://www.mrc.ac.uk/consumption/idcplg?IdcService=GET_FILE&dID=11512&dDocName=MRC002430&allowInterrupt=1. Accessed 10 August 2013.

156. Royal College of Paediatrics and Child Health (RCPCH). Children's medicines. Available at: http://www.rcpch.ac.uk/child-health/childrens-medicines/childrens-medicines. Accessed 10 August 2013.

157. Devine S, Dagher RN, Weiss KD, Santana VM. Good clinical practice and the conduct of clinical studies in pediatric oncology. Pediatr Clin North Am. 2008;55(1):187-209, xi-xii.

158. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. JAMA. 2003;290(12):1624-32.

Chapter 3

Disease burden - research match? Registered trials in child health from low-middle and high-income countries

Chapter 3: Disease burden - research match? Registered trials in child health from low-middle and high-income countries

3.1 Abstract

Objective: To compare registered clinical trials in children to the paediatric disease burden in low-and middle-income countries (LMICs) and high-income countries.

Methods: All trials on the World Health Organization (WHO) International Clinical Trials Registry Platform registered from 2005 to 2013 were reviewed. The disease-specific focus of registered trials for children was compared to the global burden of disease for 2011 using WHO disability-adjusted life-year data.

Results: Children account for 25% of the global disease burden, but represent only 15% (29 899/203 726) of registered trials. Although the number of trials in children registered annually has increased over time (from 3174 in 2005 to 3392 in 2013), the proportion of trials involving children has decreased (from 18% to 13%). Despite 98% of the paediatric illness burden being in LMIC, only 22% of all trials in child health are conducted in those countries. More trials were registered in high-income than in LMICs for the majority of the disease categories. There was moderate correlation between the number of trials and the burden of each disease within each region (Spearman's correlation r=0.6, P=0.007 and r=0.55, P=0.015 in LMICs and high-income countries, respectively).

Conclusions: Overall, children continue to be under-represented in clinical trials, particularly children from LMICs where disease burden is greatest. Trial activity correlates moderately with disease burden among the world's children. Stakeholders need to embrace an evidence-informed approach of prioritising trials to specifically address healthcare needs of children and improve the disparities.

What is known on this topic

- Many medicines in children have not been tested for safety and efficacy, particularly in low-and middle-income countries, but this has not been properly enumerated.
- Clinical trials in children are important to inform evidence-informed child healthcare.
- There are initiatives to register and conduct more trials in children, however investigations on whether the scope of all trials registered worldwide matches relevant child health therapeutic areas to inform the research agenda in children is scarce.

What this study adds

- Children account for 25% of the global disease burden, but represent only 15% of the total trials registered worldwide.
- Less than a quarter (22%) of the total registered trials in children were in the LMICs, despite 89% of the world's children living in this region and contributing to 98% of the global paediatric disease burden.
- There is mismatched focus of trials in relation to disease burden, which should be prioritised according to the therapeutic needs of children, and where the disease impact is greatest.

3.2 Introduction

The majority of the disease burden and mortality among children occurs in low-and middle-income countries (LMICs), while most of the paediatric research expertise and resources is concentrated in high-income countries [1]. The World Health Organization's (WHO) Millennium Development Goals aim to close the gap in inequitable healthcare delivery and improve outcomes for children globally [2, 3]. New research underpinning such ambitious goals, particularly trials to support the safe and effective use of interventions, is required.

Descriptive studies suggest that there are fewer trials in children, especially in resource-limited settings [4-8]. A comparison of the distribution of current trials conducted among children against child health needs is required to inform strategies for prioritising research. The WHO International Clinical Trials Registry Platform (ICTRP), a global initiative linking national trial registers, was established in 2006 to improve transparency and access to trial registration data [9, 10]. The aim of our study was to compare registered trials in children to the paediatric disease burden in low-middle and high-income countries.

3.3 Methods

3.3.1 Inclusion criteria

All trials on the WHO ICTRP from 1 January 2005 to 31 December 2013 were selected because most major journals required trial registration from 2005 [10, 11]. The WHO portal provides access to a comprehensive central database of trial records that meet the WHO International Standards for Clinical Trial Registries. The portal has a facility to allow for identification of on-going and completed child-specific trials, defined as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" [9] in participants from birth to 18 years inclusive.

3.3.2 Data extraction

Data were extracted from January 22-27, 2014. Double data extraction was performed independently with data re-extracted when discordant values were obtained. The number of registered trials rather than the number of records of trials was extracted, avoiding overestimation of trials that had multiple registrations. Registered trials in children by the country of recruitment were determined by limiting 'search for clinical trials in children.' The total number was determined by combining the trials from low-middle and high-income

countries. Trials in adults were determined by subtracting the number registered in children from the total number of trials.

The data on the number of trials were extracted yearly from 2005 until 2013. Characteristics of child-specific trials extracted according to income regions included the disease-specific scope, intervention, and primary sponsorship. Intervention was classified using an adapted list from clinicaltrials.gov [12-14]. An adapted Australian New Zealand Clinical Trials Registry (ANZCTR) list was used to classify the primary sponsor [15]. For industry sponsorship, we searched for 'commercial or pharmaceutical' and the top 25 pharmaceutical companies names [16].

3.3.3 Disease-specific scope

The WHO Global Health Estimates summary tables disease categories were used [17]. Health condition refers to an illness, disorder, injury or any health issue [12]. The disease category was specified in the 'condition' field on the portal. Malignant and other neoplasms were combined as one category. Synonymous terms for diseases were combined during data extraction.

3.3.4 Location

Recruiting countries were defined as low-and middle-income or high-income according to the World Bank list of economies, July 2012.[18] The groups are low-and middle-income (combined for low-income: $1025 or less, lower-middle income: $1026–4035, upper-middle income: $4036–12475) and high-income ($12476 or more) [18]. Individual countries from the income regions were selected in the 'countries of recruitment' field and data were extracted for all the countries combined for that region.

3.3.5 Disease burden

The population and disease burden in children was estimated from the World Bank data of 2011[18, 19]. The WHO disability-adjusted life-year (DALY) data for 2011 was used to estimate the burden of disease [17]. DALYs were calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences [9]. One DALY may be regarded as one lost year of 'healthy' life due to disease [9, 20]. Pre-defined age groups were used for the population and DALY data in the Global Health Estimates summary tables. An approximate estimate of DALYs for children 0–18 years was determined by combining DALYs for persons 0–27 days, 1–59 months, 5–14 years, and 4/15 of 15–29 years [9, 20, 21].

3.3.6 Statistical analysis

For every Global Health Estimate disease category, we calculated the DALYs for each income region using the world paediatric DALYs. The proportion of trials in each therapeutic area within each region was compared to the proportion of DALYs in that therapeutic area or region using one-sample Wald tests for binomial proportions and 95% confidence intervals calculated. Within each region, the associations between the number of trials and the DALYs for the various therapeutic areas were calculated using Spearman correlations. Statistical analyses was performed using the SAS software, version 9.3 (SAS Institute, Cary, North Carolina).

3.4 Results

3.4.1 Number and location of trials

In 2011, 24% (2319/9730 million) of the world's population were children. However, only 15% (29 899/203 726) of all trials registered worldwide between 2005 and 2013 were conducted in children. Despite a steady increase in the number of registered trials in children

worldwide, from 3174 in 2005 to 3392 in 2013, as a proportion of the total number of trials, this has decreased from 18% (3174/17 274) in 2005 to 13% (3392/25 822) in 2013 (Figure 1).

Most (89%) of the world's children live in LMICs, but only 22% of the 29 899 registered trials involve these countries. For the period 2005 to 2013, the total number of trials in children from LMICs has increased from 405 to 1033, compared to high-income countries where it has decreased from 2769 to 2359 (Figure 1). Over these nine years, the proportion of registered trials in children in the LMICs has increased from 13% (405/3174) to 30% (1033/3392).

3.4.2 Characteristics of registered trials in children

3.4.2.1 Types of intervention and sponsorship

Drug therapy was the main intervention type, comprising 31% (9357/29 899) of the total trials in children (Table 1) with the majority 77% (7233/9357) in high-income countries.

The same number of biological or vaccine trials (1918) were conducted in children in both income regions. Universities were the major sponsor of trials conducted in children worldwide with only 17% sponsored by the pharmaceutical industry.

3.4.3 Comparison of trials and disease burden for Global Health Estimate disease categories

Children contributed to 25% of the global disease burden, but only 15% (29 899/203 726) of the total number of registered trials. There was a significant mismatch in the 22% of trials (95% CI 21.7– 22.7) relative to 98% of disease burden ($p < 0.001$) among children in LMICs compared to high-income countries (Table 2).

There was moderate correlation between the number of trials and the burden of each disease within each region (Spearman's correlation r=0.6, P=0.007 and r=0.55, P=0.015 and LMICs and high-income countries, respectively). Worldwide, neonates comprise only 0·5% of the pediatric population, but neonatal conditions account for 24% of the global disease burden in children, with LMICs contributing about 99% of this burden. Only 4% of the registered trials in children were in neonatal conditions and another 3% in congenital anomalies.

Within the LMICs, the number of trials for most conditions was under-represented relative to disease burden (Table 1 and Figure 2). Most trials 1143 (17%) were in infectious and parasitic diseases which contributed the greatest burden of disease with 256 million DALYs (28%), followed by 622 (9%) trials in respiratory diseases with 15·9 million DALYs (2%), and 435 (7%) trials in neonatal conditions with a high disease burden of 223.8 million DALYs (24%).

In contrast, in high-income countries, most trials in children were over-represented relative to the disease burden. Most trials involved respiratory diseases 2386 (10%) with 1.5 million DALYs (7%), neoplasms 1969 (8%) trials with 0.7 million DALYs (3%), infectious and parasitic disease 1314 (6%) trials with 1.2 million DALYs (5%) and mental or behavioral 1192 (5%) trials with the highest disease burden of 4.9 million DALYs (22%).

3.5 Discussion

Mismatches in the proportion of registered trials in children in comparison to adults, the geographic location by national income, and disease burden were shown in our study. Interventions are not frequently studied in the children most at risk, or in countries and therapeutic areas of need. Disproportionately fewer trials are registered in children compared to adults, in LMICs compared to high-income countries, and in diseases which have a high burden in children.

Our finding that there are fewer registered trials in children compared to adults has been extensively highlighted over the last decade [20-24]. However, we observed that the gap is increasing and there are now approximately five times more trials in adults compared to children, with the number of trials in children plateauing. The reasons behind this observation are likely to be complex and include small prevalence of diseases in children, safety concerns of involving children, changing needs of populations (such as demographics, decreasing child mortality and ageing population), market-driven forces and the ethical and regulatory burden [25, 26].

Our analysis showed that registered trials in children by income regions were still moderately correlated to the disease burden [21]. The mismatched focus of trials to disease burden in all settings is possibly driven by political influences, responsive agendas of the pharmaceutical industry to economic incentives, and the academic interest of investigators [26]. Within the LMICs countries, children contributed proportionately more to disease burden, compared to the high-income countries. However, there is gross inequity as less than a quarter (22%) of the total registered trials in children were in the LMICs, despite 89% of the world's children living in this region and contributing to 98% of the global pediatric disease burden [27]. The disproportionately small number of trials in LMICs is likely to be due to less research infrastructure and investment in research, the additional complexities and challenges associated with poverty, and the prioritisation given to urgent acute care [28-32]. Classical trial designs may sometimes be inappropriate in LMICs and more effort should be spent on innovative trial designs or alternative methods like pharmacokinetic studies that may be more efficient. Although our study shows the continuing inequity in opportunities to participate in trials, based upon income, the gap between the regions appears to be narrowing [33]. We observed that trials in children in the LMICs have more than doubled over the last nine years, compared to the proportion within high-income countries. This is likely driven by

globalisation, cost imperatives, increased awareness, philanthropic effort and a greater commitment to evidence-based medicine [30, 34, 35].

Our findings confirm that the leading paediatric diseases in both regions are very different, with the focus being communicable diseases related to poverty in the LMICs, and non-communicable diseases of affluent lifestyle in the high-income countries [36-38]. Over 50% of trials in infectious and parasitic diseases are being conducted in high-income countries while LMICs carry almost 100% of the burden. These trials in high-income countries are possibly focused on rarer infections and are small studies, while those in LMICs are larger studies of important diseases such as malaria or diarrhoeal disease. Another contributory factor is that vaccines and biological trials are simultaneously trialed in both income regions, possibly because of global prioritisation of infectious diseases and the large sample size required to determine vaccine safety [19, 33, 39]. This is encouraging as medicines should be trialed in different pediatric populations to allow for indigenous data, as pharmacogenomic differences may not generate reproducible effects. Although there is concern that some interventions in children that are successful in high-income countries may not be affordable or accessible in LMICs, this should not exclude their participation as their circumstances may change and poverty is not uniform in these countries [29, 40].

Neonatal conditions and congenital anomalies are among the leading causes of disease burden and mortality in both income regions [41, 42]. However, our study corroborates other findings demonstrating that neonates, as a group, are grossly under-studied, possibly due to the narrow spectrum of neonatal diagnoses, ethical challenges, safety concerns, greater complexity and long timelines for completion [43, 44]. Mental and behavioral diseases had fewer trials as interventions are more likely to be non-randomised studies of non-drug interventions which are inherently more complex. The disease-specific focus of some of the trials (for example,

neoplasms) may also be due to health ministries' prioritisation, successful international collaborative research networks, sustainable funding, and emotional appeal [45, 46].

Some of the strengths of our study include reporting on data from the WHO portal which contained data from 16 clinical trial registers from 16 countries at the time of the study. We have used DALYs data for 2011, which is more updated than previous analysis and the established Global Health Estimate categories for health conditions. Our study has highlighted the gaps and current disease focus of trials in children and has provided the current trend of trials in children that can inform priority areas for clinical research. However, there were potential limitations to this study. There may have been trials that were not registered on the WHO primary registers and would have been excluded. There may have been non-conformity among registry records and incomplete fields. Different clinical challenges in newborns, infants and children may require different trial evidence and comparing the number of trials in certain diseases such as congenital neonatal conditions to respiratory illness may not be appropriate. Disease conditions may be over- or under-represented according to the number of trials, but there are other measures of trial "effort". The restrictions of the portal did not make it possible to extract other data, such as sample size, facilitate subgroup analyses of commercial versus non-commercial trials, or identifying trials with mixed populations of adults and children and we recommend further enhancements to the portal.

Our study has shown that there is scope for the trial data on the registries to be linked to the countries' burden of disease to identify the unmet healthcare needs in children. This is valuable to stakeholders, both locally and internationally to inform the paediatric research agenda and canvass for greater investment in trials to primarily meet the need for evidence-based care of children and ensure universal health coverage. Global research priorities should reflect the global burden of disease in children, while national health priorities should be

considered within countries. The evidence gained supports the recommendation for a WHO global observatory on health research and development to help align research investment with the demands of child health and restore the current inequities in the most disadvantaged children in LMICs [27].

3.6 Conclusions

Worldwide, children continue to be under-represented in trials, particularly in LMICs where disease burden is greatest. The numbers of trials in specific diseases correlates only moderately with the proportion of disease burden in children. There were mismatches of trial focus with disease burden, like respiratory diseases and neoplasms which were over-represented and congenital and neonatal anomalies that were under-represented. Our analysis provides a benchmark for targeting more trials in children in diseases of greatest burden and neglected therapeutic areas, in appropriate settings to inform policy and clinical practice. Stakeholders both locally and internationally need to embrace an evidence-informed approach of prioritising trials to specifically address the healthcare needs of children and improve the disparities within global child healthcare.

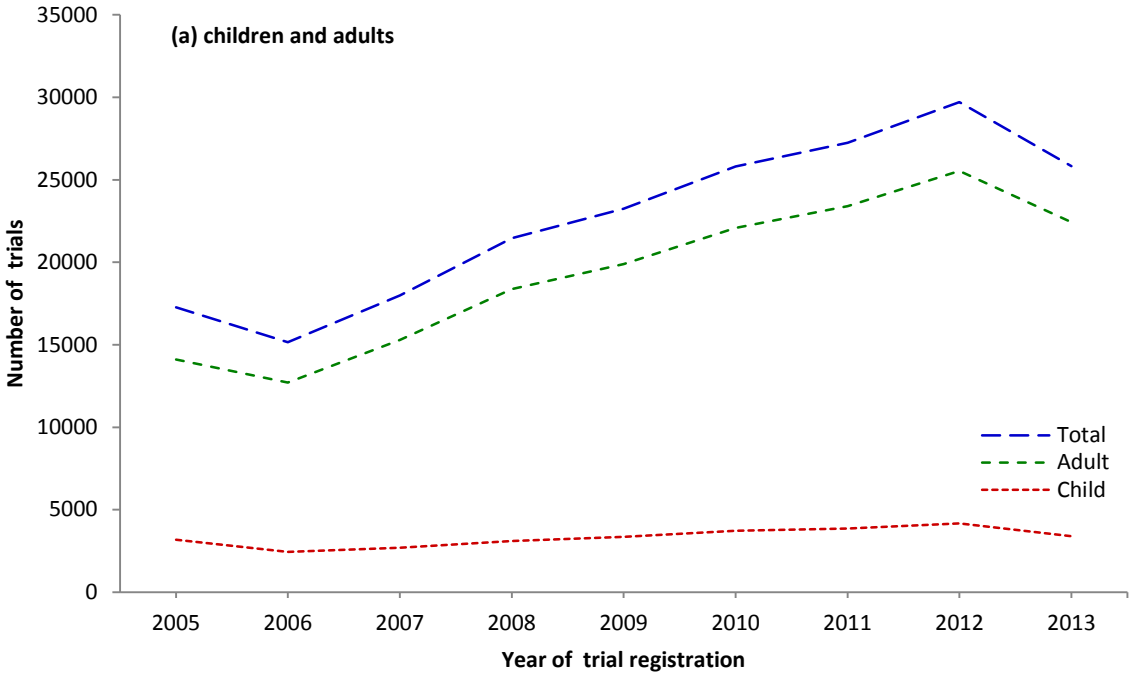
Table 3.1 Characteristics of registered trials in child health (2005–2013)

Characteristic	Region		Total (%)
	Low-middle income countries (%) n=6636 (22.2)	High-income countries (%) n=23263 (77.8)	n=29899 (100)
Intervention Type			
Drug	2124 (32.0)	7233 (31.1)	9357 (31.3)
Biological/vaccine	1918(28.9)	1918 (8.2)	3836 (12.8)
Behavioral	484 (7.3)	3159 (13.6)	3643 (12.2)
Procedure/surgery	479 (7.2)	2025 (8.7)	2504 (8.4)
Radiation	355 (5.3)	2069 (8.9)	2424 (8.1)
Genetic	272 (4.1)	1543 (6.6)	1815 (6.1)
Nutrition/dietary supplement	450 (6.8)	1057 (4.5)	1507 (5.0)
Device	221 (3.3)	1275 (5.5)	1496 (5.0)
Physical therapy	207 (3.1)	1101 (4.7)	1308 (4.4)
Other/unclassified	150 (2.3)	1883 (8.1)	2033 (6.8)
Sponsor			
University	2115 (31.9)	7012 (30.1)	9127 (30.5)
Commercial sector/industry	1316 (19.8)	3714 (16.0)	5030 (16.8)
Hospital	651 (9.8)	3958 (17.0)	4609 (15.4)
Individual	102 (1.5)	533 (2.3)	635 (2.1)
Foundation/charity/society	84 (1.3)	464 (2.0)	548 (1.8)
Government funding body	172 (2.6)	184 (0.8)	356 (1.2)
Collaborative group	27 (0.4)	132 (0.6)	159 (0.5)
Other/unclassified	2169 (32.7)	7266 (31.2)	9435 (31.6)
Disease Condition Global Health Estimate			
Respiratory diseases	622 (9.4)	2386 (10.3)	3008 (10.1)
Infectious and parasitic diseases	1143 (17.2)	1314 (5.6)	2457 (8.2)
Malignant and other neoplasms	207 (3.1)	1969 (8.3)	2176 (7.3)
Mental and behavioural disorders	215 (3.2)	1192 (5.1)	1407 (4.7)
Respiratory infections	410 (6.2)	947 (4.1)	1357 (4.5)
Neonatal conditions	435 (6.6)	847 (3.6)	1282 (4.3)
Musculoskeletal diseases	253 (3.8)	995(4.3)	1248 (4.2)
Sense organ diseases	209 (3.1)	922 (4.0)	1131 (3.8)
Diabetes mellitus	147 (2.2)	843 (3.6)	990 (3.3)
Neurological conditions	173 (2.6)	710 (3.1)	883 (3.0)
Congenital anomalies	124 (1.9)	759 (3·3)	883 (3.0)
Maternal conditions	245 (3.7)	637(2.7)	882 (2.9)
Cardiovascular diseases	99 (1.5)	706 (3.0)	805 (2.7)
Nutritional deficiencies	307 (4.6)	400(1.7)	707 (2.4)
Endocrine, blood, immune disorders	106 (1.6)	550 (2.4)	656 (2.2)
Digestive diseases	115 (1.7)	419 (1.8)	534 (1.8)
Genitourinary diseases	61 (0.9)	338(1.5)	399 (1.3)
Oral conditions	65 (1.0)	141 (0.6)	206 (0.7)
Skin diseases	25 (0.4)	109 (0.5)	134 (0.4)
Other/unclassified	1675 (25.4)	7079(30.4)	8754 (29.3)

Table 3.2 Number of trials in the Top 10 disease contributors to disability in children stratified by income region (2005–2013)

Global Health Estimate disease category	Region DALYs (millions)	World DALYs millions)	Region DALYs/World DALYs (%)	Number of trials (region)	Number of trials (world)	Proportion of trials (region/ world) (%)
Low and-middle-income countries						
Total	929.9	952.0	97.7	6636	29899	22.2
Infectious and parasitic diseases	256.4	257.6	99.5	926	2240	41.3
Neonatal conditions	223.8	226.4	98.8	435	1282	33.9
Respiratory infections	124.9	125.5	95.5	410	1357	30.2
Nutritional deficiencies	55.3	55.9	99.0	307	707	43.4
Congenital anomalies	49.5	51.6	96.0	124	883	14.0
Mental and behavioural disorders	36.6	41.5	88.2	215	1407	15.3
Respiratory diseases	15.9	17.4	91.6	622	3008	20.7
Neurological conditions	14.8	15.6	94.6	173	883	19.6
Cardiovascular diseases	14.4	14.9	96.3	99	805	12.3
Endocrine, blood, immune disorders	14.3	15.4	93.1	106	656	16.2
High-income countries						
Total	22.1	952.0	2.4	23263	29899	77.8
Mental and behavioural disorders	4.9	41.5	11.8	1192	1407	84.7
Neonatal conditions	2.7	226.5	1.2	847	1282	66.1
Congenital anomalies	2.1	51.6	4.2	759	883	86.0
Respiratory diseases	1.4	17.4	8.0	2386	3008	79.3
Infectious and parasitic diseases	1.2	257.6	0.5	1314	2240	58.7
Musculoskeletal diseases	1.2	8.3	14.5	995	1248	79.7
Endocrine, blood, immune disorders	1.1	15.4	6.9	550	656	83.8
Neurological conditions	0.8	15.6	5.4	710	883	80.4
Neoplasms	0.7	10.7	6.3	1969	2176	90.5
Respiratory infections	0.6	125.5	0.5	947	1357	69.8

Figure 3.1 Number of registered trials in (a) children and adults and (b) children by income region (2005–2013)



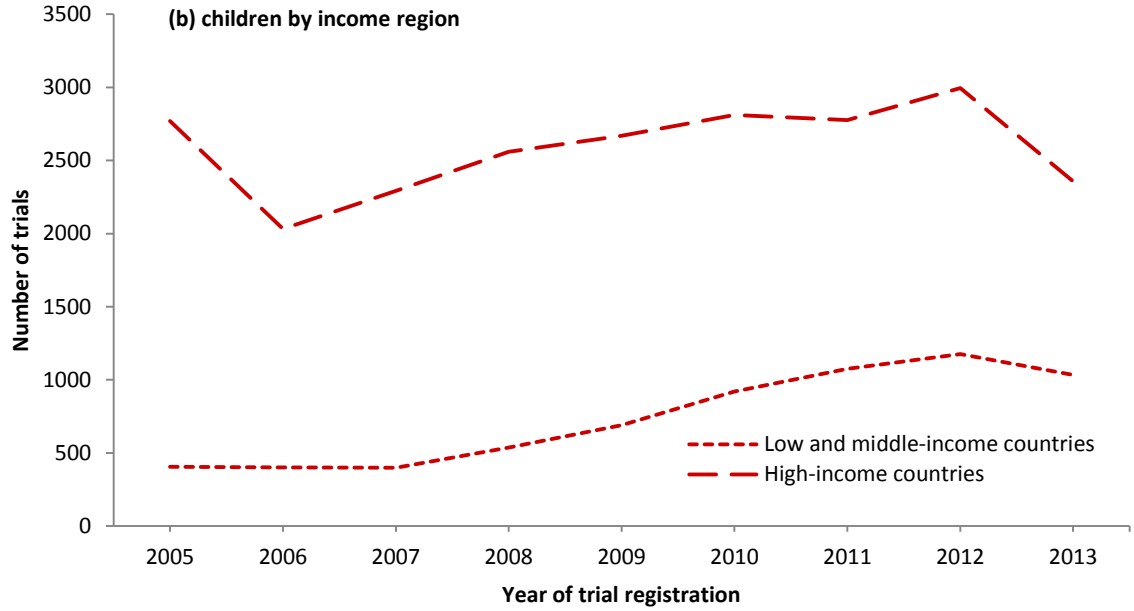
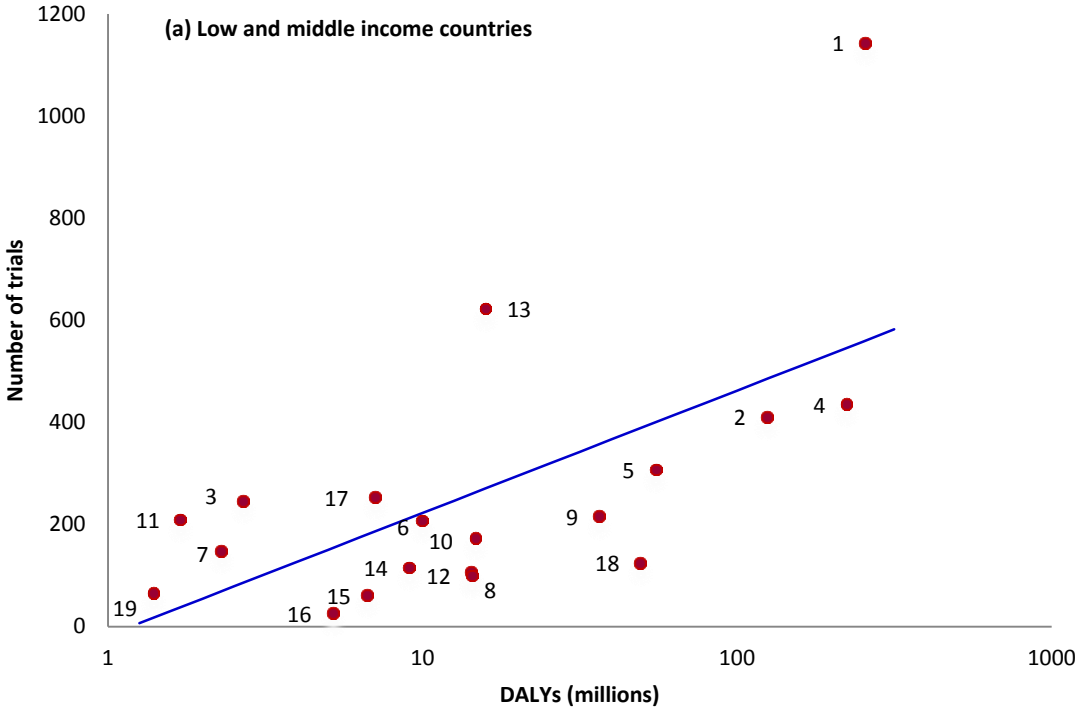
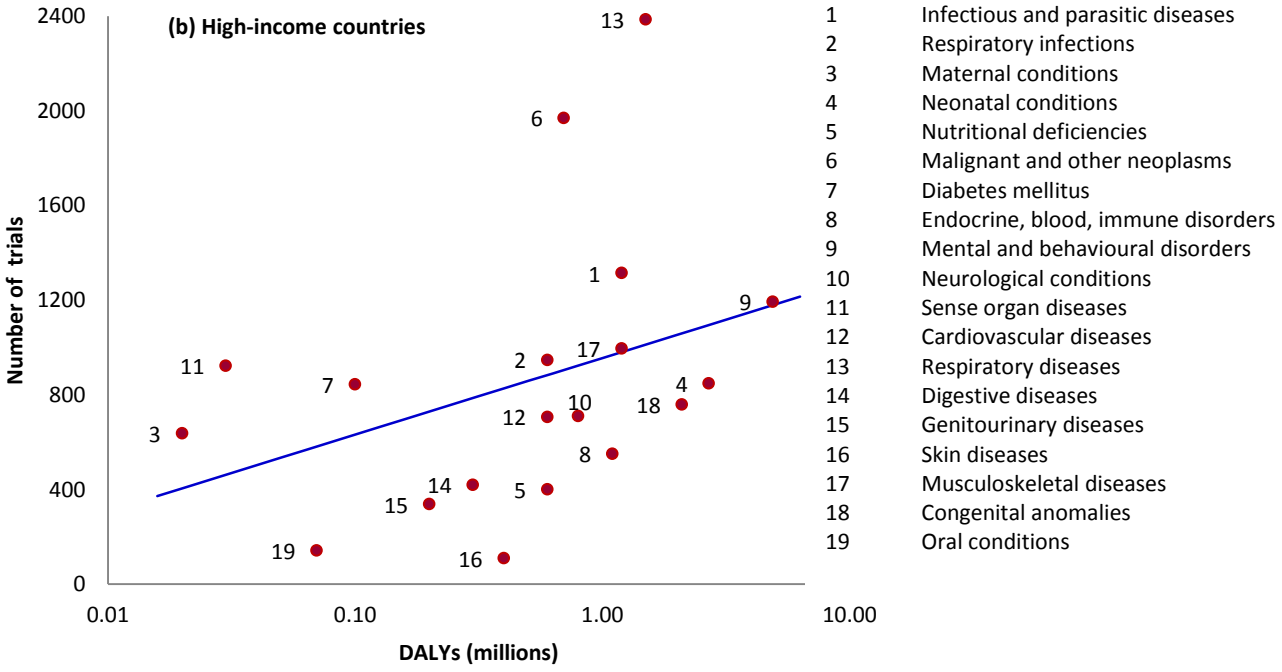


Figure 3.2 Association between disease burden and the number of registered trials in children (2005–2013) for the Global Health Estimate disease categories within (a) Low-and middle-income countries and (b) High-income countries





3.7 References

1. Zipursky A. The programme for Global Paediatric Research. Clin Invest Med. 2011;34(6):E320-E2.
2. Horton R. Closing the killer gap in children's health inequality [editorial]. The Lancet. 2013;382(9896):914.
3. World Vision International. The Killer Gap: A global index of health inequality for children. World Vision International website. Available at: http://wvi.org/thekillergap. Policy report. Published 2013. Accessed October 1, 2015.
4. Sammons HM, Choonara I. Clinical trials of medication in children 1996-2002. Eur J Clin Pharmacol. 2005;61:165-7.
5. Nor Aripin KNB, Sammons HM, Choonara I. Published Pediatric Randomized Drug Trials in Developing Countries, 1996-2002. Paediatric Drugs. 2010;12(2):99-103.
6. Aripin KNBN, Choonara I, Sammons HM. A systematic review of paediatric randomised controlled drug trials published in 2007. Arch Dis Child. 2010;95(6):469-73.
7. Walleser S, Hill SR, Bero LA. Characteristics and quality of reporting of cluster randomized trials in children: reporting needs improvement. J Clin Epidemiol. 2011;64(12):1331-40.
8. Pasquali SK, Lam WK, Chiswell K, Kemper AR, Li JS. Status of the pediatric clinical trials enterprise: an analysis of the US ClinicalTrials.gov registry. Pediatrics. 2012;130(5):e1269-77.
9. World Health Organisation. Health statistics and health information systems: Metrics: Disability-Adjusted Life Year (DALY). 2015. Available at: http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/. Accessed February18, 2014.
10. World Health Organization's International Clinical Trials Registry Platform. International standards for clinical trial registries.1.Clinical trials as topic - standards. 2.Registries – standards Geneva, Switzerland: WHO Press, World Health Organization; 2012.
11. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals:Publishing and Editorial Issues Related to Publication in Biomedical Journals: Obligation to Register Clinical Trials. 2013. Available at: http://www.icmje.org/publishing_10register.html. Accessed September 26, 2013.
12. World Health Organisation. International Clinical Trials Registry Platform (ICTRP). Version 3.2. Available at: http://www.who.int/ictrp/en/. Accessed January 22, 2013.
13. US ClinicalTrials.gov.Protocol Data Element Definitions (DRAFT). September 2014. Available at: http://prsinfo.clinicaltrials.gov/definitions.html. Accessed October 22, 2015
14. Kubiak C, Andres-Trelles F, Kuchinke W, Karl-Heinz Huemer, Steffen Thirstrup, Kate Whitfield, et al. Common definition for categories of clinical research: a prerequisite for a survey on regulatory requirements by the European Clinical Research Infrastructures Network (ECRIN). Trials. 2009;10(95):1-7.

15. Australian New Zealand Clinical Trials Registry (ANZCTR).Data Item Definition/Explanation. 2007. Available at: http://www.anzctr.org.au. Accessed April 16, 2013.

16. Current partnering. Current Partnering.Top 50 pharma (top pharmaceutical companies). 2013. Available at: http://www.currentpartnering.com/insight/top-50-pharma/. Accessed March 12, 2013.

17. World Health Organization. Global health estimates summary tables: DALYs by cause, age and sex, by world bank income group. 2013.World Health Organization, Geneva, Switzerland. Available at: http://www.who.int/healthinfo/global_burden_disease/en/. Published November 2013. Accessed December 12, 2013.

18. World Bank list of economies (July 2012). Available at: http://librarians.acm.org/sites/default/files/world%20bank%20List%20of%20Economies%20%28as%20of%20July%202012%29.pdf. Accessed April 20, 2013.

19. World Health Organization. Department of Immunizations,Vaccines and Biologicals. State of the art of new vaccines:research and development. World Health Organization. Geneva, Switzerland. 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.01_eng.pdf. Published January 2006. Accessed March 15, 2014.

20. Bourgeois FT, Murthy S, Pinto C, Olson KL, Ioannidis JP, Mandl KD. Pediatric versus adult drug trials for conditions with high pediatric disease burden. Pediatrics. 2012.;130(2):285-92.

21. Bourgeois FT, Olson KL, Ioannidis JP, Mandl KD. Association between pediatric clinical trials and global burden of disease. Pediatrics. 2014;133(1):78-87.

22. Cohen E, Goldman RD, Ragone A, Uleryk E, Atenafu EG, Siddiqui U, et al. Child vs adult randomized controlled trials in specialist journals: a citation analysis of trends, 1985-2005. Arch Pediatr Adolesc Med. 2010;164(3):283-8.

23. Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985-2004. J Clin Epidemiol. 2007;60(2):118-23.

24. Florence T. Bourgeois, Srinivas Murthy, Catia Pinto, Karen L. Olson, John P.A. Ioannidis, Kenneth D. Mandl. Pediatric Versus Adult Drug Trials for Conditions With High Pediatric Disease Burden. Pediatrics. August 2012 130(2):285–92.

25. Klassen TP, Hartling L, Craig JC, Offringa M. Children Are Not Just Small Adults: The Urgent Need for High-Quality Trial Evidence in Children. PLoS Medicine / Public Library of Science. 2008;5(8):e172.

26. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357-69.

27. Edwards D, Matlin SA, Eide M, Young AJ, Regmi S, Ardal C, et al. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet. 2013;382(9900):1286-307.

28. Emdin CA, Odutayo A, Hsiao AJ, Shakir M, Hopewell S, Rahimi K, et al. Association between randomised trial evidence and global burden of disease: cross sectional study (Epidemiological Study of Randomized Trials--ESORT). BMJ (Clinical research ed). 2015;350(jan28 24):h117-h.

29. Molyneux E, Mathanga D, Witte D, Molyneux M. Practical issues in relation to clinical trials in children in low-income countries: experience from the front line. Arch Dis Child. 2012;97(9):848-51.

30. Bairu M, Chin R, editors. Global Clinical trials playbook:capacity and capability building. first ed. Waltham, USA: Elsevier Inc.; 2012.

31. Regmi S, Kaas–Hansen BS, Iversen JH. Beyond access to medicines: Eliciting high–income country support for a new global health research and development paradigm. Journal of Global Health. 2013;3(2):020303.

32. Hoppu K, Sri Ranganathan S, Dodoo ANO. Realities of paediatric pharmacotherapy in the developing world. Arch Dis Child. 2011;96(8):764-8.

33. Dunne J, Murphy MD, Rodriguez WJ. The globalization of pediatric clinical trials Pediatrics. 2012;130(6):1583-91.

34. Pasquali SK, Burstein DS, Benjamin DK, Smith PB, Li JS. Globalization of Pediatric Research: Analysis of Clinical Trials Completed for Pediatric Exclusivity. Pediatrics. 2010;126(3):e687-e92.

35. Duke T, Fuller D. Randomised controlled trials in child health in developing countries: trends and lessons over 11 years. Arch Dis Child. 2014;99(7):615-20.

36. Gore FM, Bloem PJN, Patton GC, Ferguson J, Joseph V, Coffey C, et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. The Lancet.377(9783):2093-102.

37. Mathers C, editor. Chapter 2 Global Burden of Disease Among Women, Children, and Adolescents.2009.

38. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012;380(9859):2197-223.

39. Glass RI, Bresee JS, Parashar UD, Jiang B, Gentsch J. The future of rotavirus vaccines: a major setback leads to new opportunities. The Lancet. 2004;363(9420):1547-50.

40. Wadman M. HIV trial under scrutiny. Nature. 2013;493(7432):279-80.

41. Lawn JE, Kerber K, Enweronu-Laryea C, Bateman OM. Newborn survival in low resource settings–are we delivering? BJOG. 2009;116(suppl 1):49-59.

42. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. The Lancet.385(9966):430-40.

43. Viergever Roderik F RCMA, Ghersi Davina. Pharmacokinetic research in children: an analysis of registered records of clinical trials. BMJ openbmjcom on August 24, 2011. 2011:1-9.

44. Wang J, Avant D, Green D, Seo S, Fisher J, Mulberg AE, et al. A Survey of Neonatal Pharmacokinetic and Pharmacodynamic Studies in Pediatric Drug Development. Clin Pharmacol Ther. 2015;98(3):328-35.

45. Taylor T, Olola C, Valim C, Agbenyega T, Kremsner P, Krishna S, et al. Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. Trans R Soc Trop Med Hyg. 2006;100(7):615-22.

46. Sullivan R, Kowalczyk JR, Agarwal B, Ladenstein R, Fitzgerald E, Barr R, et al. New policies to address the global burden of childhood cancers. Lancet Oncol. 2013;14(3):e125-35.

Chapter 4

Stakeholder views of clinical trials in children in low- and middle-income countries: a systematic review

Chapter 4: Stakeholder views of clinical trials in children in low-and middle-income countries: a systematic review

4.1 Abstract

Context: Clinical trials are necessary to improve the healthcare of children, but only one-quarter are conducted in the low-middle income countries (LMICs) where 98% of the global burden of disease resides.

Objective: To describe stakeholder beliefs and experiences of conducting trials in children in LMICs to inform strategies for improving the number and relevance of trials in LMICs.

Data sources: Electronic databases were searched to August 2014.

Study selection: Qualitative studies of stakeholder perspectives on conducting clinical trials among children in LMICs.

Data extraction: Findings were analysed using thematic synthesis.

Results: Thirty-nine studies involving 3110 participants (children [n=290], parents or caregivers [n=1609], community representatives [n=621], clinical or research team [n=376], regulators [n=18] and sponsors [n=15]) across 22 countries were included. We identified five themes: centrality of community engagement (mobilising community, representatives pivotal role, managing expectations, retaining involvement); cognizance of vulnerability and poverty (therapeutic opportunity, medical mistrust); contending with power differentials (exploitation, stigmatisation, disempowerment); translating to local context (cultural beliefs, impoverishment constraints, ethical pluralism) and advocating fair distribution of benefits (healthcare, sponsor obligation, collateral community benefits).

Limitations: Studies not published in English-language were excluded.

Conclusions: Conducting trials in children in LMICs is complex due to social disadvantage, economic scarcity, idiosyncratic cultural beliefs and historical disempowerment which

contribute to inequity, mistrust and fears of exploitation. Effective community engagement in recruiting, building research capacity and designing trials that are pragmatic, ethical and relevant to the healthcare needs of children in LMICs may help to improve equity and health outcomes of this vulnerable population.

4.2 Introduction

Globally, the 2000 Millennium Development Goals and other initiatives have seen progressive improvements in child health [1, 2]. Although research has contributed positively by promoting therapeutic advances in healthcare of children, there are still inequities evident across different income settings [3]. The "10/90 gap" suggests that only 10% of global health research funds are invested into medical conditions that account for 90% of the global disease burden, which resides mainly in the low-and middle-income countries (LMICs) [4, 5]. 89% of children live in LMICs and contribute 98% to the global burden of disease, and yet only one-quarter of trials are done in this setting [6-8].

Conducting clinical trials in children in LMICs is reported to be more complex and they may be of lower methodological quality than trials in high-income countries [7]. Specific challenges include the risk of exploitation, scarce resources, deficient ethical and regulatory framework and logistical constraints [9].Qualitative research can help to explain social phenomena and provides an understanding of people's values, beliefs, and attitudes [10]. Thematic synthesis of multiple qualitative studies can generate more comprehensive insight across different stakeholder groups and settings.

The aim of this systematic review was to describe the perspectives and experiences of conducting clinical trials in children in LMICs among key stakeholders including children,

parents or caregivers, community representatives, clinical and research team, regulators and sponsors to inform strategies to improve locally relevant research in children from LMICs.

4.3 Materials and Methods

We followed the Enhancing Transparency of Reporting the Synthesis of Qualitative Research (ENTREQ) reporting guideline for systematic review of qualitative studies, as endorsed by the EQUATOR (Enhancing the Quality and Transparency Of health Research) network [11, 12].

4.3.1 Data sources and searches

The searches were conducted in MEDLINE and Embase from inception to 3rd August 2014. The search strategy is provided in Appendix B1. Google Scholar and reference lists of relevant articles and reviews were also searched. PDJ screened the titles and obtained full texts of potentially relevant studies, which were assessed for eligibility. CSH independently reviewed the search results to ensure that all studies that met the inclusion criteria were included.

4.3.2 Study selection criteria

Qualitative studies on stakeholders (children, parents or caregivers, community representatives, clinical or research team, regulators, sponsors) experiences and perspectives on conducting trials in children (aged 0-18 years) in LMICs (as classified by the World Bank) were included. Articles were excluded if they were quantitative surveys, reviews or commentaries or only reported on trials conducted in the adult population. Non-English articles were excluded to prevent potential misinterpretation of the information.

4.3.3 Quality of reporting appraisal

For each study, the comprehensiveness of reporting was independently appraised by two reviewers (PDJ and CSH) using the Consolidated Criteria for Reporting Qualitative Health Research (COREQ) framework, which included criteria relating to the research team, methods, study context, analysis and interpretations [13]. These provide contextual details for readers to evaluate the credibility, dependability and transferability of the study findings to other settings [13]. Any differences in assessment were discussed and resolved.

4.3.4 Data Extraction and Synthesis

Thematic synthesis was used to inductively generate analytical themes from the findings of the included studies [10]. All text under the ‘‘results or findings’’ or ‘‘conclusion or discussion’’ section of each article were extracted. The text were entered verbatim into HyperRESEARCH (ResearchWare, INC.2009, version 3.0.3, Randolph, MA) software for coding textual data. PDJ performed line-by-line coding of all relevant text and data. Similar concepts were categorised into themes. The themes were revised as new concepts were identified. To ensure that coding captured all relevant issues and reflected the primary data, two reviewers (CSH and PHC) independently reviewed the preliminary themes and analytical framework and discussed the addition or revision of themes with PDJ and AT. This form of investigator triangulation ensured that the coding framework and themes reflect the full breadth of data. Conceptual relationships between the themes were mapped to develop an overarching analytical thematic schema.

4.4 Results

4.4.1 Literature search and study characteristics

Overall, 39 studies involving more than 3110 participants were found to be eligible and included (Figure 4.1). Participants were children [n=290], parents or caregivers [n=1609],

community representatives [n=621], clinical and research team [n=376], regulators [n=18] and sponsors [n=15] (Box 4.1).

Box 4.1 Clinical trials in children stakeholders

Children*:* adolescents, youth, children

Parents or caregivers: mothers, fathers, caregivers, family members, adults in community

Community representatives: community health workers (CHW)/village reporters, leaders/chiefs/elders/ community advisory board members, education officers/ teachers/ school principals, community based organisations, women group leaders, traditional birth attendants/healers, HIV counselors, clergy, opinion leaders, civil society, media, mayors

Clinical or research team: health care providers, principal investigators (PI), project managers, fieldworkers (FW), field supervisors/managers, researchers, research nurses, community facilitators, head of clinical trials, research coordinators/assistants, research institutes/universities

Regulators: political officials, policy makers, ethical review bodies, research coordinating bodies

Sponsors: government, non-government organizations, pharmaceutical industry, other funding bodies

One study did not report the number of participants. The study characteristics are provided in Table 4.1. The studies were conducted across 22 countries with the majority in Africa. The perspectives were predominantly focused on trials within the specialty of infectious diseases, particularly human immunodeficiency virus (HIV), tuberculosis and malaria. Data were collected using in-depth, structured or semi-structured interviews, focus groups, open-ended surveys and observations.

4.4.2 Comprehensiveness of reporting

Reporting was variable with studies providing details on 3 to 21 of the 31 items of the COREQ framework (Table 4.2). All studies included participant quotations, 30/39 studies described the participant selection strategy, 27/39 provided the questions or topic guides, and 27/39 reported recording of the interview. Researcher triangulation (multiple researchers involved in coding and analysis) was described in 24 studies. Theoretical saturation (when

little or no new concepts are identified in subsequent data collection) was described in only 7 studies. Member checking (obtaining feedback from participants on the preliminary findings) was reported in one study.

4.4.3 Descriptive synthesis

We identified five major themes: centrality of community engagement, cognizance of vulnerability and poverty, contending with power differentials, translating to local context and advocating fair distribution of benefits. Selected quotations for each theme are provided in Table 4.3. Conceptual links among themes are depicted in Figure 4.2.

4.4.3.1 Centrality of community engagement

Mobilising community

The need for community engagement to build trust and foster acceptance of trials was emphasized by all stakeholders [14-17]. They believed that culturally appropriate strategies were necessary to educate the community about new interventions and encourage active participation in research. Community leaders in Ghana suggested using traditional community gatherings which included cultural activities like drumming and dancing [16]. Many desired "genuine, fair and effective" [18] dialogue with community members to improve trial design and conduct, strengthen ethical practice and demonstrate respect for community values.

Recognising the pivotal role of leaders and representatives

Stakeholders believed that investigators need to navigate and respect hierarchical decision-making structures in the community [14, 19]. Endorsement by "chiefs" and understanding their role as "gatekeepers and mediators" was considered necessary to "allay suspicion, to nurture trust, and to establish the researchers' credibility" [16]. Involving trusted "grass-root" [17] intermediaries like community workers was deemed vital in "opening the way" [20] for

researchers. Employing fieldworkers with knowledge of local customs was supported to facilitate recruitment of participants [16]. Researchers recognised that community representatives' could potentially enable or undermine the trial goals [15].

Managing different expectations

The transfer of material benefits such as healthcare resources was expected by the community and was believed to encourage participation, but this could undermine intrinsic motivation [19, 21]. Tensions arose as volunteer community workers were dissatisfied with their poor incentives compared to the payment of the fieldworkers employed on the trial [17, 20]. Community workers expectation to enroll participants for payment differed from researchers who felt that community workers should not be directly involved in consenting participants to avoid conflict of interest [18, 19]. Some recommended having mediators e.g. community advisory boards, to address community and researchers' expectations more effectively [19, 22].

Retaining community intermediaries' involvement

Retention of community workers was deemed critical for a trial to be successful, but potential barriers included dissatisfaction with remuneration, limited scope of responsibilities, heavy workload, work-related travel, familial opposition and negative attitudes of parents towards them [23, 24]. Community workers were motivated to participate because of recognition and appreciation, altruism, humanitarian and religious reasons, but recommended appropriate compensation and incentives to improve retention [14, 23].

4.4.3.2 Cognizance of vulnerability and poverty

Vital therapeutic opportunity

For parents, hope for free, quality medical care for children and their family was the driving force for participation in trials [25]. Some parents feared that refusal to participate would result in denial of medical care [22, 26]. The Gambian community appreciated having post-trial access to treatment [27] and mothers in Malawi valued the clinical testing provided in the trials [25]. Parents had a "therapeutic misconception" [28] that all trial interventions were beneficial, for example, believing that participating in the HIV trials would prevent their child from getting HIV [28, 29]. Altruism also motivated participation to contribute to science and provide hope for new therapies for future generations and the under-privileged [30, 31].

Medical mistrust

The community's mistrust of medical research was a barrier that researchers believed needed to be addressed sensitively [15, 22]. A major concern in Africa was the perceived dangers of taking blood samples. The community believed the blood was sold "because our blood is of higher quality than that of the white people" [32]. Parents were anxious that "the trial was a disguise for witchcraft or Satanism," [33] "children's body parts would be removed and sold" [33] or the "white people" will infect them with HIV or tuberculosis [20]. Parents in Puerto Rico were reluctant to enroll their children in a placebo-controlled trial because they "would not trust what is being injected to their children" [34]. The need to sign consent forms were regarded with suspicion and some perceived it was to absolve researchers of liability [14, 21].

4.4.3.3 Contending with power differentials

Potential for exploitation

Most stakeholders believed impoverishment rendered these communities "powerless" and vulnerable to exploitation [27]. Regulators raised concerns about LMICs being easy

recruitment sites in multinational trials where researchers "parachute in, parachute out" [27, 35]. There were concerns of inducement and conflict of interest because some leaders and trial staff were perceived to exercise their authority to "exert pressure" on the community to participate [14]. Regulators felt that providing benefits or large monetary payments to participants may lead to commodification of research, but sponsors believed that participant payments should be equitable and not based on the country's economy [22, 36]. Researchers were afraid of being involved with the media whom they perceived as exploitative, "vultures" and always "raping their work" [22].

Fearing discrimination and stigmatisation

In South Africa stakeholders advocated for fairness in community and participant selection because of the perceived discrimination where vulnerable "black people were targeted as research participants" [22]. Participants feared stigmatisation and humiliation, that their participation would be misconstrued as them having HIV in the context of the trial [26, 37, 38]. Parents in a malaria vaccine trial feared becoming a "laughing stock" by non-participants and desired that results of ineffective interventions remain confidential [15].

Disempowerment hampering informed consent

Stakeholders believed that disempowerment, poor education and difficulty in translating scientific concepts were barriers to informed decision-making [34, 39, 40]. They recommended that consent forms be simplified, presented in a culturally and linguistically appropriate format with verification of parental comprehension [37]. Parents' implicit trust in doctors was a concern as the doctor's recommendation of the trial may be misinterpreted as endorsement that the intervention is effective [29]. In patriarchal African and Indian societies, women were believed to have minimal decision-making power, [28, 41] although in some countries such as Malawi, women made decisions autonomously [25, 28, 41]. There were

conflicting views on children's decision-making capacity.Some reported children being persuaded to participate [22, 38].

4.4.3.4 Translating research to local context

Respecting beliefs and cultural practices

Cultural beliefs that conflicted with the trial were a challenge for researchers. For example parents felt that the requirement for contraception to prevent pregnancy in the vaccine trial "will encourage girls to have sexual intercourse before getting married," or "could cause infertility" [34]. In some communities, illness was believed to be due to physical or spiritual happenings and herbalists and religious leaders were trusted to protect their child's health which discouraged participation in trials [32]. The confidentiality measures required in trials was perceived by the community to be a contravention of their cultural practices and was misinterpreted that the trial was unethical or shameful [22]. Researchers also recognised that culturally accepted practices could conflict with ethical principles. For example, in Ghana, presenting the paramount chiefs with gifts at the initial trial visit was customary but this could be seen as an inducement [16].

Understanding constraints of impoverishment

Researchers advocated that international sponsors need to understand the severe economic scarcity when planning trials and to ensure interventions are feasible and sustainable in LMICs [37, 42]. Parents reported sharing therapeutic interventions with non-participants. The community in Malawi recommended that for the bottle-feeding intervention in the HIV trial to be sustained, the "sterilizing paraphernalia" needed to be provided as they could not afford them [29].

Ethical pluralism

In international trials, some supported the "universality of ethics" [22] while others argue that ethical standards varied across cultures [21, 42]. Researchers felt that rigorous international requirements of documentation were too ambitious for LMICs [15, 43]. Some believed that trials needed to produce locally relevant results and should not have "an island of excellent investigation where that's not your standard of care" [42]. African researchers were concerned that if international standards were not strictly applied locally their research quality will be unacceptable in the global arena [42]. For example serious adverse events required all co-existing medical conditions and symptoms related to poverty, for example malnutrition to be reported.

4.4.3.5 Advocating fair distribution of benefits

Supporting health care and societal needs

Stakeholders encouraged the "sharing and mutuality" [20] of research-related benefits with participants to prevent exploitation and promote the societal value of international health research [20, 35]. However, they recognised that the governance framework around provision and accountability of these benefits was inadequate [22, 44]. Stakeholders felt that "tangible benefits to host communities have been insufficient and unfairly so" [16]. Many stakeholders supported trials as a means to help address healthcare inequities including poor access and affordability of therapeutic products for children and to promote social justice [35].

Sponsor obligation

Regulators and researchers argued that sponsors had a moral responsibility to ensure availability of the proven interventions after trial completion and to improve research and healthcare capacity [22]. For example, in Kenya, the secondary benefits of a malaria vaccine trial included improved local health facilities, provision of medical equipment and up-skilling

of medical personnel [40]. Community members perceived that the primary role of sponsors was to provide access to treatment and better quality medical care [27, 44]. Reimbursement of out-of-pocket trial expenses and providing ancillary medical care were considered distinct to sharing benefits arising from the research.

Collateral community benefits

While researchers felt that trial participants, and those who did not participate (including those who withdrew) should have access to the intervention, [22] some parents felt this was unfair and only participants should benefit from the trial intervention [22, 27, 28]. Sponsors in The Gambia elected to treat non-participants and siblings of participants to maintain overall community goodwill [32]. Tensions emerged when benefits differed between studies or when there was poor clarity or disagreements on eligibility for reimbursement [40]. Researchers proposed that direct collateral community benefits should be primarily medical rather than monetary and should be maximised through engagement of the country's ministry of health [40].

4.5 Discussion

Conducting trials in children in LMICs is regarded as a complex and arduous process by a broad range of stakeholders including children, parents or caregivers, community members, clinical or research teams, regulators and sponsors due to the difficult financial scarcity and cultural contexts that have been shaped historically by disadvantage and exploitation. This disempowerment also contributed to the communities' mistrust of trials and fears of stigmatisation. Stakeholders felt that trials should be adapted to the local context with consideration of the resource constraints, cultural beliefs and ethical pluralism. Facilitators of trials were a perceived opportunity to access medical care among parents and the community, engaging the community, addressing expectations and fair distribution of research benefits.

The primary motivation of parents to participate in trials across all income settings is the opportunity of better medical care for their child, however in LMICs, participation in trials was often the only option to access treatment [3, 45]. The parents' implicit trust in doctors' recommendations to enroll children in trials was apparent, which may contrast to parental reluctance in high-income countries [45]. Involving parents and families in the protocol design is encouraged universally, however, this is more difficult in LMICs where there are specific misconceptions of trials [3]. Rumors such as "blood and organ stealing" as well as belief in witchcraft as a cause of illness and traditional medicines as a cure were often regarded as more important and relevant than biomedical risks [15]. These rumors and fears of stigmatisation for participation may be constructively addressed by contextualisation, community education to improve health literacy and engaging community representatives to help build trust by fostering mutual understanding, respect and equity [21, 33, 46-48]. Community engagement is a dynamic process and a constantly changing set of negotiated relationships to address expectations and challenges tailored to the local setting [49, 50]. Stakeholders recommended ethnographic research in preparation for commencing a trial within a community, to improve feasibility, methodological rigor and acceptability of trial protocol, while safeguarding the health and interests of child participants [29, 37]. Feedback of the trial findings to the participant and the community is complex, but was recognised as a key component of continuing social interactions and is encouraged in all trials [28, 51].

The underlying principle of consent being free, autonomous and informed is the cornerstone of trials universally [52-54]. However, findings from this literature review reaffirm observations that meaningful decision-making is further compromised in LMICs by disempowerment, cultural idiosyncrasies, extensive illiteracy and or decision-making styles [39, 41, 53]. Thus the western ethical principles of informed consent and child assent, autonomy and individualism needs to be contextualised [32, 41, 55]. Many of the

controversial ethical issues such as the use of placebo, the appropriate local standard of care and resource constraints in complying with the rigorous trial requirements we reported in this literature review is part of the international agenda [50, 54, 56, 57]. Some stakeholders reported that ethical approval and oversight of trials in children was also inadequate [7]. The rigid ethical-legal framework of children's participation in trials, arising from paternalism and poor awareness was recognised as a barrier that unnecessarily excludes children from trials [22, 38]. This systematic review's results show that there is scope for a common international ethical framework to be applied in LMICs with ethical reasoning of the moral application of these principles in these contexts [30, 58]. Researchers supported the development of a pragmatic ethical framework for children's involvement in trials that are appropriate in LMICs [15, 59, 60].

Communities in LMICs place a greater emphasis on tangible research benefits and remuneration which some stakeholders believed may be coercive and cloud objective assessment of potential risks to participants [61, 62]. Many were troubled that poverty compounded by lack of medical care, unawareness of medical rights and language barriers rendered children and communities more vulnerable to exploitation in trials [29, 37, 63]. Stakeholders reported potential vertical exploitation, where community intermediaries are encouraged by researchers to take advantage of their social relationships to coerce participants and horizontal exploitation where intermediaries influenced participation in order to increase their remuneration [64]. Some were concerned that the pharmaceutical industry may exploit LMICs by conducting trials primarily for the benefit of wealthy countries [42]. Therefore, some stakeholders supported research which investigates less expensive ways of using proven treatments for treating conditions specific to local child health priorities [42].

This systematic review's results reaffirm the on-going discourse of children and communities needing to benefit from the research to promote justice and equity [35]. Although benefit sharing and defining fair research-related benefits are standard ethical concerns in global health research, we found that its practical implementation is complex with less attention on the consequences of delivering on promises of benefits in LMICs [22, 56, 65]. Controversy and contention still exists internationally concerning the ethics of monetary compensation to parents and investigators [22, 66]. However, findings from this literature review showed that there are poorer governance structures and greater concerns of inducement or coercion in LMICs. More empiric work is needed to guide appropriate and ethical distribution of research benefits in LMICs [40, 44]. There is speculation that the lack of commercial incentives to the pharmaceutical industry (the major driver and sponsor of trials) to conduct trials in children of diseases specific to LMICs, may have contributed to a much lower allocation of resources to trials in LMICs relative to the tremendous burden of disease and addressing this gap is on the global health research and development agenda [4, 67, 68]. Stakeholders advocated for communities to receive concrete benefits to compensate for years of disadvantage and ostracism echoing the international ethics discussions that encourages sponsor investment in developing health research capacity [69].

The experiences and the practical and ethical concerns of stakeholders identified in this literature review can inform the design and conduct of clinical trials in children in LMICs. Our synthesis reflects the diversity and full breadth of data reported in the primary studies and we recognize that the majority of the findings were focused on the problems, challenges, and issues for research in LMICs. Further studies may be conducted to elicit stakeholder perspectives on the initiatives, approaches and positive developments that exist or would be effective in encouraging more, high-quality trials of clinical relevance in children in LMICs. Some studies were conducted in local languages and transcripts were translated into English,

which could be a potential limitation if linguistic and cultural nuances were not fully conveyed in the primary study [70]. Also, some of the interviews in the primary studies were conducted by the research institute or trial staff, rather than independent interviewers which may have limited the full range of issues and experiences that stakeholders, were willing to share. Studies not published in English were excluded to avoid misinterpretation of results. This systematic review focused on clinical trials in children in LMICs; however some issues are common for high-income countries as well as in the adult population.

4.6 Conclusion and future directions

The clinical trials paradigm is complex in LMICs as it is hampered by impoverishment, disempowerment, inequity and idiosyncratic cultural beliefs that have created mistrust in clinical research with fears of exploitation. Key facilitators are engaging the community in mobilising and designing trials that are pragmatic, ethical and relevant to the healthcare needs of children in these diverse settings. Fair distribution of research benefits, including investment in research infrastructure and regulatory frameworks, will help restore trust lost by the past social injustices and promote more, quality trials to improve the future of these historically disadvantaged children.

Table 4.1 Included studies

Study by country	Medical condition focus of trial(s)	Sponsor of qualitative study	n	Participants						Methodological Framework	Data collection	Analysis	Topic
				Children	Parents	Community	Clinical/ research team	Regulators	Sponsors				
Bangladesh													
Rahman et al. 2010[24]	Newborn care	Foundation/ charity/society, government	69	–	–	–	–	0	0	Qualitative design	Open-ended questions, in-depth interviews, focus group	–	Recruitment and retention of Community Health Workers
Ghana													
Abbey et al. 2014[23]	Fever	Foundation/ charity/ society	35	0	0	35	0	0	0	Mixed methods/ ecological behaviors model	Face-to-face interviews, focus groups, informal discussions; field reports	Iterative	Retention of Community Health Workers
Febir et al. 2013[70]	Malaria	Foundation/ charity/society, government	159	0	144	10	5	0	0	Qualitative design	Focus groups, in-depth interviews; cross-sectional survey	Thematic analysis	Knowledge and perception of malaria vaccines
Tindana et al. 2006[71]	Non-specific	Government	90	0	70	10	10	0	0	Qualitative design	In-depth semi-structured interviews, focus groups	Thematic analysis	Informed consent process
Tindana et al. 2011[16]	Non-specific	Foundation/ charity/society	136	0	24	104	8	0	0	Qualitative design	In-depth interviews, focus groups	–	Community engagement in biomedical research
Haiti													
Coreil et al. 1998[37]	HIV	Government	239	0	167	72	0	0	0	Ethnography	Focus groups, in-depth interviews	Content and thematic analysis	Cultural feasibility of trial
India													
DeCosta et al. 2004[41]	Non-specific	Hospital, university, government	57	57	0	0	0	0	0	Qualitative design	Structured interviews	–	Informed consent and motivation for participation
Kenya													

Study by country	Medical condition focus of trial(s)	Sponsor of qualitative study	n	Participants						Methodological Framework	Data collection	Analysis	Topic
				Children	Parents	Community	Clinical/ research team	Regulators	Sponsors				
Angwenyi et al. 2013[17]	Infection	Government, industry trust	33	25	0	0	8	0	0	Mixed methods/ multi-method social science	In-depth interviews, focus groups; observations	Thematic analysis	Practical and ethical implications of involving Community Health Workers
Angwenyi et al. 2014[14]	Malaria	Government, industry trust	57	0	19	8	30	0	0	Mixed methods	In-depth interviews, focus groups; surveys, observations, document reviews	Framework analysis	Informed consent and community engagement activities
Chantler et al. 2013[20]	Infection	University, industry trust	119	0	27	74	18	0	0	Ethnography	Observations, interviews, focus groups	Thematic analysis	Community engagement of paid volunteers
Gikonyo et al. 2008[15]	Malaria	Government, industry trust	203	0	198	0	5	0	0	Qualitative design	Structured interviews, focus groups	–	Informed consent practices
Gikonyo et al. 2013[28]	Malaria	Government, industry trust	~40	0	–	–	–	0	0	Ethnography	Observation, meeting minutes; interviews, focus groups	–	Feedback of trial findings to participants
Kamuya et al. 2013[18]	Non-specific	Government, industry trust	24	0	0	24	0	0	0	Qualitative design	Focus group, in-depth interviews; reports, self-administered questionnaires	–	Engaging communities to strengthen research ethics
Lairumbi et al. 2011[35]	Non-specific	Government, industry trust	52	0	0	–	27	15	10	Qualitative design	Face-to-face, in-depth interviews	Grounded theory	Understanding of benefit sharing in health research
Lairumbi et al. 2012[44][a]	Non-specific	Government, industry trust	52	0	0	–	27	15	10	Qualitative design	Face-to-face, in-depth interviews	Grounded theory	Research benefits expected by participants
Molyneux et al. 2004[36]	Non-specific	Government, industry trust	142	0	89	50	3	0	0	Qualitative design	Observation; hypothetical case vignettes, informal and	–	Understanding of informed consent

Study by country	Medical condition focus of trial(s)	Sponsor of qualitative study	n	Participants					Methodological Framework	Data collection	Analysis	Topic
				Children	Parents	Community	Clinical/ research team	Regulators	Sponsors			
										semi-structured group interviews		
Molyneux et al. 2005[21][a]	Non-specific	Government, industry trust	142	0	89	50	3	0	0	Qualitative design	Observation; hypothetical case vignettes, informal and semi-structured group interviews	Content analysis	Informed consent process
Molyneux et al.2005a [a] [72]	Non-specific	Government, industry trust	142	0	89	50	3	0	0	Qualitative design	Observation, hypothetical case vignettes, focus groups, interviews	Content analysis	Notion and practice of informed consent
Molyneux et al. 2012[40]	Perfusion, HIV,TB, respiratory infections, malaria, immunology	Government, industry trust	87	0	0	0	87	0	0	Qualitative design	Case vignettes, in-depth interviews, focus group, consultative workshop; e-mail survey	–	Benefits' and payments for research participants
Okello et al.2013[19]	Malaria	Foundation/ charity/society, government, industry trust,	42	0	–	–	20	0	0	Qualitative design	Observation, in-depth interviews, focus groups	–	Challenges of consent and community engagement in a school-based trial
Vreeman et al. 2012[61]	Non-specific	Government	108	0	60	48	0	0	0	Qualitative design	Traditional community assemblies/focus group	–	Community perspectives on informed consent and research participation
Lebanon													
Nabulisi et al. 2011[73]	Meningitis	University	33	0	33	0	0	0	0	Qualitative design	In-depth interviews	Thematic analysis	Parental motivation for participation
Malawi													
Corneli et al. 2007[29]	HIV	Government	133	0	100	33	0	0	0	Formative	Semi-structured interviews, focus	Content analysis	Community engagement

Study by country	Medical condition focus of trial(s)	Sponsor of qualitative study	n	Participants						Methodological Framework	Data collection	Analysis	Topic
				Children	Parents	Community	Clinical/ research team	Regulators	Sponsors				
											group, observations		informing design of protocols
Masiye et al. 2008[25]	Malaria	Government	81	0	81	0	0	0	0	Qualitative design	Focus groups	–	Motivation for participation and role of relatives in decision making
Piwoz et al. 2006[74]	HIV	Government	19	0	0	0	19	0	0	Formative	In-depth interviews	Content analysis	Feasibility of intervention to inform trial design
Multinational													
Hyder and Wali.2006[43] [c]	Non-specific	Government	78	0	0	0	78	0	0	Qualitative design	Focus groups, in-depth interviews; open ended questions in survey	–	Developing countries researcher perspectives of informed consent and collaborative research
Kass et al. 2005[39] [d]	Infectious disease	Government	26	0	26	0	0	0	0	Qualitative design	In-depth interviews	Thematic analysis	Participant motivations, understanding and voluntariness
Puerto Rico													
Perez-Guerra et al. 2012[34]	Dengue	Industry	313	111	145	39	18	0	0	Grounded theory	Interviews, focus groups	Content analysis	Community views of placebo-controlled dengue vaccine trial
South Africa													
Essack et al. 2010[22]	HIV	Government	31	0	0	16	7	3	5	Qualitative design	Semi-structured in-depth interview	–	Ethical challenges in HIV vaccine trials
Jaspan et al. 2008[38]	HIV	Government	200	57	51	92	0	0	0	Qualitative design	Focus group	Thematic analysis	Ethical issues of adolescent involvement in HIV vaccine trials

Study by country	Medical condition focus of trial(s)	Sponsor of qualitative study	n	Participants						Methodological Framework	Data collection	Analysis	Topic
				Children	Parents	Community	Clinical/ research team	Regulators	Sponsors				
Jaspan et al. 2010[26][a]	HIV	Collaborative group, government	200	57	51	92	0	0	0	Qualitative design	Focus groups	Thematic analysis	Attitudes towards the inclusion of adolescents in HIV vaccine trials
Mahomed et al.2008[31]	Tuberculosis	Foundation/ charity/society, government, industry	72	40	32	0	0	0	0	Qualitative design	Focus group; self-administered survey	Content analysis	Knowledge and attitudes of adolescent to tuberculosis trials
Tanzania													
Liheluka et al. 2013[75]	Malaria	Industry	55	0	49	6	0	0	0	Qualitative design	In-depth interviews, focus group	Thematic analysis	Secondary health benefits of malaria vaccine trials
The Gambia													
Fairhead et al. 2006[32]	Pneumonia, meningitis	Government	>60	0	–	–	10	0	0	Ethnography	Observations, narrative and semi-structured interviews	Thematic analysis	Engagement of parents in vaccine trial
Geissler et al. 2008[27]	Malaria	Foundation/ charity/society	93	0	80	0	13	0	0	Qualitative design	Semi-structured interviews	–	Relational ethics and material exchanges
Leach et al. 1999[30]	Influenza	Government	189	0	189	0	0	0	0	Qualitative design	Semi-structured interview	–	Informed consent procedure
Uganda													
Crane 2010[42]	HIV	Foundation/ charity/society	5	0	0	0	5	0	0	Qualitative design	Semi-structured interviews	–	Science and ethics in HIV transnational research in Africa
Zambia													
Kingori et al. 2010[33]	Malnutrition	University	>30	0	>25	0	5	0	0	Qualitative design	Face-to-face in-depth interviews, focus group	–	Misconception of clinical trials
Zimbabwe													
Power et al. 2004[63][b]	Sexual health	–	–			–	–	–	–	Qualitative design	Observation, in-depth interviews, focus groups	Thematic analysis	Feasibility study targeting adolescent sexual health

[a] Excluded from the total number of participants as they have the same participants as another study in this review by same author
[b] Number of participants not reported, thus not included in the total number of participants
[c] Countries of study: China, India, Thailand, the Philippines, South Africa, Tanzania, Kenya, Brazil, Colombia, Mexico
[d] Countries of study: Africa, Caribbean
– not stated, unclear, or unable to ascertain

Table 4.2 Comprehensiveness of reporting in the included studies

Item	Studies reporting on the item	n (%)
Personal characteristics		
Interviewer/facilitator identified	[14, 16-18, 20, 23, 27-37, 39-44, 61, 71, 73-75]	27(69)
Credentials	[14, 17, 18, 20, 28, 29, 35, 37, 39-44, 71, 74]	16(41)
Occupation of interview/facilitator	[14-18, 20, 26, 28, 30, 35, 39-44, 71, 73, 74]	19(49)
Gender	[16-18, 20, 32, 33, 35, 36, 39, 40, 42, 44, 71, 73]	14(36)
Experience/training in qualitative research	[14, 15, 17, 18, 23, 29-31, 35-37, 43, 44, 61, 71, 73-75]	18(46)
Relationships with participants		
Established relationships prior to study	[17, 36, 40, 71]	4(10)
Participant knowledge of interviewer	[36]	1(3)
Participant selection		
Selection method *(e.g. snowball, purposive, convenience)*	[14-18, 20, 22, 23, 25, 28-35, 39-44, 61, 70-75]	30(77)
Method of approach/ recruitment	[15-17, 19, 21, 22, 25, 26, 29, 30, 32, 34, 35, 38-41, 43, 44, 61, 70-75]	26(67)
Sample size	[14-44, 61, 70-75]	38(97)
Number/reasons for non-participation	[23, 25, 30, 33, 34, 41, 70, 74, 75]	9(23)
Setting		
Venue of data collection	[21, 25, 26, 30, 31, 34, 36, 39-42, 61, 70, 72, 73, 75]	17(44)
Presence of non-participants (e.g. clinical staff)	[27, 30, 41]	3(8)
Description of the sample	[14-17, 19-26, 28-35, 37-44, 61, 63, 70-72, 74, 75]	35(90)
Data collection		
Questions, prompts or topic guide	[14-16, 22, 23, 25-27, 29, 30, 33-35, 37-44, 70-75]	27(69)
Repeat interviews/observations	[14, 29, 72, 75]	4(10)
Audio/visual recording	[14-17, 22, 23, 25, 26, 28-32, 34, 35, 37-40, 43, 44, 61, 63, 70, 71, 73, 74]	27(69)
Field notes	[14, 16, 20, 22, 23, 29, 31, 32, 35, 37, 40, 41, 44, 61, 75]	15(38)
Duration of data collection (interview or focus group)	[16, 22, 26, 31, 34, 38, 39, 61, 72, 75]	10(26)
Data (or theoretical) saturation	[15, 22, 35, 44, 72, 73, 75]	7(18)
Participants received transcripts	[32]	1(3)
Methodological theory identified	[14-17, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 39, 40, 43, 44, 61, 63, 70, 71, 73-75]	26(67)
Data analysis		
Number of data coders	[14-17, 20, 22, 23, 26, 28, 29, 31, 32, 35, 38-40, 44, 61, 71, 74, 75]	21(54)
Researcher/expert triangulation (multiple researchers involved in coding and analysis)	[14-16, 18, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 37, 38, 40, 42, 44, 61, 71, 72, 74, 75]	24(62)
Derivation of themes or findings (e.g. inductive, constant comparison)	[14-17, 20, 22, 23, 25-29, 31, 32, 34-41, 44, 61, 63, 70-75]	31(79)
Protocol for translation	[14-17, 20, 22, 25, 26, 28-31, 35, 38, 39, 41, 44, 61, 63, 70, 71, 74]	22(56)
Protocol for data preparation/ transcription	[14-17, 20, 22, 23, 25, 26, 28, 29, 31-35, 37-40, 43, 44, 61, 63, 70, 71, 73-75]	29(74)
Use of software (e.g. NVivo)	[14, 16, 17, 20, 22, 25, 28-30, 39, 41, 43, 61, 70, 75]	15(38)
Member checking (participant feedback on findings)	[32]	1(3)
Reporting		
Participant quotations provided or raw data provided (picture, diary entries)	[14-44, 61, 63, 70-75]	39(100)
Range and depth of insight into participant perspectives on clinical trials in children issues in LMICs	[14-44, 61, 63, 70-75]	39(100)

Table 4.3 Themes and selected illustrative quotations

Subthemes	Participants quotations (italicized) and/or authors' explanations	Contributing references
	Centrality of community engagement	
Assisting in mobilising community	*"If you don't get them involved, you may in the end implement something that will be strange or something that they will not embrace at all. So it is better to get them involved to be able to source some information from them, to be able to get their view about the project to move to the next stage, because they always have important contributions to make to the project, to improve on what you have."* (NHRC research office) [16] *"Taking advantage of the structures that are already there is what makes it successful. It doesn't have to be capital-intensive or anything."* (NHRC research officer) [16]	[14-16, 18-21, 24, 26, 31, 32, 34, 36, 37, 43, 61, 73]
Recognising the pivotal role of representatives and leaders	*"If one hadn't gone through the right procedure… that is, seeing the district authorities and the paramount chiefs and the subsection chiefs and so forth, there might have been a lot more suspicion about what was going on, why we were doing this, who we were, do we have permission to do this. Essentially, this study would not have been accepted."* (External researcher) [16] *"… we went to the meeting and the assistant chief said he doesn't want to hear any rumors from anybody. He said he was an assistant chief and he had a child who was in the KEMRI study. He told people if they won't enroll in the study they should just keep quiet and anybody who will be heard spreading rumours will be arrested … After the assistant chief called the meeting, rumours stopped and for us who had already joined, we felt a bit better because rumours had stopped"* (Female parent, late consenter) [14] *''It was not difficult at all; it was difficult to convince them to join the programme, but through the long time I stayed with them I got a special relation, an independent rapport with them, so that even if they do not want to join, they couldn't say no.."* (Fieldworker) [27]	[14-16, 18-20, 27, 32]
Managing community and research expectations	*"So as we went round he [CHW] used to say 'you my colleagues earn but for me I go round and get nothing. You have bicycles and we have nothing but when we go, we go together. It's like I am helping you in your work yet no one looks after us.' So that is one of the challenges. But honestly if I look at it fairly its true; . . . if he had gone to work* [he would have] *earned something for a living . . . so it becomes hard because he wants something from there and you see I can't help them."* (Fieldworker) [17] *".....you should not say I think this is for research, when another person is dying and you have the medicines, I think it's not fair. Even if you have the equipment for research, it can be used for diagnostics if it's so needed."* (Researcher) [35]	[14-22, 26, 27, 34-36, 40, 42, 61, 73]
Retaining community intermediaries participation	*"Those who stopped complained of money saying they are suffering for nothing . . .' '. . . during the durbar the community agreed to give us (CHWs) some incentive but up to now nothing. . .'* : *'The Bible says we should love our neighbour like . . . we love ourselves, so whether the children vomit on me or not or I'm being paid or not I will still continue. . .'. 'I have become so popular and respected by the people in the community. .' …. 'I have become a friend to all children and mothers in the village. That is my benefit from this work'.* (CHW) [23] *"The trial community became a web of everyday relations well beyond the necessities of the trial: ''We are there daytime, night time, afternoon time, any time you think of. After the first trial, we do not leave but stay… we have good friends. We still visit them, and they come to us.''; ''By the end you become part of the community; you do everything together. It was sad…to leave.'* Fieldworker)' [27] *"My father is the sufferer...He used to be the alternate imam of the village. Now half of the people do not want to stand behind him in the prayers. They say his daughters work for NGOs, which is not right for a religious person."* (CHW) [24]	[17, 20, 23, 24, 27, 34]
	Cognizance of vulnerability and poverty	
Therapeutic opportunity	*"What attracted us [was that] we knew our children will receive treatment for a whole year in every disease they suffer. If you have a problem and visit the people concerned, a call is made to the …* [PI] *he brings a vehicle and [the sick person] is carried away* [to hospital]. *In fact it's something we should be happy about because nobody can bring you a vehicle that easily."* (Parent) [15] *"One good thing about it is that, there is no money involved. The parents would also benefit from the treatment given. Drugs are so expensive and are not available in government hospitals."* (Mother) [41] *'I don't see anything wrong with testing the vaccine on us . . . it's us who are dying of AIDS'* (Female adolescent) [26] *''Doctors will not give us anything that is harmful*". Another subject said, *''Doctors are in a way godly. Who would know better than them?''* [41]	[14, 15, 21, 22, 25-27, 29-32, 34, 36, 37, 39, 41, 70, 73]

Subthemes	Participants quotations (italicized) and/or authors' explanations	Contributing references
Medical mistrust	*"I don't trust experimental vaccines and moreover these vaccines brought here to Africa by scientists cannot be trusted. Because these Europeans know we are poor people and so accept any terms and conditions, they are using Africans like guinea-pigs and Africa as a dumping place for so much waste. I know it's true that experiments have to be carried out by researchers on human beings, but I don't want my child to be involved. "* (Parent) [30] *'The sickness already reduces the blood so what if more is taken?' 'won't that finish of the child?'* [36] *"If I give them my child and the child dies, then they give money that will not bring my child back. We had to explain to her until she understood. And in fact, some refused at that stage when they heard of KEMRI giving 'fidia' [compensation], they said 'we don't want our children in it. You want to take our child and give that child to the devils"…'* (Male, fieldworker). [14]	[14, 15, 21, 22, 25-27, 29-34, 36, 37, 41, 70, 73, 75]
Contending with power differentials		
Concerning potential for exploitation	When asked, why the MRC had come to Africa, many said *''to help''*, *''because we Africans are vulnerable to diseases''* and *''because they can't find these diseases in the UK''*, or *''because we are powerless people and they need to help us to know the diseases''*. ….*''because Britain has more power than Africa''*, *''it will be easier here than there''* or even *''in UK people are not willing to participate in trials."* [27] *".....they might be doing something else also without you knowing. If they are drawing blood samples, they're telling you we are doing it for Malaria, but do anybody have control over it, that those blood samples are not going out and they are doing some genetic testing or they are doing something else on it? /.../ that is my fear and concern..."* (Institutional Review Board) [35] *"… village elders tended to be coercive sometimes … you could go with them [to homes] and you know that … [research] participation is voluntary. But then for a village elder, because he wants the [research] agenda fulfilled then he says, 'we want everybody who has an eligible child to join the study, or else we will make sure you are removed even from other government projects that are brought here'. So in such a place you [fieldworker] have to come back again and try to explain that this [research] is not a must, it's voluntary"* (Male, fieldworker) [14]	[14, 22, 27, 35, 40, 42, 61, 63]
Fearing discrimination and stigmatisation	*'This might have unintended outcomes where people might feel that they are used, understand, . . . unfortunately we have a long history of apartheid where blacks were exploited'* (Male educator) [26] *". . . the community will ask . . . 'what is it that we do not want it to know if there is no danger involved in this research?'. You try to explain that there are things in a family, family situation that . . . only family members should know . . . that is where people would begin to be suspicious; and . . . confidentiality is good in that it saves the lives of the people who are participating in research and at the same time it is retarding in the community that is being encouraged to participate."* (Community Advisory board member) [22] "*The way [the FWs] are free with us; they can visit in the morning or evening to check on the kid. [So non-participants] have now started spreading rumours that they are not only KEMRI but our boyfriends."* (Mother) [15]	[15, 22, 26, 28, 29, 31, 33, 37, 38, 61]
Disempowerment hampering informed consent	If the husband says [in a household visit] '*oh yeah you go listen and join the study', then they are more likely to …* [since] *they already have permission if I may say so. But if you just speak to them [women] in a baraza* [public meeting] *and then they go explain to their husbands, the response is not so good"* (Trial staff) [14] *"Research project? They build houses?"* A translator for a woman whose child was in the placebo-controlled malaria trial explained, *"She does not know what research is. She thought they have already done the research, and they are trying to implement the results of the research with these children."* (Stakeholder) [39] "*Your main concern is to get your child treated. They could even ask you to stand by a fire all day, and you'd do it!"* (Mother) [72]	[15, 19, 22, 23, 25, 29-32, 34, 36-39, 41, 43, 61, 71-74]
Adapting research to local context		
Respecting beliefs and cultural practices	*"……..somewhere in the north, when a child is born it is not brought out until after one month or so. So if we are looking at a vaccine targeting children of four weeks or less, that can possibly be a barrier to such children getting access to the vaccine"* (Religious leader) [70] *"...I was uncomfortable discussing topics like reproductive organs because according to our Shona culture it's taboo."* (Teacher) [63] This was illustrated in the breast-feeding study regarding the issue of random assignment of mothers-infant dyads to breast- or bottle-feeding groups. Although randomization alone posed no ethical problems (assuming proper support of safe bottle-feeding was provided),	[16, 22, 29, 31, 33, 37, 63, 70, 74]

Subthemes	Participants quotations (italicized) and/or authors' explanations	Contributing references
	such a procedure clearly clashed with prevailing cultural expectations that parents should choose an infant's feeding method. [37] *"Time is such a big constraint because sometimes you go to inform the chief and he says*, "*Come back in 2 or 3 days."…. you need to add about a month just to complete the community process."* (NHRC social scientist) [16] *"It is part of our culture; whatever you are doing, if there is no tobacco, it is not proper*." (Elder) [16]	
Understanding resource constraints	Additionally, the Haitian custom of sharing food with needy neighbors and housemates would have to be respected and taken into account, thus the provision of grain was recommended as a measure to discourage consumption of the baby formula by other family members. [37] *"My children are also malnourished. I would share the supplements with them so they can also have good health."*(Mother) [29] The paediatric wards at UTH during the conduct of this study were often congested. 'Floor beds', which were temporary beds, could be found on the wards due to the large number of patients and insufficient resources. [33] However, it was acknowledged that: *"being completely altruistic and participating in research that is [going to] benefit society and future generations, is sometimes a little hard to expect from people who're struggling to keep their family fed "* (Site staff) [22]	[29, 31, 33, 37, 42, 63, 70]
Ethical pluralism	*"Many of the people in the regulatory divisions in the US or the West have really conducted trials in the West. And they're very good, but in resource-limited settings, they actually sometimes don't understand the context of the patients being very sick, you as a researcher being their primary clinician so you're dealing not only with the study component, but you're also providing care and treatment. And so there are a lot more visits that go beyond the study visits that you have to take care of as a researcher. So there are a lot of severe, adverse events that are not related to the drug, but actually are severe, adverse events that are part and parcel of a child growing up in Africa with a high infant mortality rate, a lot of malaria and pneumonia, diarrhea. Just the common illnesses that all need to be reported as serious adverse events. You know, we're not denying that they should be reported, but there is a heavy load on the staff that are doing the studies."* (Investigator) [42] *"My opinion is that we should use the standard of care here. Because it makes more sense if you are investigating whether something is useful, you should compare it with what is being done here rather than what is being done in the US, which will take a long time actually to be done here."* (Investigator) [42] *"I said to them, 'this is very good, but why are you giving a placebo to this other group? Do you know that the transmission is obviously proven? It's there. So, can you really give placebo to this group?' They said, 'Yeah. But you know, in as far as we are concerned, there is no other study regarding this so we really want to give placebo to prove it.' I said, 'No way! There's no way! You know that these mothers are at a disadvantage. The children are at a disadvantage. How do you say you are going to give placebo? You are deliberately infecting those children!' Right? So we refused and that group was given nevirapine and this other group received the new drugs. So they did the study…'It's the science and the ethics. Tell me in Sweden, in the States, in Canada, in France, would this research pass the ethics committee? Would children American children, Canadian children, Swedish children, French, Norwegian children be deliberately exposed to milk that was HIV-infected and be given placebo? And compared with a group that was receiving anti-retroviral drugs? Would that pass your ethics committee?'* (Investigator) [42] *'Sometimes people don't even look at the issues, you know, they might be interested in what they are going to get out of the trial in terms of money'* (Research Ethics Committee). …*'The problem is, if you start agonizing over inducements then you come out saying that if a person is poor we will give less to be in the trial than if they are rich.'* (Sponsor) [22]	[15, 22, 27, 30, 35, 36, 42, 43, 72]
Advocating fair distribution of benefits		
Supporting health care and societal needs	*"…we want to ensure that if you are carrying research within a particular community, you need to give them something back for instance a hospital or something, even if you are doing clinical research. It can be anything else that can benefit the community. Some sort of infrastructure, so that they can at least see that they are benefiting. Once you have done that, actually they will feel that they are part of the process..."* (Civil Society Organization) [44] *"... he likes to talk about 'brain gain' as opposed to 'brain drain'. I mean the fact is, we are being able to provide interesting research work for lots of scientists.... but there are a lot of Doctors that are able to do what they want to do which is to stay in their own country and work in their own country"* (Public private partnership1) [44] The effective and fast treatment offered to trial participants as well as non-participants. ……	[16, 27, 44, 75]

Subthemes	Participants quotations (italicized) and/or authors' explanations	Contributing references
	"The death of children has been massively reduced in the pediatric ward." (Health worker) [75]	
	"Even if the parents or guardians do not have money they still get quality health service, this project does not segregate between rich people and poor people…" (48-year-old Female) [75]	
Sponsor obligation	"*...in the previous decade (the industry) was seen to just purely profit from human suffering and people had a very negative view of the Pharmaceutical Industry. And in the last 10 years, we are sort of re-modeling our self and trying to make sure we project our self in a very responsible manner..."* (Pharmaceutical company 1) [35]	[16, 22, 35, 40]
	"... I think you should be realistic, that nobody is going to come back and you may not be there to enforce that somebody should give back to the community...and once they find what they are looking for, they may just take off..." (Institutional Review Board) [35]	
Collateral community benefits	*''We cannot serve the entire community, but neither can we only serve volunteers and leave out their wives and children… these people are all related - but where would we end?''* (Fieldworker) [27]	[22, 27, 28, 32, 40]
	"We do not accept! We do not accept it at all! And if you do so, we will withdraw completely from the study! We want to be vaccinated: us, our children, our husbands and even our dogs!" "Maybe they [non-participants] are the ones that will be bitten by dogs and we will not get that vaccine . . ." (Mothers) [28]	
	'Even with fares; a study will give exact fare, another one will give extra - like one and a half the amount that people are charged, so sometimes it brings problems and you know sometimes they are in one study when they complete then maybe another child is in another study, so they are like, "why is it that I was given double fare and now you are giving me only one way" (Clinical officer) [40]	

Italicized quotations are from study participants.

Figure 4.1 Flowchart of review of qualitative studies on the conduct of trials in children in low-and middle-income countries

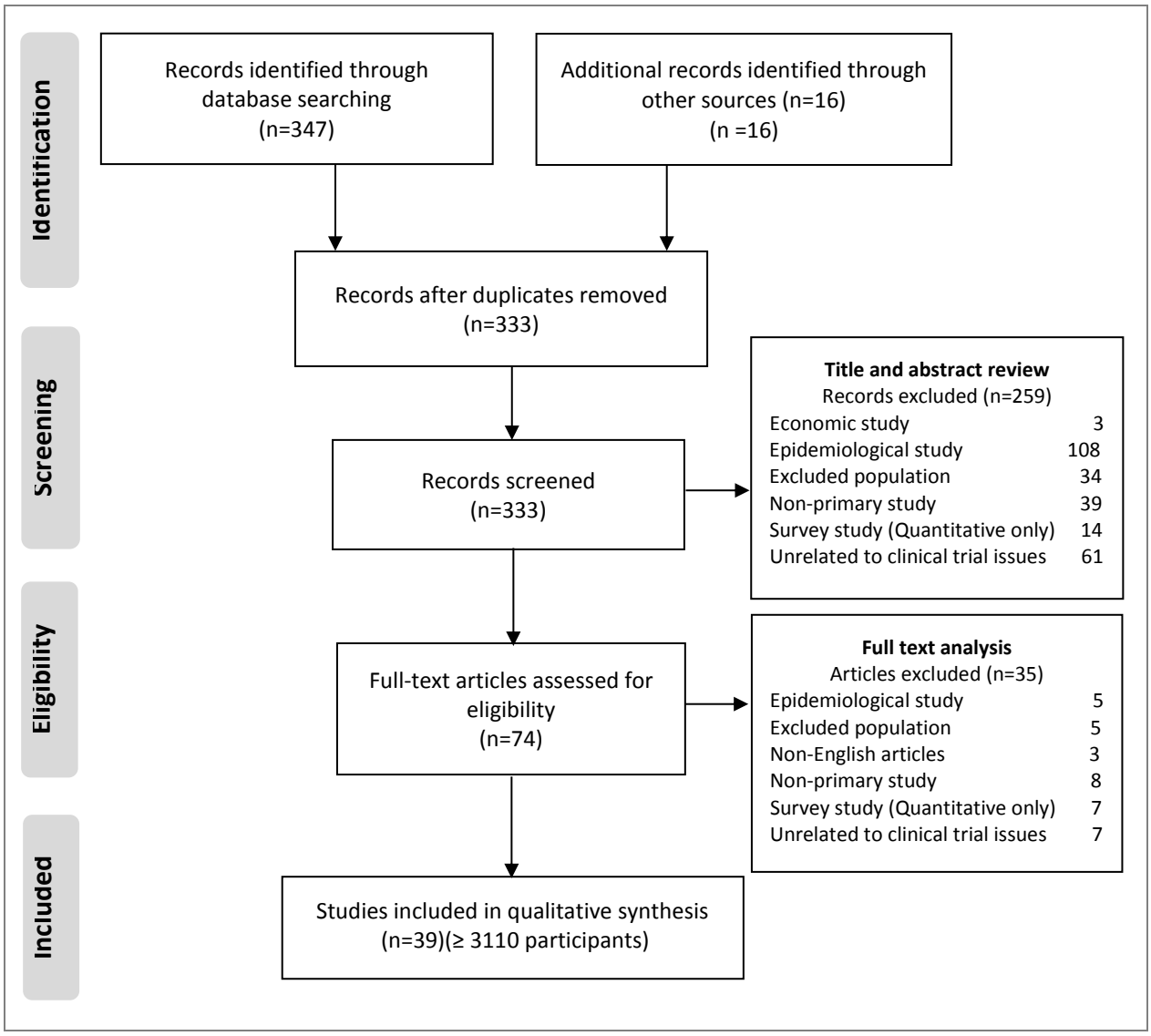
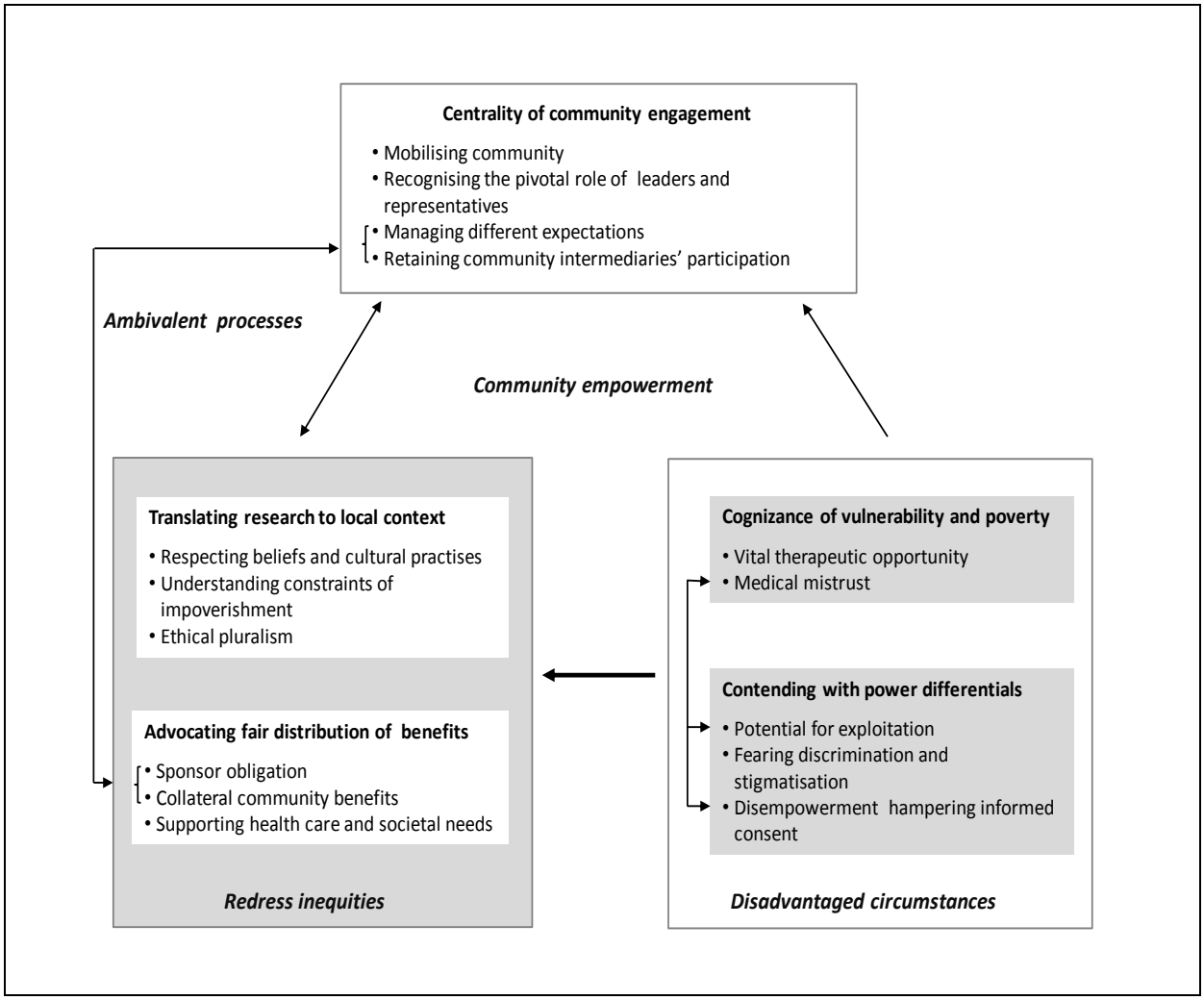


Figure 4.2 Thematic schema of redressing inequities and disadvantaged circumstances



4.7 References

1. Lozano R, Wang H, Foreman KJ, Rajaratnam JK, Naghavi M, Marcus JR, Dwyer-Lindgren L, Lofgren KT, Phillips D, Atkinson C, Lopez AD, Murray CJL. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet. 2011;378(9797):1139-65.
2. Bryce J, Black R, Victora C. Millennium Development Goals 4 and 5: progress and challenges. BMC Med. 2013;11(1):225.
3. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J of Clin Pharmacol. 2015;79(3):357-69.
4. Zipursky A. The programme for Global Paediatric Research. Clin Invest Med. December 2011;34(6):E320-E2.
5. Global Forum for Health Research. The 10/90 report on health research 2003–2004. 1-5 route des Morillons, PO Box 2100, 1211 Geneva 2, Switzerland: Global Forum for Health Research; 2004.
6. Joseph PD, Caldwell PHY, Craig JC. Disease burden - research match? Registered trials in child health from low-middle and high-income countries. Unpublished work. 2015.
7. Nor Aripin KN, Sammons HM, Choonara I. Published pediatric randomized drug trials in developing countries, 1996-2002. Paediatr Drugs. 2010;12(2):99-103.
8. Dunne J, Murphy MD, Rodriguez WJ. The globalization of pediatric clinical trials. Pediatrics. 2012;130(6):1583-91.
9. Molyneux E, Mathanga D, Witte D, Molyneux M. Practical issues in relation to clinical trials in children in low-income countries: experience from the front line. Arch Dis Child. 2012;97(9):848-51.
10. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8(1):45.
11. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(1):181.
12. Equator Network. Enhancing the QUAlity and Transparency Of health Research. Available at: http://www.equator-network.org. Accessed September 8, 2015.
13. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349-57.
14. Angwenyi V, Kamuya D, Mwachiro D, Kalama B, Marsh V, Njuguna P, Molyneux S. Complex realities: Community engagement for a paediatric randomized controlled malaria vaccine trial in Kilifi, Kenya. Trials. 2014;15(1):1-16.
15. Gikonyo C, Bejon P, Marsh V, Molyneux S. Taking social relationships seriously: lessons learned from the informed consent practices of a vaccine trial on the Kenyan Coast. Soc Sci Med. 2008;67(5):708-20.
16. Tindana PO, Rozmovits L, Boulanger RF, Bandewar SVS, Aborigo RA, Hodgson AVO, Kolopack P, Lavery JV. Aligning Community Engagement With Traditional

Authority Structures in Global Health Research: A Case Study From Northern Ghana. Am J Public Health. 2011;101(10):1857-67.

17. Angwenyi V, Kamuya D, Mwachiro D, Marsh V, Njuguna P, Molyneux S. Working with Community Health Workers as 'Volunteers' in a Vaccine Trial: Practical and Ethical Experiences and Implications. Dev World Bioeth. 2013;13(1):38-47.
18. Kamuya DM, Marsh V, Kombe FK, Geissler PW, Molyneux SC. Engaging communities to strengthen research ethics in low-income settings: selection and perceptions of members of a network of representatives in coastal Kenya. Dev World Bioeth. 2013;13(1):10-20.
19. Okello G, Jones C, Bonareri M, Ndegwa SN, McHaro C, Kengo J, Kinyua K, Dubeck MM, Halliday KE, Jukes MCH, Molyneux S, Brooker SJ. Challenges for consent and community engagement in the conduct of cluster randomized trial among school children in low income settings: Experiences from Kenya. Trials. 2013;14(1):1-11.
20. Chantler T, Otewa F, Onyango P, Okoth B, Odhiambo F, Parker M, Geissler PW. Ethical challenges that arise at the community interface of health research: village reporters' experiences in Western Kenya. Dev World Bioeth. 2013;13(1):30-7.
21. Molyneux CS, Peshu N, Marsh K. Trust and informed consent: insights from community members on the Kenyan coast. Soc Sci Med. 2005;61(7):1463-73.
22. Essack Z, Koen J, Barsdorf N, Slack C, Quayle M, Milford C, Lindegger G, Ranchod C, Mukuka R. Stakeholder perspectives on ethical challenges in HIV vaccine trials in South Africa. Dev World Bioeth. 2010;10(1):11-21.
23. Abbey M, Bartholomew LK, Nonvignon J, Chinbuah MA, Pappoe M, Gyapong M, Gyapong JO, Bart-Plange C, van den Borne B. Factors related to retention of community health workers in a trial on community-based management of fever in children under 5 years in the Dangme West District of Ghana. Int Health. 2014;6(2):99-105.
24. Rahman SM, Ali NA, Jennings L, Seraji MHR, Mannan I, Shah R, Al-Mahmud AB, Bari S, Hossain D, Das MK. Research Factors affecting recruitment and retention of community health workers in a newborn care intervention in Bangladesh. Hum Resour Health. 2010;8(1):1-14.
25. Masiye F, Kass N, Hyder A, Ndebele P, Mfutso-Bengo J. Why mothers choose to enrol their children in malaria clinical studies and the involvement of relatives in decision making: evidence from Malawi. Malawi Med J. 2008;20(2):50-6.
26. Jaspan HB, Soka NF, Mathews C, Flisher AJ, Mark D, Middelkoop K, Wood R, Bekker LG. A qualitative assessment of perspectives on the inclusion of adolescents in HIV vaccine trials in South Africa. Int J STD AIDS. 2010;21(3):172-6.
27. Geissler PW, Kelly A, Imoukhuede B, Pool R. 'He is now like a brother, I can even give him some blood' – Relational ethics and material exchanges in a malaria vaccine 'trial community' in The Gambia. Soc Sci Med. 2008;67(5):696-707.
28. Gikonyo C, Kamuya D, Mbete B, Njuguna P, Olotu A, Bejon P, Marsh V, Molyneux S. Feedback of research findings for vaccine trials: experiences from two malaria vaccine trials involving healthy children on the Kenyan Coast. Dev World Bioeth. 2013;13(1):48-56.
29. Corneli AL, Piwoz EG, Bentley ME, Moses A, Nkhoma JR, Tohill BC, Adair L, Mtimuni B, Ahmed Y, Duerr A, Kazembe P, van der Horst C, Team UNCPBS.

Involving communities in the design of clinical trial protocols: the BAN Study in Lilongwe, Malawi. Contemp Clin Trials. 2007;28(1):59-67.

30. Leach A, Hilton S, Greenwood BM, Manneh E, Dibba B, Wilkins A, Mulholland EK. An evaluation of the informed consent procedure used during a trial of a Haemophilus influenzae type B conjugate vaccine undertaken in The Gambia, West Africa. Soc Sci Med. 1999;48(2):139-48.

31. Mahomed H, Shea J, Kafaar F, Hawkridge T, Hanekom WA, Hussey GD. Are adolescents ready for tuberculosis vaccine trials? Vaccine. 2008;26(36):4725-30.

32. Fairhead J, Leach M, Small M. Public engagement with science? Local understandings of a vaccine trial in the Gambia. J Biosoc Sci. 2006;38(1):103-16.

33. Kingori P, Muchimba M, Sikateyo B, Amadi B, Kelly P. 'Rumours' and clinical trials: a retrospective examination of a paediatric malnutrition study in Zambia, southern Africa. BMC Public Health. 2010;10:556.

34. Perez-Guerra CL, Rodriguez-Acosta RL, Soto-Gomez E, Zielinski-Gutierrez E, Pena-Orellana M, Santiago LM, Rivera R, Cruz RR, Ramirez V, Tomashek KM, Dayan G. Assessing the interest to participate in a dengue vaccine efficacy trial among residents of Puerto Rico. Hum Vaccin Immunother. 2012;8(7):905-15.

35. Lairumbi GM, Parker M, Fitzpatrick R, Mike EC. Stakeholders understanding of the concept of benefit sharing in health research in Kenya: a qualitative study. BMC Med Ethics. 2011;12:20. Epub 2011/10/04.

36. Molyneux CS, Peshu N, Marsh K. Understanding of informed consent in a low-income setting: three case studies from the Kenyan coast. Soc Sci Med. 2004;59(12):2547-59.

37. Coreil J, Losikoff P, Pincu R, Mayard G, Ruff AJ, Hausler HP, Desormeau J, Davis H, Boulos R, Halsey NA. Cultural feasibility studies in preparation for clinical trials to reduce maternal-infant HIV transmission in Haiti. AIDS Educ Prev. 1998;10(1):46-62.

38. Jaspan HB, Soka NF, Strode AE, Mathews C, Mark D, Flisher AJ, Wood R, Bekker LG. Community perspectives on the ethical issues surrounding adolescent HIV vaccine trials in South Africa. Vaccine. 2008;26(45):5679-83.

39. Kass NE, Maman S, Atkinson J. Motivations, Understanding, and Voluntariness in International Randomized Trials. IRB. 2005;27(6):1-8.

40. Molyneux S, Mulupi S, Mbaabu L, Marsh V. Benefits and payments for research participants: Experiences and views from a research centre on the Kenyan coast. BMC Med Ethics. 2012;13:1-15.

41. DeCosta A, Souza ND', Krishnan S, Chhabra MS, Shihaam I, Goswami K. Community based trials and informed consent in rural north India. J Med Ethics. 2004;30:318–23.

42. Crane J. Adverse events and placebo effects: African scientists, HIV, and ethics in the 'global health sciences'. Soc Stud Sci. 2010;40(6):843-70.

43. Hyder AA, Wali SA. Informed consent and collaborative research: perspectives from the developing world. Dev World Bioeth. 2006;6(1):33-40.

44. Lairumbi G, Parker M, Fitzpatrick R, English M. Forms of benefit sharing in global health research undertaken in resource poor settings: a qualitative study of stakeholders' views in Kenya. Philos Ethics Humanit Med. 2012;7(1):7.

45. Caldwell PHY, Butow PN, Craig JC. Parents' attitudes to children's participation in randomized controlled trials. J Pediatr. 2003;142(5):554-9.

46. Dickert N, Sugarman J. Ethical Goals of Community Consultation in Research. Am J Public Health. 2005;95(7):1123-7.

47. Nuffield Council on Bioethics. The ethics of research related to healthcare in developing countries : a follow-up Discussion Paper. 2005. Available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/HRRDC_Follow-up_Discussion_Paper.pdf. Accessed April 6, 2015.

48. Ananworanich J, Puthanakit T, Saphonn V, Cooper DA, Ruxrungtham K. Lessons from a multicentre paediatric HIV trial. Lancet. 2008;372(9636):356-7.

49. Lavery JV, Tinadana PO, Scott TW, Harrington LC, Ramsey JM, Ytuarte-Nuñez C, James AA. Towards a framework for community engagement in global health research. Trends Parasitol. 2010;26(6):279-83.

50. UNAIDS (Joint United Nations Programme on HIV/AIDS). Ethical Considerations in Biomedical HIV Prevention Trials. 2007(Report):1-140.

51. Fernandez CV, Skedgel C, Weijer C. Considerations and costs of disclosing study findings to research participants. CMAJ. 2004;170(9):1417-9.

52. ICH Expert Working Group. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, ICH harmonised tripartite guideline: Guideline for Good Clinical Practice E6 (R1).1996. Current Step 4 version. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed April 7, 2014.

53. Benatar SR. Reflections and recommendations on research ethics in developing countries. Soc Sci Med. 2002;54(7):1131-41.

54. Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva, Switzerland: Council for International Organizations of Medical Sciences. 2002. Available at: www.cioms.ch/publications/layout_guide2002.pdf. Accessed March 3, 2015.

55. Riessman CK. Exporting ethics: a narrative about narrative research in South India. Health Soc Care Community. 2005;9(4):473-90.

56. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. October, 2013. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed March 31, 2014.

57. Nuffield Council of Bioethics. National Bioethics Advisory Commission. Ethical and policy issues in international research:clinical trials in developing countries: executive summary. United States.2001.

58. Brewster D. Science and ethics of human immunodeficiency virus/acquired immunodeficiency syndrome controversies in Africa. J Paediatr Child Health. 2011;47(9):646-55.

59. Lang T, Cheah PY, White NJ. Clinical research: time for sensible global guidelines. Lancet. 2011;377(9777):1553-5.

60. Tangwa GB. Between Universalism and Relativism: A Conceptual Exploration of Problems in Formulating and Applying International Biomedical Ethical Guidelines. J Med Ethics. 2004;30(1):63-7.

61. Vreeman R, Kamaara E, Kamanda A, Ayuku D, Nyandiko W, Atwoli L, Ayaya S, Gisore P, Scanlon M, Braitstein P. A qualitative study using traditional community assemblies to investigate community perspectives on informed consent and research participation in western Kenya. BMC Med Ethics. 2012;13:23.

62. Marsh VM, Kamuya DK, Parker MJ, Molyneux CS. Working with Concepts: The Role of Community in International Collaborative Biomedical Research. Public Health Ethics. 2011;4(1):26-39.

63. Power R, Langhaug L, Nyamurera T, Wilson D, Bassett M, Cowan F. Developing complex interventions for rigorous evaluation-a case study from rural Zimbabwe. Health Educ Res. 2004;19(5):570-5.

64. Landy DC, Sharp RR. Examining the Potential for Exploitation by Local Intermediaries. Am J Bioeth. 2010;10(3):12-3.

65. Arras JD. Fair Benefits in International Medical Research. The Hastings Center Report [HWWilson - GS]. 2004;34(3):3.

66. Grady C. Payment of clinical research subjects. J Clin Invest. 2005;115(7):1681-7.

67. Regmi S, Kaas–Hansen BS, Iversen JH. Beyond access to medicines: Eliciting high–income country support for a new global health research and development paradigm. Journal of Global Health. 2013;3(2):020303.

68. Edwards D, Matlin SA, Eide M, Young AJ, Regmi S, Ardal C, Guzman J, Terry RF, Røttingen JA, Viergever RF. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet. 2013;382(9900):1286-307.

69. Council on Health Research for Development (COHRED). Are international health research programmes doing enough to develop research systems and skills in low and middle income countries? Geneva. COHRED. 2007. Available at: http://www.cohred.org/wpcontent/uploads/2013/08/4.ResponsibleVerticalProgrammingLOWRES.pdf. Accessed March 27, 2015.

70. Febir L, Asante K, Dzorgbo D, Senah K, Letsa T, Owusu-Agyei S. Community perceptions of a malaria vaccine in the Kintampo districts of Ghana. Malar J. 2013;12:156. Epub 2013/05/09.

71. Tindana P, Kass N, Akweongo P. The Informed Consent Process in a Rural African Setting: A Case Study of the Kassena-Nankana District of Northern Ghana. IRB. 2006;28(3):1-6.

72. Molyneux C, Wassenaar D, Peshu N, Marsh K. 'Even if they ask you to stand by a tree all day, you will have to do it (laughter)…!': Community voices on the notion and practice of informed consent for biomedical research in developing countries. Soc Sci Med. 2005;61(2):443-54.

73. Nabulsi M, Khalil Y, Makhoul J. Parental attitudes towards and perceptions of their children's participation in clinical research: a developing-country perspective. J Med Ethics. 2011;37(7):420-3.

74. Piwoz E, Ferguson Y, Bentley M, Corneli A, Moses A, Nkhoma J, Tohill B, Mtimuni B, Ahmed Y, Jamieson D, van der Horst C, Kazembe P, Team tUPBS. Differences between international recommendations on breastfeeding in the presence of HIV and the attitudes and counselling messages of health workers in Lilongwe, Malawi. Int Breastfeed J. 2006;1(1):2.

75. Liheluka EA, Lusingu JP, Manongi RN. Community perceptions on the secondary health benefits established by malaria vaccine trials (RTS,S phase 2 and phase 3) at the Korogwe site in North Eastern Tanzania. Malar J. 2013;12:157.

Chapter 5

Completeness of protocols of clinical trials in children submitted to ethics committees

Chapter 5: Completeness of protocols of clinical trials in children submitted to ethics committees

5.1 Abstract

Abstract

Background: Empiric studies of published clinical trials involving children have shown methodological flaws and high risk of bias but it is unclear if this reflects editorial processes of true problems in design and conduct. We aimed to ascertain the completeness of the reporting of key domains in the conduct of clinical trials involving children by evaluating the protocols of pharmacological interventions for trials submitted to the Human Research Ethics Committees (HRECs) of Children's Hospitals in Australia.

Method: HRECs of all Children's Hospital were invited to participate. De-identified trial protocols submitted for review in 2012 were evaluated using checklists based on CONSORT (CONsolidated Standards of Reporting Trials), the Cochrane risk of bias tool and Good Clinical Practice guidelines.

Results: Four of 8 hospitals agreed to participate and 69 protocols were analysed. The domains most frequently reported were clustered around the background and trial plan (planned interventions for each group (99%), specific objectives (97%), and scientific background (96%)). Domains that were reported least frequently were clustered around the statistical analysis plan (66%), the justification for a new trial based upon a systematic review of the published literature (48%), and child-specific domains (48%).

Conclusions: Protocols of trials involving children assessed by Ethics Committees are generally comprehensive, but many key domains in trial design and conduct are not reported. Problems in the design and conduct of clinical trials may lead to misleading conclusions in the healthcare of children. There is a need for development, implementation and compliance

with standards in the design of trial protocols to help improve the quality of trials, minimize risk of harm and generate reliable results to inform evidence-based child healthcare.

What's known on this subject

Published trials in children are often analysed as high or unclear risk of bias, but it is uncertain whether this reflects editorial practices or whether this does indicate important omissions in the design and conduct of clinical trials involving children.

What this study adds

Paediatric trial protocols are generally comprehensive, but over 20% have major gaps, focused on the statistical analysis plan including sample size, and data analysis methods, and a justification for why an additional trial is needed, based upon a systematic review.

5.2 Introduction

It is well established that randomised controlled trials (RCTs) may result in over-optimistic and misleading treatment effects when key elements in the design and conduct are either not reported or are reported and are not appropriate. These problems have been found more frequently in trials involving children [1-5]. However it is unclear whether these problems reflect editorial practices, where 'methods' elements are removed in favor of 'content' elements because of space constraints, for example, or whether these observations do reflect deficiencies in actual trial design and conduct.

A trial protocol is a research plan that describes the background, rationale, objectives, design, methodology, statistical considerations, and organisation of the trial and is an essential document for all trial stakeholders [6]. The Human Research Ethics Committee (HREC) is responsible for the ethical and scientific review of trial protocols according to stringent local and international guidelines, balancing research risks with potential benefits and contribution

to existing knowledge [7, 8]. The fundamental assessment of the scientific rigor of a trial protocol is of paramount importance in validating the results of the trial. A recent study of reviews by HRECs of pediatric multi-center drug trials recommended that applicants ensure that the trial documents are informative to researchers, regulators and consumers [9]. Almost all empiric studies of the quality of research have assessed published reports, but this may not reflect actual design and conduct. We aimed to evaluate how comprehensive protocols of pediatric trials of pharmacological interventions were, as submitted to the HRECs among Australian Children's Hospitals, and to identify areas for improvement.

5.3 Methods

5.3.1 Study Design

This is a retrospective cohort study of trial protocols of pharmacological interventions involving children submitted from 1 January to 31 December 2012 to the HRECs of Children's Hospitals in Australia. The study was conducted over 18 months from June 2013 to December 2014. Ethics approval to conduct the study was received from the HRECs of participating Children's Hospitals.

5.3.2 Practice Selection and Setting

All Children's Hospitals in Australia were invited to participate in the study. The inclusion criteria were, clinical trials (phase 1 to 1V) of drug or medicines, complementary or herbal medicines or devices containing a therapeutic agent, which were to be conducted in children aged 0-18 years or in a mixed population of children and adults and which were submitted to the HREC during 2012. Only the scientific components of the protocols were assessed and not the ethical aspects.

5.3.3 Study Procedures

The study investigated the characteristics and reporting of the domains of trials submitted to HRECs using a standardised checklist. The checklist was piloted to establish feasibility, and completeness of quality assessment criteria. The data were extracted from all protocols submitted the first time for consideration by any HREC and relevant supporting documentation. All eight pediatric hospitals were invited to be part of the study with a nominated investigator, who was a member of the local HREC or its sub-committee, being responsible for data extraction. All data were de-identified.

5.3.4 Data collection

The World Health Organization (WHO) International Classification of Diseases (ICD) was used for classifying the disease or health condition studied [10]. Data on the background, rationale, objective(s), design, methodology, statistical considerations, and organisation of each trial were extracted using a consolidated checklist adapted from the CONSORT (CONsolidated Standards of Reporting Trials) and Cochrane risk of bias tool [11, 12]. A compilation of other protocol elements of importance to trials and in particular child-specific domains such as reporting disease prevalence in children and long-term safety monitoring informed by current International Conference on Harmonisation Guideline for Good Clinical Practice guidelines (E6R1) [6] and WHO Paediatric clinical trials guidance for assessors [7] were also included [13]. Some of these items now appear on Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [14] and proposals for CONSORT-Children and SPIRIT-Children [15]. The Cochrane Collaboration's risk of bias tool contains seven domains and we assessed five of these (sequence generation, allocation concealment, blinding, incomplete outcome data (intention to treat analysis), and "other sources of bias (trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses)" [12, 13]. Given that each trial was in protocol stage some items

such as attrition bias were not relevant and not considered. We checked all the trials after ethics approval to determine whether they were registered on the WHO International Clinical Trials Registry Portal [16].

5.3.5 Data analysis

The data from the checklist was captured on a Microsoft Excel® spreadsheet for analysis. Descriptive techniques were used to analyse the data. For each of the core domains (title, background and objectives, trial design, participants, recruitment, interventions, outcomes, harms or unintended effects, sample size, randomisation, blinding, statistical methods, trial registration, funding, reporting) the proportion of protocols that included or described the domain, was reported. The Cochrane risk of bias domains was reported as high, low or unclear risk of bias. Frequency of reporting across the domains were displayed using a two-dimensional radar plot generated in Microsoft Excel®. Adequate reporting of domains was defined pragmatically as more than 80%.

5.4 Results

5.4.1 Characteristics of study sites and included trials

Four of the eight pediatric hospitals in Australia participated. Non-participation was due to institutional restrictions, resources and time constraints. Characteristics of the included trials appear in Table 5.1. Of the 69 protocols included in the study, 57 (83%) were RCTs, 47 (68%) recruited children only, 58 (84%) were multi-center of which 34 (49%) recruited multi-nationally and 51 (74%) were phase III trials. The main health conditions studied were respiratory (18), neoplasms (9), hematological and immunological (9), and infectious diseases (8). Eleven of the protocols did not include the proposed sample size that could be potentially be recruited by the site. The planned site sample size of the 58 remaining trials ranged between 1 to 1920 participants, with 44 (76%) estimating a sample size of 100 or less and 24

(41%) a sample size of 10 or less. The main comparators for the RCTs were current standard patient care (25) and placebo (21). Of the 38 studies that stratified the randomisation, 13 were by age and 10 by gender. The main endpoints in most trials were efficacy (65) and safety (52). Only 6 trials planned to evaluate quality of life (QOL).

5.4.2 Completeness in the reporting of trial domains

Figure 5.1 and the supplementary Table in Appendix E1 show the frequency of reporting of the CONSORT criteria. The domains that were reported almost always (90%) were: funding, scientific background, specific objectives, description of trial design, study setting , eligibility criteria, interventions for each group to allow replication, description of similarity of interventions, intervention maximum dose or threshold levels, compliance measurement, pre-specified outcome measures, blinding of personnel after assignment of interventions. The domains that were reported almost always (75-90%) included dates defining the periods of recruitment and follow-up, statistical methods to compare group outcomes, type of randomisation and details of any restriction, method used to generate the random allocation sequence, person who generated the random allocation sequence and enrolled assigned participants, method used to implement the random allocation sequence, harms or unintended effects, sample size calculation and trial registration. The trial domains that commonly and often missed were: descriptive title, mechanism used to implement the random allocation sequence, methods for subgroup or adjusted analyses and explanation of interim analyses and stopping guidelines.

The checklist of child-specific and other important items for trial protocols appears in Figure 5.2 and the supplementary Table in Appendix E2. The domains that were almost always done (90%), maximum dose or threshold levels of intervention, compliance measurement and safety data on the therapeutic intervention. The domains that were frequently reported (75-

90%) were: disease prevalence in children, impact of the disease in children, participant timeline, continuous safety monitoring and planned reporting of study results. The trial domains that were reported least frequently were: background systematic review justifying need for the study; dose adjustment by age, weight or body surface area, post-trial provisions of effective interventions, age and development specific outcomes, protocol modification conditions, long-term safety monitoring, and inclusion of a Data Safety Monitoring Board.

5.4.3 Assessment of risk of bias

The assessments of risk of bias that were most frequently reported were as follows: random sequence generation (88%), blinding of participants and personnel (87%), blinded outcome assessment (81%), allocation concealment (80%). Poorly described domains were: specified intention to treat analysis or incomplete outcome data (54%) and other bias (51%) (Figure 5.2).

5. 5 Discussion

Our study was designed to determine the completeness of reporting of important domains in the design and conduct in trials of pharmacological interventions based upon trial protocols submitted to Ethics Committees of Children's Hospitals in Australia. We found that in most trial protocols the core content domains were reported, in particular funding, scientific background, objectives, disease prevalence in children, planned interventions and risk of bias. However, there were incomplete reporting of domains mainly clustering around systematic review of the literature, impact of disease in children, age and development specific outcomes, and most elements of the statistical analysis plan.

It is likely that the domains that were well reported such as funding and objectives reflects the standard templates or checklists that investigators are required to use for submitting trial

protocols to the Ethics Committees [8, 17]. The training and guidance provided to investigators also improves their familiarity with the content requirements of the protocol. Domains related to the research question and rationale was reported in 96% of the trials in our study. However, fewer than 50% of trial protocols provided evidence of having undertaken a systematic review of the existing literature to inform the primary research proposed. Evidence of a systematic review is important for reviewers to ensure that the trial is necessary, and has not been answered previously. As the ethics applications are often guided by the institutional templates, some of the templates may not have included the need for a systematic review of the literature. Thus a systematic review may not have been included in the submitted protocol even though it may have been conducted by the investigators.

Most elements of statistical analysis were poorly reported in our study. Appropriate sample size calculations ensure that studies are adequately powered to provide conclusive findings and detect modest but clinically relevant outcomes including adverse effects [5, 18]. However, our results indicate that only 73% of the trial protocols addressed sample size. Calculation of an adequate sample size is also important to prevent research waste and unnecessarily subjecting children to poor research. A priori subgroups (e.g. neonates, infants, preschoolers, children and adolescents) within the pediatric population may respond differently to therapies and need to be identified, with trials adequately powered to minimise the chances of a type II error occurring in these subgroups [5, 19].

Evaluation of adverse effects need to consider that children are more susceptible to the harmful effects of medicines, and that adverse effects may present much later in children who are still undergoing growth and development. Independent Data Monitoring Committees (DMCs) or Data Safety Monitoring Boards (DSMBs) safeguard the interests of trial participants by monitoring safety and adverse drug reactions (ADRs) and the scientific

integrity of the trial for example decisions on interim analysis and early stopping of trials. Not all trials require stopping guidelines, interim analyses or a DMC; however it is still important for this to be justified in the protocol. DMCs play a pivotal role in the scientific validity, results and clinical impact of a trial and are recommended for all appropriate pediatric trials [20, 21]. Our study showed 62% of the trials described measurement of harms or unintended effects with only 12% indicating long-term safety monitoring. A review of 739 published trials in children (1996-2002) showed that 71% of the trials reported an ADRs, 20% reported a serious ADRs, but only 2% of the trials had a DMC [22]. A later review of trials (2005-2007) showed that 17% reported on DMCs, interim analysis or early stopping [23]. We found that 73% of protocols defined the criteria for stopping the trial and 71% of the protocols indicated that there was to be a DMC. Although the previous studies reflects published trials and our study is of protocols submitted, this data suggests that trialists are becoming more aware of the importance of pharmacovigilance in children and the need to comply with scientific standards and a framework for DMCs [16, 23-28].

Completion of the risk of bias domains in the protocols were reported well in comparison to previous analysis of published pediatric trials that were judged to have high risk of bias. [4],[1] An analysis of published pediatric trials indicated that only 27% (1996-2001) and 17% (2002-2006) of pediatric trials adequately addressed allocation concealment [4]. It is possible that in the publication of trials, the authors may not have reported all aspects due to journal editorial practices, although these may have been included in the trial design and conduct [4]. A study looking at the risk of bias in RCTs in children (2008-2009) showed improvement in reporting with a low risk of bias for random sequence generation (59%) and blinding of outcome assessment (63%). Researchers need to comply with standards containing the risk of bias in trials in children [29]. There is a need for evidence-informed guidelines on the selection of appropriate clinical comparators in trials in children. Our findings indicated that 36% of the

comparators of the RCTS used the current standards and 30% used placebo, however we did not assess the appropriateness of the comparators. The use of placebos in children poses ethical dilemmas. A sound rationale must exist for its use to ensure children are not exposed to the risks of placebo or an inferior therapy when better therapies are available [26, 30, 31].

The child-specific elements of the protocols were poorly described in our study. For example age and development specific outcomes, which are important in children, were often not included. In our study only 13 trials had randomisation stratified by age. The selection of endpoints should be objective, clinically relevant and measurable in a valid and reliable method minimising the risk of bias. There are some initiatives underway looking at selection of outcomes in the general population [32-38].Well-defined and reliable trials outcome assessments for recording treatment benefit in children in most therapeutic areas, considering their different manifestations of diseases and the variable developmental changes are lacking [39]. In our study, plans to measure children's quality of life were only mentioned in 9 (13%) of the trials and this has been identified as a gap previously [40]. Although there are some initiatives underway to develop patient reported outcomes in the general population, [41] there is a need to develop age-appropriate measurement strategy of children and adolescents reported outcomes [42].

This study has shown that the reporting of scientific components of protocols of trials in children submitted to Ethics Committees is generally comprehensive. However, many key domains in trial design and conduct are not reported in the submitted protocols. This may be due to the different requirements in the Australian context and the institution ethics applications templates or lack of oversight by researchers. Consistency was maximised by a standardised, widely used checklist with training and guidance provided for completion of the checklist to ensure data validity. Although the study was conducted in Australia where the

ethics processes and research standards may be different to other countries, there is potential for the findings to be extrapolated to other developed countries. However, there are limitations with our study. Due to resourcing and time constraints, only 69 protocols were analysed. We used a checklist for reporting of core components of the trial protocols submitted to the ethics committees. This is not an analysis of the revised final protocols used in practice or an assessment of how well the trials were conducted. Given the issues of confidentiality there was no capacity for double extraction of data by the same two researchers. However, a previous study demonstrated that there was high interrater agreement for reviewers by adherence to a standardised checklist and agreed definitions by reviewers [43]. At the time of the study Standard Protocol Items for RCTs (SPIRIT) [44] was not available and we therefore used the CONSORT checklist.

Our study findings have implications for policy and clinical practice. We encourage improvements in explicit and transparent inclusion of all core elements of paediatric trial protocols. This will assist regulators in their critical evaluation, researchers in the conduct and registration of the trial, and clinicians in synthesising the evidence potentially improving quality and saving time of all users [45, 46]. In the design of our checklist to assess the protocols, we noted inadequacies in the current guidance for protocols and reporting of child-specific issues in trials in children, but acknowledge some initiatives are underway [21]. Two recent systematic reviews gathered evidence and recommendations for including child-specific items in protocols, SPIRIT-Children (SPIRIT-C) [44, 47] and reporting of trials in children CONSORT-Children (CONSORT-C) [15, 48]. It is imperative for stakeholders including HRECs and research institutions to collaborate locally and internationally and invest in researcher's training on protocol development. This includes supporting the development and use of evidence-based standards and guidance such as standardised protocol templates to promote best research practices [13,34].

A similar assessment of completion of scientific items in protocols of paediatric trials conducted in less developed countries would be useful to determine their specific gaps that could be different due to resource constraints. Future research should evaluate the completeness of the inclusion of the ethical components of relevance to children in the protocols and related trial documents to inform improvements in trial design. We recommend further research into the conduct of trials including frequency and procedures for auditing trial conduct.

5. 6 Conclusions

Protocols of clinical trials involving children assessed by Ethics Committees were comprehensive and well-described. However, many key domains in trial design and conduct remain incompletely reported in protocols and could be improved. These cluster around statistical analysis, safety monitoring and child-specific elements, such as appropriate randomisation stratified by age. Problems in the design and conduct of clinical trials may lead to misleading conclusions in child healthcare. There is a need for development, implementation and compliance with standards in the design of protocols that consider the unique needs of children. This could help improve the quality of trials in children, minimise risk of harm to children and generate reliable results to be implemented in the clinical care of children.

Table 5.1 Characteristics of included trials (n=69)

Characteristics of trial	Number of trials (%)
Type of trial	
Randomised controlled trial	57 (83)
Non-randomised controlled trial	13(17)
Initiated by	
Industry	36 (52)
Investigator	33 (48)
Phase	
Phase 1	4 (6)
Phase 2	10 (15)
Phase 3	51 (74)
Phase 4	4(6)
International Classification of Disease (ICD)	
Respiratory	18 (26)
Neoplasms	9 (13)
Haematological and immunological	9 (13)
Infectious	8 (12)
Endocrine, nutritional and metabolic	5 (7)
Environmental	5 (7)
Other	15 (22)
Intervention use	
Treatment	51 (74)
Prevention	17 (25)
Diagnosis	1 (1)
Participants	
Children (0-18 years)	47 (68)
Children and adults	22 (32)
Recruitment sites[a]	
Multinational	34 (51)
Multi-centre	58 (87)
Single centre	9 (13)
Inclusion of sample size	58 (84)
Sample size of 100 or less participants	44 (76)
Sample size of 10 or less participants	24 (41)
Recruitment methods[b]	
Face-to-face/referral	47 (68)
Advertising	9 (13)
Mail out/telephone	7 (10)
Follow-up trial	3 (4)
Stratification of treatment[c]	38 (55)
Age	13(34)
Gender	10 (26)
Previous treatment	4 (11))
Severity of illness	3 (8)
Weight	1 (3)
Other	13(34)
Primary and secondary endpoint(s)[b]	
Efficacy	65 (94)
Safety	52 (75)
Tolerability	14 (20)
Optimum dosage schedule	7 (10)
Pharmacokinetics	7 (10)
Quality of life (QOL)	7 (10)
Other	8 (12)
Type of comparator	
Current standards of patient care	25(36)
Placebo	21 (30)
Different regimens of same intervention	13(19)
Other	2(3)

[b] some items were unclear and were excluded from the denominator

[a] more than one category permissible

[c] n is less than 69 as domain did not apply to some trials

Figure 5.1 Radar chart of frequency of CONSORT domains in paediatric trial protocols submitted to ethics committees

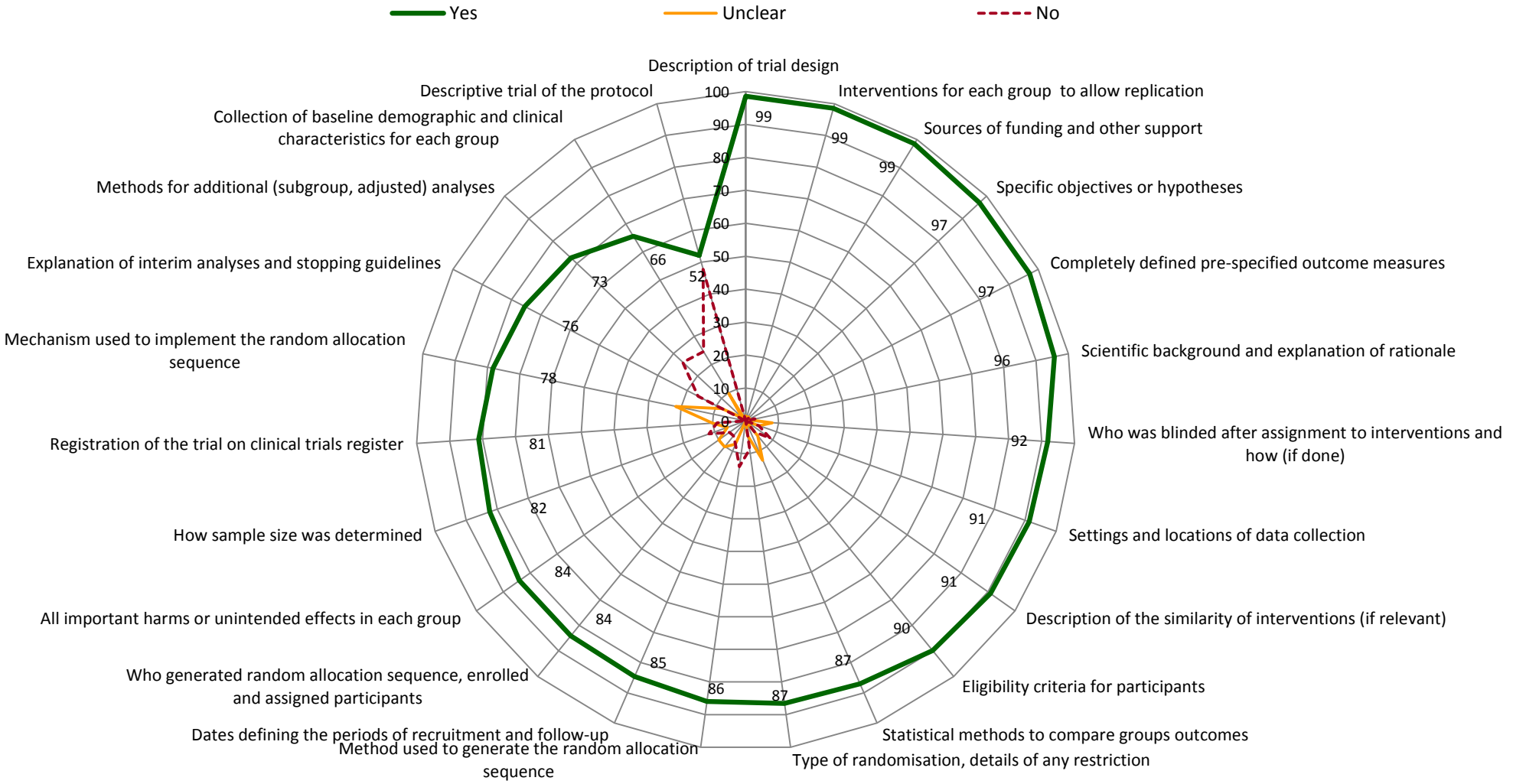


Figure 5.2 Radar chart of frequency of other important domains of paediatric trial protocols submitted to ethics committees

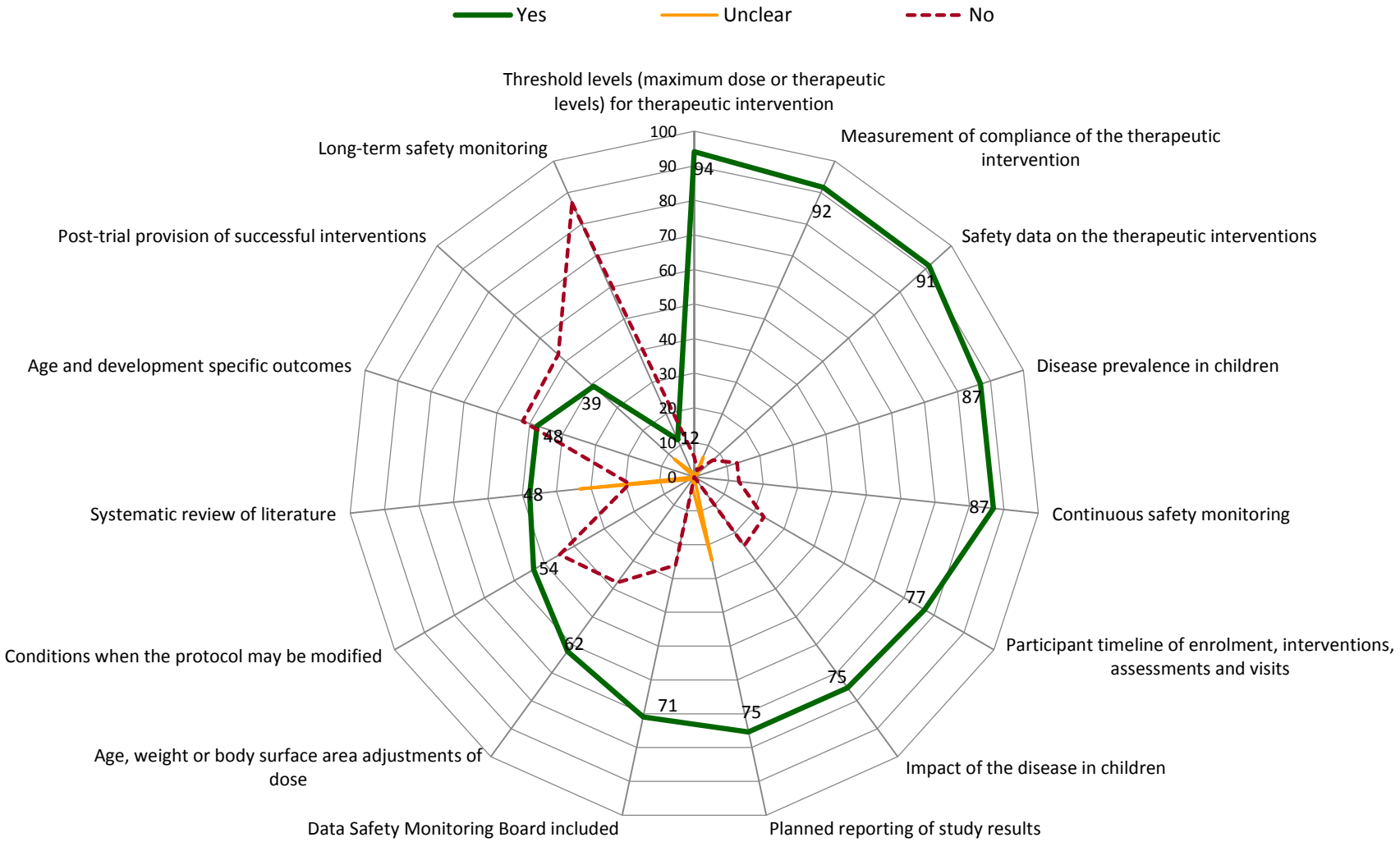
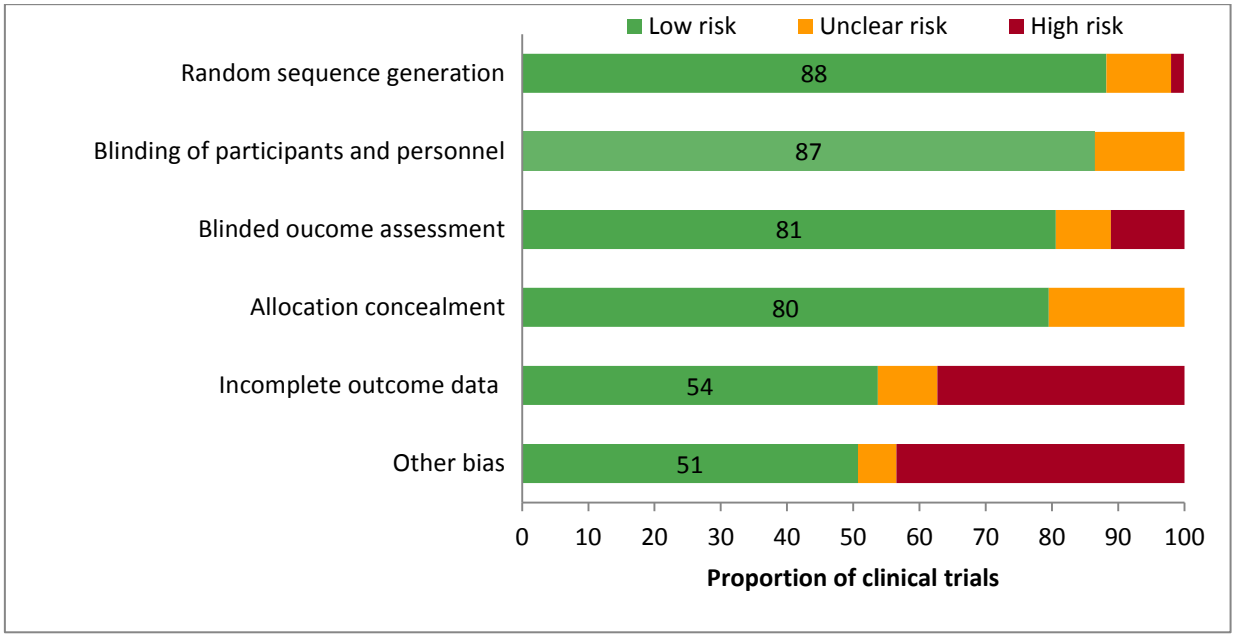


Figure 5.3 Risk of bias for paediatric trial protocols submitted to ethics committees



5.7 References

1. Crocetti MT, Amin DD, Scherer R. Assessment of risk of bias among pediatric randomized controlled trials. Pediatrics. 2010;126(2):298-305.
2. Aripin KNBN, Choonara I, Sammons HM. A systematic review of paediatric randomised controlled drug trials published in 2007. Archives of Disease in Childhood. 2010;95(6):469-73.
3. Nor Aripin KN, Sammons HM, Choonara I. Published pediatric randomized drug trials in developing countries, 1996-2002. Paediatr Drugs. 2010;12(2):99-103.
4. Thomson D, Hartling L, Cohen E, Vandermeer B, Tjosvold L, Klassen TP. Controlled trials in children: Quantity, methodological quality and descriptive characteristics of pediatric controlled trials published 1948-2006. PLoS ONE. 2010;5(9):1-9.
5. Klassen TP, Hartling L, Craig JC, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS medicine. 2008;5(8):e172.
6. International Conference on Harmonisation (ICH) Expert Working Group. International Conference on Harmonisation of technical Requirements for registration of pharmaceuticals for human Use. ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice (E6R1). Version date 10 June 996. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed 14 November 2015.
7. World Health Organization. Paediatric clinical trials guidance for assessors. June 2011. Available at www.who.int/childmedicines/CTguidance.pdf. Accessed May 22, 2013.
8. National Health and Medical Research Council, Australian Research Council, Australian Vice-Chancellors' Committee. National Statement on Ethical Conduct in Human Research. 2007, updated 2009. Available at: http://www.nhmrc.gov.au/guidelines/publications/e72. Accessed May 20, 2015.
9. Needham AC, Kapadia MZ, Offringa M. Ethics Review of Pediatric Multi-Center Drug Trials. Pediatric Drugs. 2014;17(1):23-30.
10. CONSORT Group. 2010 CONSORT checklist of information to include when reporting a randomised trial. http://www.consort-statement.org/consort-statement/overview0/. Accessed May 18, 2013.
11. Cochrane Collaboration. The Cochrane Collaboration's tool for assessing risk of bias. Available at: http://ohg.cochrane.org/sites/ohg.cochrane.org/files/uploads/Risk%20of%20bias%20assessment%20tool.pdf. Accessed May 20, 2013.
12. New South Wales Health Ministry of Health. Policy Directive: PD2007_035.Human Research Ethics Committees: Standards for Scientific Review of Clinical Trials. 2007. Available at: http://www0.health.nsw.gov.au/policies/pd/2007/pdf/PD2007_035.pdf. Accessed May 5, 2013.
13. Clyburne-Sherin AVP, Thurairajah P, Kapadia MZ, Sampson M, Chan WWY, Offringa M. Recommendations and evidence for reporting items in pediatric clinical trial protocols and reports: two systematic reviews. Trials. 2015;16(1):417.
14. Higgins JPT, (editors) GS, editors. Assessing risk of bias in included studies. In Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org.Accessed November 11, 2015.

15. World Health Organisation. ICD-10 Version:2010 - International Statistical Classification of Diseases and Related Health Problems 10th Revision. Available at: http://apps.who.int/classifications/icd10/browse/2010/en. Accessed June 1, 2013.

16. Ellenberg S, Fernandes RM, Saloojee H, Bassler D, Askie L, Vandermeer B, et al. Standard 3: Data monitoring committees. Pediatrics. 2012;129(3):S132-S7.

17. Saary MJ. Radar plots: a useful way for presenting multivariate health care data. J Clin Epidemiol. 2008;61(4):311-7.

18. Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gulmezoglu AM, et al. How to increase value and reduce waste when research priorities are set. Lancet. 2014;383(9912):156-65.

19. Van Der Tweel I, Askie L, Vandermeer B, Ellenberg S, Fernandes RM, Saloojee H, et al. Standard 4: Determining adequate sample sizes. Pediatrics. 2012;129(3):S138-S45.

20. Williams K, Thomson D, Seto I, Contopoulos-Ioannidis DG, Ioannidis JPA, Curtis S, et al. Standard 6: Age groups for pediatric trials. Pediatrics. 2012;129(3):S153-S60.

21. Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, et al. Issues in data monitoring and interim analysis of trials. Health Technology Assessment. 2005;9(7):1.

22. Van't Hoff W, Offringa M, Star Child Health g. StaR Child Health: developing evidence-based guidance for the design, conduct and reporting of paediatric trials. Archives of Disease in Childhood. 2015;100(2):189-92.

23. Sammons H, Gray C, Hudson H, Cherrill J, Choonara I. Safety in paediatric clinical trials – a 7-year review. Acta Pædiatrica. 2008;97:474-7.

24. Fernandes RM, Van der Lee JH, Offringa M. Data monitoring committees, interim analysis and early termination in paediatric trials. Acta Paediatrica. 2011;100(10):1386-92.

25. Hibberd PL, Weiner DL. Monitoring participant safety in phase I and II interventional trials: Options and controversies. Journal of Investigative Medicine. 2004;52(7):446-52.

26. Neubert A. Pharmacovigilance in pediatrics: current challenges. Paediatr Drugs. 2012;14(1):1-5.

27. Parellada M, Moreno C, Moreno M, Espliego A, de Portugal E, Arango C. Placebo effect in child and adolescent psychiatric trials. Eur Neuropsychopharmacol. 2012;22(11):787-99.

28. Thom EA, Klebanoff MA. Issues in clinical trial design: Stopping a trial early and the large and simple trial. American Journal of Obstetrics and Gynecology. 2005;193(3):619-25.

29. Yuill K, Carandang C. Safety methodology in pediatric psychopharmacology trials. J Child Adolesc Psychopharmacol. 2013;23(3):148-62.

30. Hartling L, Hamm M, Klassen T, Chan A-W, Meremikwu M, Moyer V, et al. Standard 2: Containing risk of bias. Pediatrics. 2012;129(3):S124-S31.

31. Dickey M, Clark P. Changing the outcomes of pediatric drug trials: APNs making a difference. J Pediatr Health Care. 2013;27(3):222-5.

32. Zaccara G, Giovannelli F, Schmidt D. Placebo and nocebo responses in drug trials of epilepsy. Epilepsy Behav. 2015;43:128-34.

33. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13(1):132.

34. Sinha I, Jones L, Smyth RL, Williamson PR. A Systematic Review of Studies That Aim to Determine Which Outcomes to Measure in Clinical Trials in Children. PLoS Med. 2008;5(4):e96.

35. Prinsen CAC, Vohra S, Rose MR, King-Jones S, Ishaque S, Bhaloo Z, et al. Core Outcome Measures in Effectiveness Trials (COMET) initiative: protocol for an international Delphi study to achieve consensus on how to select outcome measurement instruments for outcomes included in a 'core outcome set'. Trials. 2014;15(1):247.

36. COMET (Core Outcome Measures in Effectiveness Trials) Initiative. Available at: http://www.comet-initiative.org/. Accessed, November 6, 2015.

37. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of Life Research. 2010;19(4):539-49.

38. Maarten Boers JRK, Peter Tugwell, Dorcas Beaton, Clifton O. Bingham III, Philip G.Conaghan, Maria-Antonietta D'Agostino, Maarten de Wit, Laure Gossec, Lyn March, Lee S. Simon Jasvinder A Singh, Vibeke Strand, George Wells The (Outcome Measures in Rheumatology) OMERACT Handbook. Available at: http://www.omeract.org/resources.html. Published April 2015.Accessed October 22, 2015.

39. EnRICH Lab: Enhancing Research Impact in Child Health. Available at:http://www.sickkids.ca/Research/EnRICH/index.html. Accessed November 6, 2015.

40. Frakking FN, van der Lee JH, Klassen TP, et al. Survey of current guidance for child health clinical trials. The StaR Child Health Project: Standards for Research in Children. Available at: http://www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf.Published 2009. Accessed November 20, 2015.

41. Fayed N, de Camargo OK, Elahi I, Dubey A, Fernandes RM, Houtrow A, et al. Patient-important activity and participation outcomes in clinical trials involving children with chronic conditions. Quality of Life Research. 2014;23(3):751-7.

42. Patient-Reported Outcomes Measurement Information System (PROMIS) (Dynamic Tools to Measure Health Outcomes from the Patient Perspective). Available at: http://www.nihpromis.org/. Accessed November, 6 2015.

43. Macefield RC, Jacobs M, Korfage IJ, Nicklin J, Whistance RN, Brookes ST, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). Trials. 2014;15(1):49.

44. Sinha YK, Craig JC, Sureshkumar P, Hayen A, Brien JAE. Risk of Bias in Randomized Trials of Pharmacological Interventions in Children and Adults. Journal of Pediatrics. 2014;165(2):367-U206.

45. Stafoggia M, Lallo A, Fusco D, Barone AP, D'Ovidio M, Sorge C, et al. Spie charts, target plots, and radar plots for displaying comparative outcomes of health care. J Clin Epidemiol. 2011;64(7):770-8.

46. Kush R. Can clinical trial protocols be standardized. Clinical Data Interchange Standards consortium (CDISC) Website.Available at :

http://www.cdisc.org/system/files/all/reference_material/application/pdf/cdisk_ed.pdf. Acessed November 20, 2015.

47. ClinicalTrials.gov. Protocol Data Element Definitions (DRAFT). September Oct2014. Available at: http://prsinfo.clinicaltrials.gov/definitions.html. October 22, 2015

48. Sinha IP, Altman DG, Beresford MW, Boers M, Clarke M, Craig J, et al. Standard 5: Selection, Measurement, and Reporting of Outcomes in Clinical Trials in Children. Pediatrics. 2012;129(Supplement 3):S146-S52.

49. Saint-Raymond A, Hill S, Martines J, Bahl R, Fontaine O, Bero L. CONSORT 2010. The Lancet.376(9737):229-30.

Chapter 6

Researchers', regulators' and sponsors' views on trials in children: a multinational study

Chapter 6: Researchers', regulators' and sponsors' views on trials in children: a multinational study

6.1 Abstract

Background: 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. This study aims to describe the attitudes and opinions of stakeholders towards trials in children, to inform additional strategies to promote more high-quality, relevant paediatric trials across the globe.

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

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

Conclusions: Stakeholders acknowledged that changes in the regulatory environment have encouraged more trials in children to be undertaken, but they contended that inequities, 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. Increasing international collaboration, establishing sustainable centralised trials infrastructure, and aligning research to child health priorities were suggested to encourage more high-quality trials that address global child healthcare needs.

What's known on this subject

Conducting 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 mitigated these challenges somewhat.

What this study adds

Stakeholder views on mitigating the inequities by addressing children's unique needs, integrating trials into clinical care, streamlining regulatory approvals, building infrastructure, increasing international collaboration, and aligning research to child health priorities to facilitate the conduct of high-quality relevant paediatric trials.

6.2 Introduction

The last decade has thus seen major changes in the regulatory framework for clinical trials in children, resulting in substantial incentivisation for industry and investigators to rigorously evaluate new therapies through the conduct of clinical trials [1-3]. Several pediatric research networks have also been established to support trials in children, with variable success [4, 5]. Despite these advances, all too often, children remain "therapeutic orphans" as the majority of medicines prescribed for children have still not been adequately validated for safety and efficacy, and disparities exist compared to adults and by income regions [1].

Trials in children are complex and can be challenging due to the unique requirements of children, safety concerns, stringent ethical requirements and the lack of commercial interest [6, 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 are perceived as reluctant to conduct trials in children, while pediatricians' concerns regarding risks are seen as barriers [1].

This study aims 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.

6.3 Methods

We followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) framework for interviews and focus groups [10].

6.3.1 Respondent Selection and Practice Setting

Respondents were eligible if they were researchers, regulators, or sponsors, who were involved in trials in children. The stakeholder groups are defined in Box 6.1.We recruited respondents via professional networks who were purposively selected to capture a range of age, gender, income settings, and experience in trials. 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.

Box 6.1. Professional[a] (researcher, regulator and sponsor) stakeholders of clinical trials in children

Researchers: academic, administrator, clinicians/paediatrician, clinical pharmacologist, investigators/researcher, methodologist, networks/working groups, clinical trials center/clinical research facility, trial coordinators/assistants.
Regulators: Institutional Review Board (IRB) (bioethicist, ethics committee member, ethical review bodies, ethics subcommittee/scientific advisory committee member), networks/working groups, Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)/local safety monitor, regulatory body, policy makers, research governance.
Sponsors: academic sponsor, charitable organisations, clinical research assistants (CRA), government funding body, monitors, pharmaceutical industry, Contract Research Organization (CRO), consultancy work with sponsors.

[a]Professional stakeholders excludes consumers (children, families and the public)

6.3.2 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 (Appendix F1, provided as online supplementary material). From October 2013 to August 2014, PDJ conducted face-to-face interviews in offices or meeting rooms or via the telephone. Respondent recruitment ceased when theoretical saturation (i.e. when little or no new information was being obtained from subsequent interviews) was reached [11, 12]. We audio-recorded and transcribed all interviews.

6.3.3 Analysis

Transcripts were entered into HyperRESEARCH software (ResearchWare Inc, United States, Version 3.5.2,). Based on grounded theory [13] and thematic analysis, [12] PDJ coded transcripts line-by-line, and translated similar and different concepts into existing or new codes, respectively, as they emerged in the data. We grouped similar concepts into themes and subthemes, and revised the coding structure until all concepts relating to barriers and enablers

of trials in children were captured. We identified relationships and patterns between themes 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 emailed to all respondents who were given 2 weeks to include additional viewpoints (i.e. member checking). Their feedback was coded and incorporated into subsequent revisions of the analytical framework.

6.4 Results

6.4.1 Study Respondents

In total, 35 (88%) of the 40 invited stakeholders participated. They were from 10 countries [high-income countries (n=20) and LMICs (n=15)] (Table 6.1). Non-participation was due to non-availability or institutional restrictions. The duration of the interview ranged from 20 to 70 minutes. Eight interviews were conducted face-to-face.

6.4.2 Themes

We identified 5 major themes: 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 6.2 and Appendix F2. Figure 6.1 shows the conceptual relationships among themes and subthemes.

6.4.2.1 Addressing pervasive inequities

Paucity 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 be potentially harmed due to "treatment uncertainties" and "practicing un-researched healthcare" as 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 felt 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," whilst 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 put forward as the main reasons for insecurity and hesitation among local researchers to conduct trials in children. Historical fears were believed as damaging public trust of trials involving children, for example, the unethical trials conducted during the Second World War in Germany.

Challenging double standards

The "double-standard" of the bureaucratic burden and regulatory requirements to conduct trials in children, compared to 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 LMIC countries, where the international standard of care was not routinely available. Regulators in the UK and US queried why it was "illegal" to pay children anything beyond trial expenses reimbursements, while in adult trials it was "fair to pay" for participation.

Ensuring contextual relevance

A "disconnect" between the paediatric burden of disease and countries where trials were conducted was felt by respondents. Researchers thought "data which is not Indigenous" may not be relevant to local settings because of "pharmacogenomic differences" and variability in healthcare.

Market driven forces

Respondents believed industry would "leverage their resources" in trials where 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 surmised that it had been "a happy marriage between industry and regulators" to conduct trials with a large sample size as a "pre-authorization 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 authorisation. In contrast, investigator-initiated trials were deemed to be of a "poor quality," "curiosity-driven" or for academic promotion. Clinicians suspected that investigators reluctantly participated in industry-sponsored trials, so they could "pay the rent" and subsidise their own research. Industry sponsors felt that the majority of industry "get tainted in that stigma" by the minority of pharmaceutical companies who conduct research unethically. They felt "damned if they do and damned if they don't" involve children from LMICs in trials.

Dissuaded by prohibitive costs

The "manifold costs" of regulatory oversight was 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 polarised regarding the perception that they were "shifting" to the LMICs where it was a "cheaper" option.

6.4.2.2 Contending with infrastructural barriers

Overwhelming resource constraints

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

Dearth of paediatric trial expertise

Respondents noted a critical lack of expertise in paediatric trials. Some researchers from LMICs acknowledged that they developed expertise from participating in industry-sponsored trials.

Traversing logistical complexities

All respondents had to confront logistical complexities such as shipping samples overseas. This was 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.

6.4.2.3 Navigating complex ethical and regulatory frameworks

"Draconian" oversight

Researchers believed that "draconian" ethical and regulatory oversight were 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," whilst 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 felt that children in LMICs were exploited to address the healthcare needs primarily of wealthy nations. Ethics committee members opposed "exposing children to inappropriate level of research risk absent of any prospective direct benefit" e.g. inserting a central line for placebo administration. The new mandatory requirement of audio-visual consent in India was believed to protect respondents, although some felt this was excessive and could stigmatise adolescents who preferred to be de-identified.

Excessive paternalism and unwarranted exclusion

Researchers and sponsors felt that parents and regulators had "paternalistic attitudes" and were "over cautious" about including children in trials. However, some argued that excluding children was discriminatory as "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 felt that it was easier to justify

testing medicines in neonates where there is limited or no clinical practice evidence, than trialling treatments which are currently used in children without evidence.

Precariousness of coercion vs. 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 standardised and should be reflective of the economy, as payment of disproportionately high amounts of reimbursement could unduly influence participation.

6.4.2.4 Respecting uniqueness of children

Embracing paediatric research paradigms

Respondents advocated for stakeholders to "embrace paediatric paradigms" and consider the "uniqueness" of children regarding treatment response, disease pathophysiology and expression. Clinicians prioritised 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 micro-analysis 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 needed to be scheduled to minimise interference with school attendance.

Facilitating family-centred empowerment

Involving families in setting child healthcare research priorities, designing and conducting of trials was proposed. The clinical team highlighted that when "recruiting a child, you are recruiting the whole family." In the UK, families and children involved in trial networks have lobbied to have trial results provided to respondents.

6.4.2.5 Driving evidence-based child health

Promoting research advocacy

"Great strides" in benefits of children's participation in trials was recognised, however 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 healthcare cost savings and involving families to obtain "public acceptance" and policy-makers support were encouraged. Many felt that clinicians required appropriate rewards and "career pathing" to enhance participation in trials.

Creating and seizing opportunities

Proponents of trials in children encouraged global "societal commitment" to dedicate funds and attract investment in paediatric trials. Respondents felt that strong networking opportunities contributed to the success of trials in paediatric oncology. Researchers from LMICs welcomed opportunities for participation in international trials. They advocated for research improving the health system and philanthropic investment to build local trial and healthcare capacity.

Supporting best practice

Respondents supported the development of consensus trial regulations and resources that could be adapted to local contexts. They felt that it would be "utopia" to have one

"amalgamated" national ethical review process. However, some regarded this as a "double-edged sword" as a central ethical review would eliminate the inherent quality control provided by multiple reviewers. Many encouraged collaboration and sharing of expertise, and emphasised the need for a centralised 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 harmonisation 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 paediatric research into practice and policy was encouraged.

Prioritising research productivity

Multi-stakeholder collaboration to improve trials in child healthcare globally and reduce research waste was deemed crucial. Prioritisation of child healthcare needs based on epidemiological or trial registries data analysis was recommended. Burden of disease, balanced by scientific opportunities in rare diseases was considered important to justify expenditure in prioritising funding universally.

6.5 Discussion

A broad range of stakeholders involved in the conduct of clinical trials in children recognised that much had been done to promote trial-informed clinical care of children, but that large-scale cultural and behavioral change, coupled with substantial infrastructural enhancement

was still required to promote the conduct of more trials, that were of high quality and relevant. They felt that there was still a scarcity of child healthcare safety and efficacy data, most notably in LMICs, child-specific diseases, neonates, off-patent medicines and child-appropriate formulations. Challenges and specific paediatric disparities were believed to arise from fears of harming children, political and economic influences, lack of resources for paediatric trials, and the bureaucratic regulatory framework. Global multi-stakeholder collaboration, integration of trials as part of clinical care, sustainable centralised trials infrastructure, harmonisation of regulatory approvals and alignment of the pediatric research agenda through analysis of trial registries and epidemiological data, were believed to enhance global capacities to conduct paediatric trials.

A recent systematic review of stakeholder views of trials in children in LMICs identified challenges related to social disadvantage, idiosyncratic cultural beliefs and historical disempowerment, with community engagement as the main enabler [14]. In our study, more challenges were identified by respondents in LMICs, where few trials are conducted despite the enormous paediatric disease burden. Some respondents were concerned about safety and exploitation of children, while others maintained that trial participation protects children from harm caused by non-evidenced based healthcare [15, 16].

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, [17-19] researchers in our 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 harmonising and expediting ethical review and developing local and international standards was recommended

[20, 21]. Professional stakeholders were polarised regarding the current regulations forbidding payment to children for participation in trials [22].

Stakeholders encouraged regulators worldwide to adopt appropriate regulations for the conduct of trials in children. They recognised that market exclusivity incentives supporting patent protection were not designed to meet the current needs of children and this was corroborated in a recent examination of drugs granted exclusivity [23]. Stakeholders endorsed improved regulations and incentives addressing child-specific therapeutic needs, off-patent medicines and rare child-hood diseases [24, 25]. To accommodate the low disease prevalence in children, innovative and optimum methodologies were suggested [26-28].

Amalgamated government and philanthropic investment with strengthened multi-stakeholder partnership was regarded as necessary to improve drug development for paediatric use. Stakeholders supported multi-centre 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 [29]. Incorporating analysis of epidemiological 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.

There is an apparent urgent need to invest in training and progress investigator-initiated trials to regulatory standards with the potential to inform paediatric labelling changes of medicines. Guidance and standards to improve paediatric trial design, conduct and reporting has been recognised as vital with some initiatives underway [4, 30, 31]. Establishing networks to collaborate and support trials was deemed essential. Investing into a centralised 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 in the highly-successful UK Medicines for Children Research Network (MCRN) [32].

Our international study highlights a wide spectrum of opinions of paediatric trials experts and decision-makers across different income and healthcare settings. We applied member checking to ensure the analysis reflected the range and depth of the data collected. Our study outlines recommendations to enable more high-quality trials primarily by making more explicit and informed decisions concerning child health research priorities (Table 6.3). However, there are some potential limitations. The transferability of the findings to countries that were not included in our study is uncertain and we recommend extending similar research to other countries.

6.6 Conclusions

Despite an apparent increase in the number of initiatives that have encouraged trials in children, disparities still exist, particularly in LMICs, neonates, off-patent medicines and rare diseases. Embracing unique paediatric needs and creating a culture of embedding trials as part of routine clinical care were recommended. International collaboration, sustainable centralised paediatric trials infrastructure, development of paediatric trial expertise and alignment of research to child healthcare priorities are suggested to encourage more high-quality, appropriate trials that address the healthcare needs of children globally.

Table 6.1 Respondent characteristics (n=35)

Characteristics	Number (%))
Gender	
Male	25 (71)
Female	10 (29)
Age group (years)	
<40	5 (14)
40-49	9 (26)
50-59	12 (34)
60-69	9 (26)
Country of practice	
High-income countries	
Australia	5 (14)
Canada	5 (14)
Finland	1 (3)
France	1 (3)
UK	3 (5)
USA	5 (14)
Low-and middle-income countries (LMICs)	
India	5 (14)
Nigeria	4 (11)
Papua New Guinea	1 (3)
South Africa	5 (14)
Role[a]	
Researchers/clinicians	30 (50)
Regulators	20 (33)
Sponsor	10 (17)
Speciality area[a]	
General Paediatrics	13 (21)
Subspeciality[b]	46 (72)
Other	3 (5)
Clinical trial experience (years)	
<10	13 (37)
10-20	11 (31)
21-30	7 (20)
>30	4 (11)

[a]Numbers do not equal 35 as multiple categories apply to some individuals
[b]Number of respondents in subspecialities: Cardiology (1), Clinical Pharmacology (2), Emergency (1), Endocrinology (2), Immunology and infectious disease (8), Intensive care (3), Haematology (3), Neonatology (7), Nutrition (1), Oncology (8), Psychological Medicine or Mental Health (2), Renal (3), Respiratory (4), Musculoskeletal or rheumatology (1) Other: ethics (1), methodology (2)

Table 6.2. Selected quotes to support each theme

Subthemes	Illustrative quotations
	Addressing pervasive inequities
Paucity of safety and efficacy data	We know that children's health professionals have a background of working without an evidence base, because that is all that they could do up to now. (Researcher, research facility, network, UK)
Knowledge disparities	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 as compared to an internet savvy, educated one. (Researcher, trial coordinator, India)
Volatile environment	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 paediatric research. (IRB, CRO, India) The other challenge that one could face in Nigeria is the challenge of conducting studies in places where you have political skirmishes. Where there are such skirmishes it can affect research, especially if the investigator is not experienced. (Researcher, IRB, monitor, Nigeria)
Challenging double standards	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, paediatrician, Nigeria) If I want to treat a child and it is not so much as here take this medicine. If I want to recruit them into a trial and give them the same medicine, I have to give them a 20 page information sheet and go through a vast number of hoops. There seems to be double standards which one might argue inappropriate standards for research. (Regulator, paediatrician, UK)
Ensuring contextual relevance	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) I don't do pie in the sky research. I don't have the time, to be honest. All my research, everything I prepare, and even published, has clinical relevance…are all based on clinical need. (Researcher, IRB, regulator, South Africa)
Market driven forces	So in most cases those drugs are developed for adults because that is where the biggest need is. And now we have laws that require us to also study those drugs in children. And that's great. But it doesn't mean that we're looking carefully to study drugs for a need for children primarily. (Researcher, paediatrician, industry sponsor, US)
Industry sponsorship bias	Within the physician environment, definitely industry-sponsored trials are seen as with a bit of bias and real question as to whether or not physicians soil themselves by getting involved with industry. (Researcher, IRB, governance, Canada) So even a high quality investigator-initiated study doesn't change any market authorisation for children or even lead to include other new findings if necessary, unless the pharmaceutical company who has the market authorisation for this product is willing to then submit the data for regulatory approval. (Researcher, paediatrician, IRB, Finland)
Dissuaded by prohibitive costs	Investigator-initiated trials were sometimes possible here like the neonatal trials around caffeine for apnoea. But they all cost $5 million each to answer one question and so there's no more money in the public arena to sponsor trials that are that expensive. (Researcher, paediatrician, academic, Canada) There are not a lot of rewards for the faculty who are involved, particularly when there are small numbers of patients that would be enrolled at any one site to warrant their spending time, very considerable time on putting through the consent forms, the contracts, the IRB approvals and then looking for the one or two patients that they may be able to involve. (Researcher, paediatrician, industry sponsor, US)
	Contending with infrastructural barriers
Overwhelming resource constraints	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) We have turned downed studies on occasions where we didn't have the resources to carry them out. (Researcher, IRB, South Africa)

Subthemes	Illustrative quotations
Dearth of pediatric trial expertise	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) When companies submit proposals for paediatric clinical trials for regulatory approval, they don't get an answer. Because nobody is really able to assess the appropriateness of the study. (Researcher, paediatrician, IRB, Finland) They are not robust so the science behind what gets submitted is sometimes not good quality, so people often have not thought about…sample size calculations, recruitment, the feasibility of the study and…the practicalities of actually conducting the trials. (Researcher, paediatrician, IRB, Australia)
Traversing logistical complexities	We have some issues like 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 bio-specimens and other items are kept properly. (Researcher, Nigeria) So if you need to get samples for central review or for collaborative studies they have to arrive within 24 to 48 hours. That can be logistically impossible from Australia. (Trial coordinator, trial center, Australia)
Navigating complex regulatory and ethical frameworks	
"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, paediatrician, South Africa) I mean the 17 page sort of consent forms outlining every conceivable risk is counter-productive to good clinical practice, it's counter-productive to good science, it's counter-productive to moving things forward and making things better for everyone. (Researcher, regulator, government sponsor, Australia)
Ambiguous requirements	One area of uncertainty appears to be the definitions of key terms like minimal risk and minor increase over minimal risk, in the paediatric context. (Regulator, IRB, governance, US) 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, paediatrician, industry sponsor, US)
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 - socio-economically 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, paediatrician, 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 cut off that we are going to do it in adults first then children should not exist. (Researcher, IRB, regulator, South Africa)
Precariousness of coercion vs. 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 like laboratory, x-ray, and ultrasound whatever is needed for the trial that remains there after the trials. But these are ethically very difficult 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, paediatrician, IRB, Finland)
Respecting uniqueness of children	
Embracing paediatric research paradigms	Regulatory agencies need to move away from a very narrow interpretation of indications in terms of paediatric studies…right now so much of it's still based on the adult indications and the paediatric-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 two indications are very different as is the populations…So we're moving towards 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, US) 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

Subthemes	Illustrative quotations
	clinical trials in rare diseases…optimally paediatric trials should use methods that are designed for small size clinical trials. (Researcher, paediatrician, 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 paediatric treatments even if they are considered current choice of treatment, have not been well documented.(Researcher, paediatrician, 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 co-ordinator, trial centre Australia)
Facilitating family-centred 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 centre, Australia)
	I think parents, children and young people need to be at the centre 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 which best works with networks. (Researcher, regulator, industry consultant, UK)
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 like WHO, maybe others to engage more children, families, clinicians and researchers across the world. (Researcher, paediatrician, academic, Canada)
Creating and seizing opportunities	The most feasible way 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, paediatrician, 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 (MCRN) going. And they have accomplished a lot of success.(Researcher, paediatrician, academic, Canada)
Supporting best practice	Up to 80 or 90% of paediatric clinical trials are at an uncertain or high risk of bias when it to comes to randomisation 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, paediatrician, 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…non-trial evidence, epidemiological evidence showing the burden of the problem. (Researcher, paediatrician, 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, paediatrician, 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. Paediatrics 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 towards 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 prioritise the research in the right way! (Researcher, IRB, regulator, South Africa)

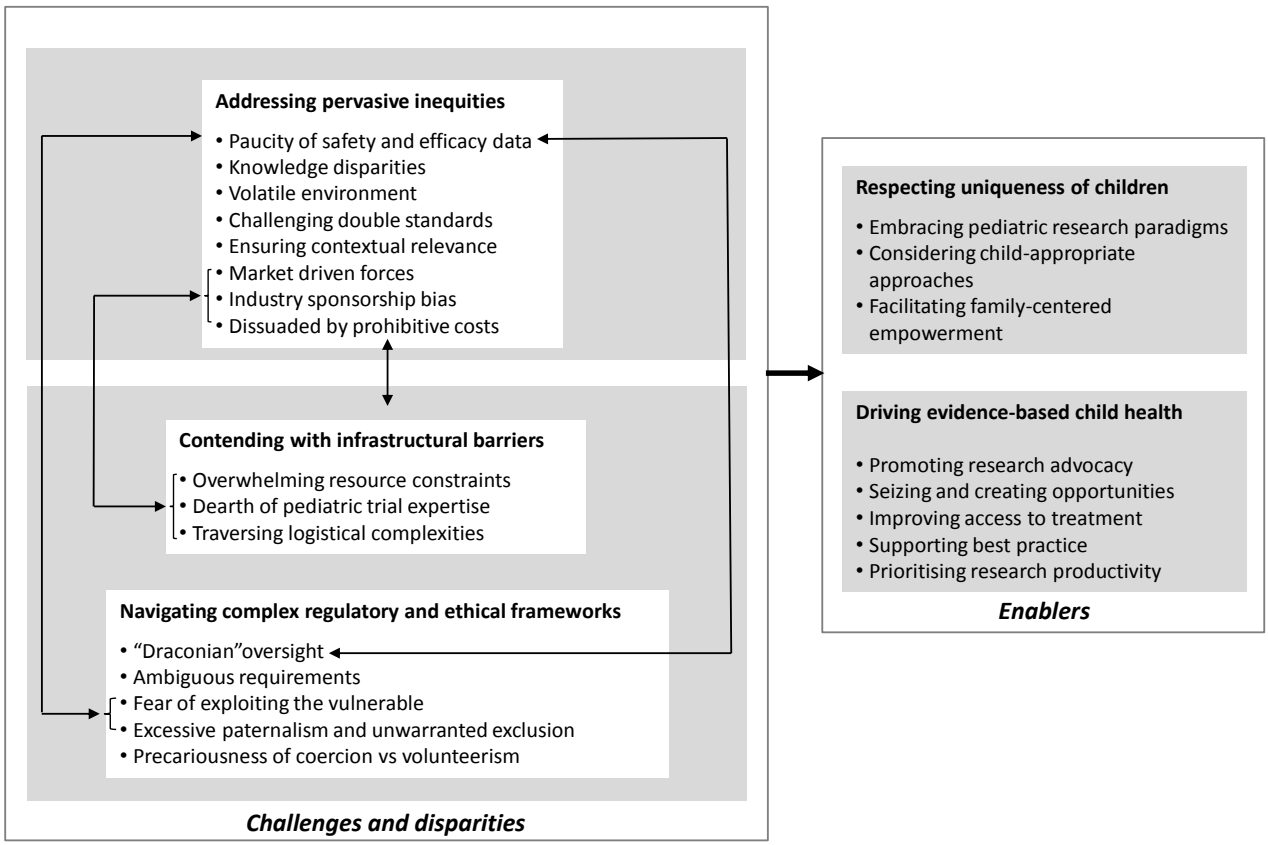
Table 6.3 Implications for practice and policy to address barriers and inequities

Key Issues	Recommendations or suggested research and policy priorities *(examples and initiatives underway)*
Advocate for trials in children	• Campaign for children's participation in trials, using both ethical and economic justification strategies. • Analyse health, epidemiological and registries data to inform clinical research needs in children. • Align the academic, pharmaceutical sponsor and policy maker's agendas to prioritise research in response to child health needs through a multinational consortium. • Invest and direct prioritisation of trials in children from government. • Incentivise trials of off-patent medicines *(e.g. priority list of off-patent medicines developed by the US Paediatric Trials Network [33]).* • Improve initiatives to study rare diseases (*e.g. FDA priority review voucher [34], International Rare Diseases Research Consortium (IRDiRC) [35]*). • Encourage philanthropic approaches to conduct high-quality research that change paediatric labelling. • Provide better incentives to encourage clinicians' participation and enthusiasm.
Strengthen and develop paediatric trial capacity	• Invest in sustainable centralised 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 non-industry sponsored trials (*e.g. MCRN [32])*. • Develop standards and guidance on trial design, conduct and reporting (such as valid child health outcomes including child-reported outcomes) explicit definitions e.g. minimal risk, adequate sample size; selection of appropriate comparators; reduction of risk of bias *(e.g. StaR Child Health [36], Toronto Outcomes Research in Child Health (TORCH)[37], Enhancing Research Impact in Child Health (ENRICH)[38], Standard Protocol Items for Randomised Trials-Children (SPIRIT-C) [39], Consolidated Standards of Reporting Trials-Children (CONSORT-C) [40]* • Invest in training and standards for consistency and high-quality review of ethics applications. • Develop guidelines for data safety monitoring committees. • Implement programs to audit the conduct of trials at sites.
Mitigate disparities in LMICs	• 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 healthcare 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 health education of the community. • Encourage sponsor provision of ongoing supportive medical care post-trial and ancillary care to siblings and other family members.
Enhance regulatory frameworks	• Adopt paediatric regulations and incentives globally to encourage pharmaceutical industry to trial medicines in children (*e.g. the US and EU regulations*). • Improve paediatric regulations and incentive to encourage trials in child-specific diseases, including trials of off-patent medicines *(e.g. Pediatric Trials Network initiatives)[33]* • Establish a global level paediatric medicines regulatory framework under the leadership of WHO to regulate and harmonise country of trials conduct, transferability of results, availability of medicines and improve medicine access and reimbursement strategies *(e.g. Transcelerate [41] 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 therapeutic gaps (*e.g. enpr-EMA [42], MCRN, Global Research in Paediatrics (GRIP) [43] initiatives).*
Improve evidence-base practice	• Encourage multi-center collaborative trials to reduce research waste. • Develop good referral network amongst paediatric clinicians to enhance recruitment.

Key Issues	Recommendations or suggested research and policy priorities *(examples and initiatives underway)*
	• 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 paediatric labelling. • Invest in developing formulation of medicines appropriate for children in all income regions (*e.g. suspensions).* • Review medicine reimbursement strategies to improve access of medicines addressing paediatric needs. • Embed clinical research as part of routine clinical care and in disease specific registries *(e.g. Key Performance Indicator of organisation 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 paediatric needs with consultation and partnering with the academic, practicing community and families. e.g. UK, Young Peoples Advisory Group (YPAG) [44], International Children's Advisory Network (ICAN)[45]. • Develop guidelines to engage children and parents in setting priorities, designing and conducting *trials (e.g. 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 (*e.g. distraction techniques such as DVDs*). • Develop alternative robust strategies to monitor compliance in children (*e.g. devices that can monitor use*). • Further research to develop guidelines on adequate paediatric 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.
Streamline ethical review	• Develop clear ethical review regulations to reduce the ambiguity of current guidelines. • Standardise and simplify ethics processes and templates *(e.g. consent forms).* • Clarify definition of key terms like minimal risk and minor increase over minimal risk in the paediatric context. • Recommend education and adherence to Data Monitoring Committees (DMC) standards in paediatric trials. (*e.g. Star Child Health group DMC Standard*)[46] • Harmonise and expedite authorization of paediatric protocols (*e.g. MIYCRN (Maternal Infant Youth and Child Research Network [47] and GRIP initiative*). • Develop guidelines to manage incidental findings of whole genome sequencing that may have lifelong relevance. • Develop explicit and shared guidelines for the retention of bio-specimens and how to engage children in consent for the ongoing use of stored specimens once children become adults.
Equity in trial participation	• Develop explicit and shared guidelines on when it is appropriate to conduct phase I clinical trials in children. • Support the design and conduct of appropriate trials in pregnancy, obese children, premature infants and newborns [48]. • Develop explicit and shared policies regarding appropriate incentives for child participation. • Investigate payment to children for participating in optional research not offering the possibility of treatment.

The suggested research and policy priorities were formulated by respondents and discussion among the research team

Figure 6.1 Thematic Schema of challenges and enablers of clinical trials in children



6.7 References

1. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J of Clin Pharmacol. 2015;79(3):357-69.
2. Permanand G, Mossialos E, McKee M. The EU's new paediatric medicines legislation: Serving children's needs? Arch Dis Child. 2007;92(9):808-11.
3. Field MJ, Ellinger LK, Boat TF. IOM Review of FDA--approved biologics labeled or studied for pediatric use. Pediatrics. 2013;131(2):328-35.
4. Craig JC, Offringa M, Hartling L, Wittmeier KDM, van der Lee JH, Klassen TP, et al. StaR Child Health: developing evidence-based guidance for the design, conduct, and reporting of pediatric trials. Clin Pharmacol Ther. 2011;90(5):727-31.
5. Slora EJ, Harris DL, Bocian AB, Wasserman RC. Pediatric clinical research networks: Current status, common challenges, and potential solutions. Pediatrics. 2010;126(4):740-5.
6. Rumney P, Anderson JA, Ryan SE. Ethics in pharmacologic research in the child with a disability. Paediatr Drugs. 2015;17(1):61-8.
7. Schechter T, Grant R. The complexity of consenting to clinical research in phase I pediatric cancer studies. Paediatr Drugs. 2015;17(1):77-81.
8. Pathma D Joseph, Patrina HY Caldwell, Allison Tong, Hanson CS, Craig JC. Stakeholder views of clinical trials in low and middle-income countries: a systematic review Pediatrics (accepted for publication).
9. MacLeod SM, Knoppert DC, Stanton-Jean M, Avard D. Pediatric clinical drug trials in low-income countries: key ethical issues. Paediatr Drugs. 2015;17(1):83-90.
10. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. 2007;19(6):349-57.
11. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(1):181-.
12. Kuper A, Reeves S, Levinson W. Qualitative Research: An Introduction to Reading and Appraising Qualitative Research. BMJ. 2008;337(7666):404-7.
13. Strauss AL, Corbin JM. Basics of qualitative research: techniques and procedures for developing grounded theory. Thousand Oaks: Sage Publications; 1998.
14. Joseph PD, Caldwell PH, Tong A, Craig JC. Stakeholder Views of Clinical Trials in Low- and Middle-Income Countries: A Systematic Review. Pediatrics. Accepted for publication.
15. Sammons HM. Avoiding clinical trials in children. Arch Dis Child. 2011;96(3):291-2.
16. Jenkins T, Wendler D. Children's and Their Parents' Views on Facing Research Risks for the Benefit of Others. Arch Pediatr Adolesc Med. 2008;162(1):9-14.
17. Shah S, Wendler D, Wilfond B, Gensler G, Whittle A. How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research? JAMA. 2004;291(4):476-82.
18. Ezzat H, Ross S, Von Dadelszen P, Morris T, Liston R, Magee LA, et al. Ethics review as a component of institutional approval for a multicentre continuous quality

improvement project: The investigator's perspective. BMC Health Serv Res. 2010;10(1):223-.

19. Altavilla A, Manfredi C, Baiardi P, Dehlinger-Kremer M, Galletti P, Pozuelo AA, et al. Impact of the new european paediatric regulatory framework on ethics committees: overview and perspectives. Acta Paediatr. 2012;101(1):e27-32.

20. Roth-Cline MD, Gerson J, Bright P, Lee CS, RM N, editors. Ethical considerations in conducting pediatric research. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM254315.pdf. Accessed August 28, 2015.1st ed. In press: Springer.

21. Needham AC, Kapadia MZ, Offringa M. Ethics Review of Pediatric Multi-Center Drug Trials. Pediatric Drugs. 2014;17(1):23-30.

22. Tishler CL, Reiss NS. Pediatric drug-trial recruitment: enticement without coercion. Pediatrics. 2011;127(5):949-54.

23. Rivera DR, Hartzema AG. Pediatric exclusivity: evolving legislation and novel complexities within pediatric therapeutic development. Ann Pharmacother. 2014;48(3):369-79.

24. Giacoia GP, Taylor-Zapata P, Zajicek A. Drug studies in newborns: a therapeutic imperative. Clin Perinatol. 2012;39(1):11-23.

25. Stoyanova-Beninska VV, Wohlfarth T, Isaac M, Kalverdijk LJ, van den Berg H, Gispen-de Wied C. The EU paediatric regulation: effects on paediatric psychopharmacology in Europe. Eur Neuropsychopharmacol. 2011;21(8):565-70.

26. Emdin CA, Odutayo A, Hsiao AJ, Shakir M, Hopewell S, Rahimi K, et al. Association between randomised trial evidence and global burden of disease: cross sectional study (Epidemiological Study of Randomized Trials--ESORT). BMJ (Clinical research ed). 2015;350(jan28 24):h117-h.

27. Junker A, Klassen T. Improving standards for paediatric clinical trials. Paediatr Child Health. 2011;16(9):539-40.

28. Saint-Raymond A, Hill S, Martines J, Bahl R, Fontaine O, Bero L. CONSORT 2010. Lancet.376(9737):229-30.

29. Laughon MM, Benjamin DK, Jr., Capparelli EV, Kearns GL, Berezny K, Paul IM, et al. Innovative clinical trial design for pediatric therapeutics. Expert Rev Clin Pharmacol. 2011;4(5):643-52.

30. Baiardi P, Giaquinto C, Girotto S, Manfredi C, Ceci A, Teddy Network of Excellence. Innovative study design for paediatric clinical trials. Eur J Clin Pharmacol. 2011;67 Suppl 1:109-15.

31. Knibbe CA, Krekels EH, Danhof M. Advances in paediatric pharmacokinetics. Expert Opin Drug Metab Toxicol. 2011;7(1):1-8.

32. UK, Medicines for Children Research Network (MCRN), Clinical Trials Unit. Available at: https://www.mcrnctu.org.uk/. Accessed October 20, 2015.

33. Pediatric Trials Network (PTN). Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Available at: http://pediatrictrials.org/. Accessed October 22, 2015.

34. US Food and Drug Administration. Rare Pediatric Disease Priority Review Voucher Program. Available at:

http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm. Accessed September 25, 2015.

35. International Rare Diseases Research Consortium (IRDiRC). 2012-2015. Available at: http://www.irdirc.org/. Accessed October 27, 2015.
36. StaR Child Health. Available at: http://www.starchildhealth.org/. Accessed October 20, 2015.
37. Toronto Outcomes Research in Child Health (TORCH).Hospital for Sick Children. Available at: http://www.sickkids.ca/Research/EnRICH/Research-Projects-and-Initiatives/TORCH/index.html. Accessed October 22, 2015.
38. The Hospital for Sick Children (SickKids), EnRICH Lab: Enhancing Research Impact in Child Health. Available at: http://www.sickkids.ca/Research/EnRICH/index.html. Accessed October 20, 2015.
39. Standard Protocol Items for Randomized Trials-children (SPIRIT-C). Available at: http://www.sickkids.ca/Research/EnRICH/Research-Projects-and-Initiatives/SPIRIT-C/index.html. Accessed October 22, 2015.
40. Consolidated Standards of Reporting Trials-children (CONSORT-C). Available at: http://www.sickkids.ca/Research/EnRICH/Research-Projects-and-Initiatives/CONSORT-C/index.html. Accessed October 20.
41. Transcelerate Biopharma Inc. Accelerating the development of new medicines. Available at:http://www.transceleratebiopharmainc.com/initiatives/pediatric-trial-efficiencies/.Accessed September 25, 2015.
42. European Medicines Agency (EMA). Enpr-EMA. Available at: http://enprema.ema.europa.eu/enprema/. Accessed October 22, 2015.
43. Global Research in Paediatrics, Network of excellence. Available at: http://www.grip-network.org/index.php/cms/en/Home. Accessed September 25, 2015.
44. UK, Clinical Research Network Children, Young Peoples Advisory Group (YPAG) Available at: https://www.crn.nihr.ac.uk/children/pcpie/young-persons-advisory-group/. Accessed October 22, 2015.
45. International Children's Advisory Network (ICAN). Available at: http://www.icanresearch.org/. Acessed August 22, 2015.
46. Ellenberg S, Fernandes RM, Saloojee H, Bassler D, Askie L, Vandermeer B, et al. Standard 3: Data monitoring committees. Pediatrics. 2012;129(3):S132-S7.
47. Maternal Infant Child and Youth Research Network (MICYRN). Research Enabling initiatives. Ethics Platform. Available at: http://www.micyrn.ca/ResearchEnablingPlatformInitiatives.html. Accessed September 29, 2015.
48. Matsui D. Ethics of studies of drugs in pregnancy. Paediatr Drugs. 2015;17(1):31-5.

Chapter 7

Discussion and conclusions

Chapter 7: Discussion and conclusions

7.1 Overview

This chapter summarises how this thesis addresses the overarching research question of equity, quality and relevance of clinical trials in children to improve evidence-informed child healthcare worldwide. In this thesis, we provide an in-depth understanding of the current context of paediatric trials, the challenges, disparities, gaps and the adoption of appropriate strategies suggested by key stakeholders through both quantitative and qualitative techniques. We showed that there is still a paucity of safety efficacy evidence across most therapeutic areas in paediatric healthcare; gross inequities still exist in the number of trials in children conducted within income regions and in comparison to adults; and that trials were mismatched to paediatric burden of disease. Continued reform and advocacy is crucial to encourage more, high-quality, appropriate trials in children. The urgent need for improvement of paediatric trial design, conduct and reporting was also highlighted. This thesis is one of the first major attempts to comprehensively look at the equity, quality and relevance of clinical trials in children to inform better evidence-based child healthcare worldwide.

7.2 Key Findings

7.2.1 Trial equity and relevance to child health

A common theme throughout this thesis is the paucity of safety and efficacy evidence of treatments in children. The narrative review described some of the medical mishaps and fatalities that have resulted from exposing children to untested medicines. These mishaps catalysed regulatory change that sought to protect children from untested medicines, but also stimulated "draconian," bureaucratic ethical and regulatory oversight of paediatric trials because of fears of harming children. The interviewed professional stakeholders believed that

the involvement of children in trials was also hampered by medical mistrust of parents and fears of their child being treated as a "guinea-pig." This was magnified by the clinician's reluctance to involve children because of safety concerns, and a lack of interest from the pharmaceutical industry because of poor economic returns. Major strides have occurred in the last decade and clinical trials in children have now been recognised as essential in protecting children and advancing child healthcare. Although there is advocacy for the need for more appropriate testing of pharmaceutical products in children, the stakeholders felt that further cultural and behavioural changes are warranted. All stakeholders including parents, the public, clinicians and regulators need to embrace the concept that trials in children is crucial in protecting children and improving their healthcare.

The concern of the pervasive disparities that exist in trials conducted in children compared to adults was present across the narrative review, analyses of trials registered in children, and the multinational interview study of professional paediatric trial stakeholders. The analyses of registered trials in children showed that children account for 25% of the global burden of disease, but represent only 15% of registered trials. We showed that trials in children are more challenging than in adults. This is due to the lack of funding and resources; ethical concerns of exposing children to untested medicines in trials; recruitment difficulties because of the lower prevalence of childhood diseases and the need for tailored study designs considering the heterogeneous age groupings of the paediatric population and their unique needs. The gap between the number of trials in children and adults is increasing, driven by political and economic factors. There are now approximately five times more trials in adults compared with children. It is pleasing to acknowledge several initiatives encouraging more trials in children, such as the US and EU paediatric legislation and economic incentives to include children in trials. However, the literature, in addition to stakeholder perspectives, suggest that these legislations and incentives encourage children's participation in trials that focus mainly

on health issues in adults. Researchers and clinicians stressed that there is a critical need to incentivise trials addressing unique childhood diseases, neonatal conditions, medicines that are off-patent and to stimulate more trials in LMICs.

The analyses of registered paediatric trials showed that the high-income countries boast the majority of trials. Disproportionately few trials (22%) are registered in LMICs in comparison to their enormous illness burden (98%). This could be due to the lack of commercial incentives for the pharmaceutical industry to invest in this region. The systematic review of stakeholder views of trials in children in LMICs showed that another contributing factor to the scarcity of trials in these regions are that trials in these contexts are further hindered by impoverishment, disempowerment, inequity and idiosyncratic cultural beliefs that have created mistrust in clinical research with great fears of exploitation. Engaging the community in mobilising and designing trials in LMICs is essential. Fair distribution of research benefits and investment in research infrastructure and regulatory frameworks in LMICs are recommended to promote justice and equity. Researchers supported trials being conducted in all income regions as data that is not indigenous could be invalid because of "pharmacogenomic differences" and variability in healthcare.

In the analyses of registered trials, we showed that there was only a moderate correlation between the number of trials and the burden of disease within each region.We found that paediatric trial focus was mismatched to disease burden.The high-income countries disproportionately had the majority of paediatric trials for most of disease categories in comparison to the burden of disease in children. It is crucial that these misaligned research priorities be redressed through a global collaborative effort of greater investment and support of paediatric trials that addresses child healthcare priorities worldwide.

7.2.2 Quality of trial design, conduct and reporting

The narrative review highlighted some of the special considerations when designing any of the four phases of clinical trials in children [1]. Children are mostly involved from phase III trials, to protect them from exposure to harm in the early Phase I and II trials. Professional stakeholders in our study believed that this may delay children's access to potentially useful medicines. They suggested that this artificial cut-off should not exist for medicines that are assessed to be safe and early phase trials should be conducted simultaneously in children. Ethics Committees and Data Monitoring Committees are also there to safeguard the interests of children's participation in appropriate early phase trials. Protocols of clinical trials involving children assessed by Ethics Committees were comprehensive and well-described. However, many key domains in trial design and conduct remain incompletely reported and could be improved. Despite widespread recognition of how problems in the design and conduct of clinical trials may lead to misleading conclusions, investigators still appear to be omitting key elements in trial protocols. Gaps were observed across all domains that could be minimised through development of standards in the design of protocols that consider the unique needs of children, training and adherence to guidelines [2]. This could help improve the quality of trials in children, minimise risk of harm to children and generate reliable results to be implemented in the clinical care of children.

In the systematic review and interviews, researchers in LMICs advocated that international sponsors needed to understand the severe lack of research infrastructure and capacity when planning trials. In these contexts, trials in LMICs should be appropriate, pragmatic, feasible, and sustainable. Researchers felt that the rigorous international requirements for level of documentation were sometimes too ambitious and impractical for certain LMICs. However, they were concerned that if they did not comply with international standards, their research quality would not be acceptable in the global paediatric research community. Researchers

questioned the "double-standard" of the bureaucratic burden and regulatory requirements to conduct trials in children, compared to the ease of using untested treatments in routine clinical care of children. Researchers and sponsors felt that excessive paternalism of parents and ethics committees still hinders trials and that excluding children from participating in trials is discriminatory. From the evidence we gathered, including the key informant interviews of researchers, regulators and sponsors we concluded that conducting trials in children is challenging and arduous due to logistical, methodological and ethical issues that hinder progress of evidence-based child healthcare. Our studies proposed strategies to address this.

7.2.3 Strategies to enhance paediatric trials

The findings of these studies demonstrate that investment of dedicated, centralised trial infrastructure and the development of paediatric specific standards are critical to support trials in children. Guidance for paediatric protocol development includes both the scientific and ethical components of trials such as SPIRIT-Children and CONSORT-Children for the reporting of paediatric issues of relevance was needed [3]. Standards for the ethics application and review process, auditing of trials and dissemination of trial results is necessary to enhance the evidence base of child health. The harmonisation of ethical and regulatory processes was deemed necessary within countries and potentially extended internationally, as most trials are multi-centre and increasingly becoming multinational [4]. There was support for stakeholders to embrace paediatric research paradigms that consider the uniqueness of children with regard to treatment response, disease pathophysiology and expression. Child-appropriate approaches in the design and conduct of trials were important. For example, the integration of trials as part of core paediatric clinical care in all specialties was suggested. This has already been demonstrated to be effective and successful in the paediatric oncology trials in accelerating the evidence-base care. The key understandings developed from this thesis are that improving evidence-based child healthcare is the responsibility of all stakeholders including children and

families, the community, researchers, regulators, sponsors, and policy-makers, through engagement and collaboration. There needs to be greater attention at the highest political level to advocate for more investment into paediatric trials. Engaging and empowering children and adolescents to inform the paediatric research agenda and trial conduct is essential to improvements. Collaboration on trials and the developing and sharing of resources were deemed essential both locally and internationally to reduce duplication and waste of research resources and increase the value of trials in children.

7.3 Strengths of our study

The work presented here encompasses a narrative review, and original quantitative research, qualitative research including a systematic review of qualitative studies (thematic synthesis), in-depth face-to-face interviews, and document analysis. The strengths of our studies include providing a comprehensive literature review of the important issues of clinical trials in children in the current context, and highlighting challenges, disparities and gaps. We also proposed strategies informed by key multinational stakeholders to address these issues both nationally and on an international level. The WHO International Clinical Trials Registry Portal, which is the most comprehensive, robust repository of trials from several registries was used to determine trial activity in children and we compared this to the recent DALYs data and established Global Health Estimates. Our systematic review of stakeholder views of trials in LMICs further explored the challenges and facilitators of testing medicines in children in these contexts. We applied member checking to ensure the analysis reflected the range and depth of the data collected generating relevant and novel findings and fulfilling the study objectives. In our evaluation of the scientific completeness of trial protocols, we used a consolidated checklist based on the validated CONSORT and Cochrane Risk of Bias measurement tool and incorporated child-specific and other domains of importance in protocols. Our international interview study highlights a wide spectrum of opinions of trial

experts and decision makers across different income and healthcare settings on paediatric trials. We applied member checking to ensure that the analysis reflected the range and depth of the data collected. The important strategies summarised in Table 6.3 informed by the synthesis of evidence gathered and key stakeholders, has important policy and clinical practice implications.

7.4 Problems encountered and study limitations

Some problems and limitations were encountered with the various studies comprising the thesis. Systematically reviewing the clinical trials in children as a topic was broad and generated a very large number of titles and abstracts that needed to be reviewed, including the hand-searching of relevant articles, which was time-consuming. The restrictions of the WHO ICTRP did not permit extraction of data such as sample size or facilitate subgroup analyses of commercial versus non-commercial trials, and we recommend investment to enhance the capabilities of the WHO ICTRP. The study looking at the completeness of protocols of trials in children submitted to the Ethics Committees was constrained by time and the institutional requirements, thereby limiting the study to four of the eight paediatric hospitals and 69 trials. Obtaining ethics approval to conduct this study from multiple sites with variable ethical and site requirements and application forms was a challenge. Confidentiality issues related to access of the protocols precluded data validation by having the same two researchers extract the data. The interviews of multinational key researcher, regulator and sponsor informants were limited by time and resources for all interviews to have been conducted face-to-face. Resource constraints also limited the number of countries that could participate in the study.

7.5 Clinical practice and policy implications

Important clinical practice and policy implications was generated from the various studies. An informative summary of the current issues of relevance to trials in children was produced in

the comprehensive narrative review, which is helpful to educate all paediatric trial stakeholders. The analysis of registered trials in children provides a benchmark for targeting trials aligned to paediatric diseases of greatest burden and neglected therapeutic areas in appropriate settings. We showed the value of linking trial data and epidemiological information to align the paediatric research agenda to child health priorities. The systematic review of stakeholder views of trials in LMICs has highlighted the complex issues that researchers, regulators and sponsors need to consider when conducting trials in these areas. The systematic review also showed the important enablers of trials in LMICs, such as community engagement that can inform more successful trials in these regions. The assessment of the completeness of essential domains in trial protocols has shown the benefit of having paediatric specific checklists for development of protocols of trials in children that consolidate items of importance to address the unique considerations in children. Our studies helped to identify the current infrastructural and paediatric trial resource gaps that can be addressed to support high-quality trials worldwide.

7.6 Future directions of work

Future research and implementation into practice of the findings and recommendations presented in this thesis could be helpful to all paediatric trial stakeholders in informing improvements of the design, conduct and reporting of appropriate clinical trials in children. We recommend analysis of trial registry and epidemiological data to help prioritise paediatric research aligned to disease burden and child health priorities like rare diseases. It is hoped that the gaps identified in the essential paediatric specific guidance and standards for the trial design, for example child and adolescent reported outcomes and definition of the age of assent will inform development of these resources. Future investigation should also look at the gaps in the conduct and public disclosure of trial results on registries as well as to participants, for

example provision of trial results to families that can bring about practice changes. We noted the existence of non-conformity in the trial registries, which is an area requiring further development to improve the robustness of the data captured on registries, and to facilitate aggregate analysis. We recommend increased investment into the WHO International Clinical Registries Portal to improve the capabilities of data extraction. For example, enhancements to the portal to facilitate improved analysis, such as size of paediatric trials and sub-group analysis of commercial vs. academic research are important. There needs to be greater investment to develop and implement mechanisms to monitor and report trials conducted both locally and internationally to identify the gaps in the conduct of trials in children that may be improved.

We explored researchers', regulators' and sponsors' views of barriers and facilitators of trials; however it is important to also explore the views of children and families in light of current developments. Further research looking at payment for children's participation is important to inform standards and practice. The perspectives of key informant stakeholders in other countries like China where the paediatric research practices may be different would be valuable. The poor dissemination of trial results and publication bias stimulated advocacy for the prompt reporting and disclosure of trial results to reduce waste and re-align research priorities [5,6]. We suggest research in analysing published paediatric trials in the last five years using, the clinical trials registry number to determine the current trends in publication of trials and to identify gaps to inform further research and practice changes. We determined the completeness of scientific protocols of trials in children for the core trial domains; however, future research should look at the completeness of inclusion of essential and child-specific ethical components, which is complex in children. It will also be useful to assess the quality of the conduct of trials in children.

7.7 Conclusions

This thesis provides a comprehensive and detailed understanding of the issues of equity, quality and relevance of clinical trials in children in addressing global child healthcare needs. The main gaps, challenges and disparities that hinder progress with trials in children were identified, such as paucity of trials, mismatched paediatric trial focus to child healthcare needs and deficiencies in child specific trial standards and guidance. Our research provides important strategies and future research to improve evidence-informed child healthcare, for example, the imperative to embed trials as part of core clinical care and the need for dedicated centralised paediatric trials infrastructure with sustainable research funding. This thesis concludes that more, high quality appropriate trials in children globally, are vital to improve evidence-informed child healthcare. All paediatric trial stakeholders need "to protect children not from research, but through research!"

7.8 References

1. Chau K, Koren G. The principle of equipoise in pediatric drug trials. Paediatr Drugs. 2015;17(1):17-21.
2. Van't Hoff W, Offringa M, Star Child Health group. StaR Child Health: developing evidence-based guidance for the design, conduct and reporting of paediatric trials. Arch Dis Child. 2015;100(2):189-92.
3. Clyburne-Sherin AVP, Thurairajah P, Kapadia MZ, Sampson M, Chan WWY, Offringa M. Recommendations and evidence for reporting items in pediatric clinical trial protocols and reports: two systematic reviews. Trials. 2015;16(1):417.
4. Needham AC, Kapadia MZ, Offringa M. Ethics Review of Pediatric Multi-Center Drug Trials. Pediatric Drugs. 2014;17(1):23-30.
5. Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gulmezoglu AM, Howells DW, Ioannidis JPA, Oliver S. How to increase value and reduce waste when research priorities are set. Lancet. 2014;383(9912):156-65.
6. Edwards D, Matlin SA, Eide M, Young AJ, Regmi S, Ardal C, Guzman J, Terry RF, Røttingen JA, Viergever RF. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet. 2013;382(9900):1286-307.

Appendices

Appendices

Appendix A1 - Search strategy for literature review: clinical trials in children

MEDLINE		Embase	
1	Child/	1	exp Adolescent/
2	exp Infant/	2	exp Adolescence/
3	Adolescent/	3	exp Child/
4	child*.tw.	4	exp Childhood/
5	infant*.tw.	5	exp Newborn/
6	girls.tw.	6	child*.tw.
7	boys.tw.	7	infant*.tw.
8	p?ediatric*.tw.	8	girls.tw.
9	newborn*.tw.	9	boys.tw.
10	or/1-9	10	p?ediatric*.tw.
11	exp Pharmaceutical Preparations/	11	newborn*.tw.
12	drug*.mp.	12	or/1-11
13	medicin*.mp.	13	exp ANIMAL/
14	11 or 12 or 13	14	12 not 13
15	exp Clinical trials as Topic/	15	exp Drug/
16	10 and 14 and 15	16	drug*.mp.
17	limit 16 to yr="2000 -Current"	17	medicin*.mp.
18	limit 17 to "review articles"	18	15 or 16 or 17
		19	exp Clinical Trial/
		20	14 and 18 and 19
		21	limit 20 to (phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
		22	20 not 21
		23	limit 22 to yr="2000 -Current"
		24	limit 23 to "review"

Appendix B1 - Search strategy for systematic review: stakeholder views of clinical trials in LMICs

MEDLINE **1946 – August Week 3 2014**		**Embase** **Week 34 1974 – Week 34 2014**	
1	Child/	1	exp Adolescent/
2	exp Infant/	2	exp Adolescence/
3	Adolescent/	3	exp Child/
4	child*.tw.	4	exp Childhood/
5	infant*.tw.	5	exp Newborn/
6	girls.tw.	6	child*.tw.
7	boys.tw.	7	infant*.tw.
8	p?ediatric*.tw.	8	girls.tw.
9	newborn*.tw.	9	boys.tw.
10	or/1-9	10	p?ediatric*.tw.
11	exp Clinical trials as Topic/	11	newborn*.tw.
12	10 and 11	12	or/1-11
13	developing country/	13	limit 12 to human
14	underdeveloped.tw.	14	exp Clinical Trial/
15	under-developed.tw.	15	13 and 14
16	less developed.tw.	16	limit 15 to (phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
17	resource limited.tw.		
18	resource constrain*.tw.	17	15 not 16
19	resource poor.tw.	18	developing country/
20	third world.tw.	19	underdeveloped.tw.
21	low income.tw.	20	under-developed.tw.
22	middle income.tw.	21	less developed.tw.
23	low socioeconomic.tw.	22	resource limited.tw.
24	exp africa/ or exp caribbean region/ or exp central america/ or latin america/ or south america/ or exp asia/	23	resource constrain*.tw.
		24	resource poor.tw.
		25	third world.tw.
25	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	26	low income.tw.
		27	middle income.tw.
26	12 and 25	28	low socioeconomic.tw.
27	exp qualitative research/	29	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
28	qualitative.tw.		
29	interview$.tw.	30	17 and 29
30	focus group$.tw.	31	exp qualitative research/
31	(thematic$ or theme$).tw.	32	qualitative$.tw.
32	grounded theory.tw.	33	interview$.tw.
33	phenomenol$.tw.	34	focus group$.tw.
34	content analysis.tw.	35	(thematic$ or theme$).tw.
35	ethnograph$.tw.	36	Content analysis.tw.
36	exp decision making/	37	grounded theory.tw.
37	exp Knowledge/ or Health Knowledge, Attitudes, Practice/	38	phenomenology.tw.
		39	phenomenological$.tw.
38	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	40	ethnograph$.tw.
		41	exp social psychology/
39	26 and 38	42	exp decision making/
		43	exp illness behavior/
		44	exp health belief/ or exp social belief/
		45	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
		46	30 and 45

Appendix C1 - Checklist for reporting of paediatric trial protocol scientific domains

Study Trial Number		Initiated by: □Investigator □ Industry □Collaborative group □Other, specify…….	
Date of data collection		The trial is being conducted through: □ CTN	□CTX

Section/ Topic	Item No	*CONSORT Checklist item* (STUDY Checklist item)	YES/NO/ Unclear/ NA
Title			
	1a	Descriptive title of the protocol	
Introduction			
Background and objectives	***2a***	***Scientific background and explanation of rationale***	
	2a (1)	Indication of systematic review (where applicable)	
	2a(2)	Health condition(s) or problem(s) studied (WHO ICD): ……..	
	2a(3)	Mention of disease prevalence in children	
	2a(4)	Impact of the disease in children	
	2b	***Specific objectives or hypotheses***	
Methods			
Trial design	***3a***	***Description of the trial design (e.g. parallel, cluster, non-inferiority/equivalence) including allocation ratio***	
	3a(1)	Is this trial design: □ Randomised controlled □ RCT Parallel □ RCT Cluster □ Nonrandomised □ Cross-over □ Superiority □ Non-inferiority □ Equivalence	
	3a(2)	Indication of the allocation ratio of the treatment arms	
	3a(3)	Indication of the phase of trial	
	3a(4)	Phase of the trial: □ Phase 1 □ Phase 2 □ Phase 3 □ Phase 4	
Participants	***4a***	***Eligibility criteria for participants***	
	4a(1)	Is this a mixed population of adults and children?	
	4a(2)	Participant age range:……..	
	4a(3)	Participant timeline of enrolment, interventions, assessments and visits	
	4b	***Settings and locations where the data were collected***	
	4b(1)	Number of recruitment sites: □Single centre □ Multi-centre sites…… 4b (2) Inside Australia……. 4b (3) Outside Australia……	
Recruitment	***14a***	***Dates defining the periods of recruitment and follow-up***	
	14a(1)	Indication of the period of recruitment	
	14a(2)	Indication of the follow up period	
	14a(3)	Description of recruitment process and forms of recruitment	
	14a(4)	If Yes, which of the following forms of recruitment were used: □ Face-to-face □ Mail out □ Internet □ Advertising □ Referral □ Other, specify…….	
	14a(5)	Total duration of the clinical trial: …… (years) if included	
Baseline data	***15***	***Indication of collection of baseline demographic and clinical characteristics for each group***	
Interventions	***5***	***The interventions for each group with sufficient details to allow replication, including how and when they were actually administered***	
	5(1)	The WHO Anatomical Therapeutic Chemical (ATC) classification http://www.whocc.no/atc_ddd_index/ of the Investigational Medicinal Product(s) (IMPs):……..	
	5(2)	Registration status of IMP:	

Section/ Topic	Item No	*CONSORT Checklist item* (STUDY Checklist item)	YES/NO/ Unclear/ NA
		□ ARTG unregistered □ (a) Registered in other countries □ (b) First Time in Human □ ARTG registered, but unlicensed for use in children □ ARTG registered in children, but not for indication trialled (off-label use) □ Other: specify……..	
	5(3)	Use of the IMP: □ Diagnosis □ Treatment □ Prevention □ Other……	
	5(4)	Description of measurement of compliance to the IMP(s)	
	5(5)	Indication of age, weight or body surface area adjustments of dose	
	5(6)	If applicable, explanation of why the formulation of the drug is inappropriate for use in children.....	
	5(7)	Defined threshold levels (maximum dose or therapeutic levels) for IMP.	
	5(8)	Inclusion of safety data e.g. drug interactions, contraindications regarding the proposed usage of the IMP.	
	5(9)	Post-trial provision: Consideration of the ongoing treatment of trial subjects should they respond to the pharmaceutical product(s) under investigation.	
Outcomes	***6a***	***Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed***	
	6a(1)	Number of primary outcome measures =…….	
	6a(2)	Number of secondary outcome measures =……	
	6a(3)	Type of endpoint(s): □ Safety □ Efficacy □ Optimum dosage schedule □ Tolerability □ QOL □ Pharmacokinetics □ Other, specify……	
	6a(4)	Age and development specific outcomes included	
	19	***All important harms or unintended effects in each group***	
	19(1)	Description of continuous safety monitoring	
	19(2)	Description of long-term (until the child participant reaches adulthood) safety monitoring where applicable	
	19(3)	Inclusion of a Data Safety Monitoring Board	
Sample size	***7a***	***Description of sample size estimation***	
	7a(1)	Performance of a sample size calculation	
	7a(2)	Target sample size for trial:…….	
	7a(3)	Target sample size for site:……. or □ Not specified	
	7b	***When applicable, explanation of any interim analyses and stopping guidelines***	
	7b(1)	Defined rules for stopping the trial earlier	
	7b(2)	Inclusion of guidelines for the end of study for an individual patient	
Randomisation			
Sequence generation	***8a***	***Method used to generate the random allocation sequence***	
	8a(1)	Adequate generation of the allocation sequence	
	8b	***Type of randomisation; details of any restriction (such as blocking and block size)***	
	8b(1)	Description of stratification of treatment	
	8b(2)	If YES, indicate the stratification: □ Age □ Weight □ Gender □ Severity of illness □ Other, specify……	
Allocation concealment mechanism	***9***	***Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned***	
	9(1)	Adequate concealment of allocation	
Implementation	***10***	***Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions***	
Blinding	***11a***	***If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes)***	

Section/ Topic	Item No	*CONSORT Checklist item* (STUDY Checklist item)	YES/NO/ Unclear/ NA
		and how	
	11a(1)	Adequate prevention of the knowledge of the allocated interventions during the study.*	
	11a(2)	Blinding of randomised controlled trial	
	11a(3)	If YES, who was blinded: □ Participants □ Care providers □ Study personnel □ Data analyst □ Other specify……..	
	11a(4)	Explanation of why blinding was not done, or was not possible.	
	11b	***If relevant, description of the similarity of interventions***	
	11b(1)	Is the comparator (control treatment arm), if applicable: □ Placebo □ Current standards of patient care □ Other, specify……..	
	11b(2)	Rationale for the type of control or placebo used	
Statistical methods	***12a***	***Statistical methods used to compare groups for primary and secondary outcomes***	
	12a(1)	Professional statistical consideration of the trial (is there a statistician as part of the study team or has a statistician been consulted).	
	12b	***Methods for additional analyses, such as subgroup analyses and adjusted analyses***	
	12b(1)	Outcome measures. Indication of what analysis will be done on outcome measures to answer the research question.	
	12b(2)	Numbers analysed. Specification of intention to treat analysis.	
	12b(3)	Planning of subgroup analysis	
	12b(4)	If YES, indicate subgroup analysis: □ Age □ Weight □ Gender □ Severity of illness □ Other, specify……..	
	12b(5)	Limitations. Specification of trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses.	
Other information			
Registration	23(1)	Inclusion of trial on the WHO International Clinical Trials Registry Portal (ICTRP)	
	23(2)	Indication on which clinical trials registry trial is registered ……..	
Protocol	24 (1)	Conditions for when the protocol may be modified.	
Funding	***25***	***Sources of funding and other support (such as supply of drugs), role of funders***	
	25(1)	Primary sponsor: □ Industry □ Hospital □ University □ Collaborative group □ Other, specify……..	
	25(2)	Funding for the study: □ Full □ Partial □ None □ Pharmaceutical product only	
Reporting	26(1)	Reporting: Details of how the study results will be reported.	
	26(2)	Indication if results will be published.	

*Using Cochrane Risk of Bias

Appendix C2 - Descriptive data of ethics and governance processes at Children's Hospitals

1. Ethics approval processes

   1.1 Human Research Ethics Committee procedures of pharmaceutical clinical trial review:

   ……

   ……

   1.2 Are there HREC guidelines for submitting clinical trials: □ YES □ NO

   1.3 Which ethics application form(s) are being used:

   □ NEAF □ Site form □ Other, specify……

   1.4 Acceptance of multi-centre ethics approval: □ YES □ NO

   1.5 Is the site an approved Lead Paediatric HREC: □ YES □ NO

   1.6 Is the site accredited under the Streamlined Ethical Review Process (SERP) for the review of clinical trials □ YES □ NO

   1.7 Is the site certified under the NHMRC Harmonisation of Multi-Site Ethical Review (HoMER): □ YES □ NO

2. Institutional governance approval process of paediatric clinical trials:

   ……

   ……

3. Is there training and support of clinical trials ethics submissions and conduct:

   □YES □ NO

   If YES, specify:……

   ……

4. Clinical trial registration: Institution recommendations/guidelines on trial registration if any:

   ……

   ……

5. Clinical trials activity: average number of paediatric pharmaceutical trial HREC applications/year:……

6. Number of paediatric pharmaceutical trials submitted to the Human Research Ethics Committee (HREC) for the period 1 January 2012 – 31 December 2012……

7. Number of paediatric pharmaceutical trials submitted for site approval for the period 1 January – 31 December 2012……

8. Any additional information:……

Appendix D1 - Professional stakeholder interview invitation

Discipline of Paediatrics and Child Health
Clinical School
Faculty of Medicine

ABN 15 211 513 464

Dear Colleague,

Interview invitation: "Stakeholder experiences and perspectives of paediatric clinical trials"

We are conducting research to improve our understanding of issues faced when conducting paediatric clinical trials internationally. As a stakeholder involved with trials in children you are in an ideal position to give us valuable first-hand information from your own perspective and experiences. We would like to invite you to participate in an interview as part of this study.

There is a research imperative to conduct more quality clinical trials that are relevant to the paediatric population. However, there are major barriers which limit the conduct of trials in children in different settings. This study will examine paediatric clinical trial stakeholders' (clinical/investigating team, government/ethics/regulators and sponsors) views on clinical trials in children. The study will use qualitative methods (key informant interviews or focus groups) to gain a better understanding of the experiences and challenges experienced by stakeholders. We hope this study will help to inform strategies and provide potential solutions to the challenges faced in the design and conduct of quality paediatric trials in different settings.

This study involves stakeholders from the international trials community who are invited to participate in one, semi-structured face-to-face or telephone interview about your individual views and personal opinions about the issues faced in clinical trials in children. The interview will take about 30 minutes. Being in this study is completely voluntary and you are not under any obligation to consent. All aspects of the study, including results, will be strictly confidential and only the investigators will have access to information on participants. A report of the study will be submitted for publication, but individual participants will not be identifiable in such a report. All participants will be sent a final report of the study which may be of interest to you in your role or involvement in paediatric trials. You can tell other people about this study, and welcome your nomination of additional people who may be interested in taking part in the study that we can approach.

If you are willing to participate please suggest the days and times that you are available and we will do our best to accommodate your requirements. If you would like to know more at any stage, please feel free to contact Pathma D Joseph, PhD candidate, The Discipline of Paediatrics and Child Health, University of Sydney on +61 2 9845 2697 or e-mail: pathma.joseph@health.nsw.gov.au.

We thank you and greatly appreciate your assistance.

Dr Patrina Caldwell
Staff Specialist, Centre for Kidney Research
Senior Lecturer, Discipline of Paediatrics and Child Health
The University of Sydney
The Children's Hospital at Westmead
Locked Bag 4001 Westmead NSW 2145, Phone: +61 2 9845 3406
Email: patrina.caldwell@health.nsw.gov.au, Web: http://www.sydney.edu.au

Appendix D2 - Participant information statement

THE UNIVERSITY OF SYDNEY

Discipline of Paediatrics and Child Health
Clinical School
Faculty of Medicine

ABN 15 211 513 464

Dr Patrina Caldwell
Staff Specialist, Centre for Kidney Research
Senior Lecturer, Discipline of Paediatrics and Child Health

The University of Sydney
The Children's Hospital at Westmead
Locked Bag 4001 Westmead NSW 2145
Phone: +61 2 9845 3406
Email: patrina.caldwell@health.nsw.gov.au
Web: http://www.sydney.edu.au

Stakeholder experiences and perspectives of paediatric clinical trials

Participant Information Statement: Interview

(1) What is the study about?

You are invited to participate in a study of your experiences and perspectives of clinical trials in children. There is a research imperative to conduct more quality clinical trials that are relevant to the paediatric population. However, there are major barriers which limit the conduct of trials in children in different settings. This study will examine paediatric clinical trial stakeholders' (clinical/investigating team, government, ethics/regulators and sponsors) views on clinical trials in children. The study will use qualitative methods (key informant interviews /focus groups) to gain a better understanding of the experiences and challenges from the perspective of stakeholders involved in paediatric clinical trials. We hope this study will help to inform strategies and provide potential solutions to the challenges faced in the design and conduct of quality paediatric trials in different settings.

(2) Who is carrying out the study?

The study is being conducted by Ms Pathma D Joseph, Senior Pharmacist and Clinical Lecturer and will form the basis for the degree of Doctor of Philosophy at The University of Sydney under the supervision of Dr Patrina Caldwell, Staff Specialist and Senior Lecturer.

(3) What does the study involve?

You have been approached because we want to talk with stakeholders involved in clinical trials in children. This study involves participating in one, semi-structured face-to-face or telephone interview about your individual views and personal opinions about the issues in the conduct of clinical trials in children, which will be audio recorded. The interview will be either face-to-face or via the telephone. Face-to-face interviews will take place at a suitable date, time and location nominated by you. Telephone interviews will be pre-arranged at a suitable date and time nominated by you.

(4) How much time will the study take?

We expect that the interview to take approximately half to one hour to complete

(5) Can I withdraw from the study?

Being in this study is completely voluntary - you are not under any obligation to consent and - if you do consent - you can withdraw at any time without affecting your relationship with The University of Sydney.

You may stop the interview at any time if you do not wish to continue, the audio recording will be erased and the information provided will not be included in the study.

(6) Will anyone else know the results?

All aspects of the study, including results, will be strictly confidential and only the researchers will have access to information on participants. A report of the study will be submitted for publication, but individual participants will not be identifiable in such a report.

(7) Will the study benefit me?

All participants will be sent a final report of the study which may be of interest to you in your role or involvement in paediatric trials.

(8) Can I tell other people about the study?

You can tell other people about this study, and welcome your nomination of additional people who may be interested in taking part in the study that we can approach.

(9) What if I require further information about the study or my involvement in it?

When you have read this information, Pathma D Joseph will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact Pathma D Joseph, PhD candidate, The Discipline of Paediatrics and Child Health, University of Sydney on +61 2 9845 2697 or e-mail: pathma.joseph@health.nsw.gov.au.

(10) What if I have a complaint or any concerns?

Any person with concerns or complaints about the conduct of a research study can contact The Manager, Human Ethics Administration, University of Sydney on +61 2 8627 8176 (Telephone); +61 2 8627 8177 (Facsimile) or ro.humanethics@sydney.edu.au (Email).

This information sheet is for you to keep

Appendix D3 - Participant consent form for interview

Discipline of Paediatrics and Child Health
Clinical School
Faculty of Medicine

ABN 15 211 513 464

Dr Patrina Caldwell
Staff Specialist, Centre for Kidney Research
Senior Lecturer, Discipline of Paediatrics and Child Health

The University of Sydney
The Children's Hospital at Westmead
Locked Bag 4001 Westmead NSW 2145
Phone: +61 2 9845 3406
Email: patrina.caldwell@health.nsw.gov.au
Web: http://www.sydney.edu.au

Participant consent form for interview

I, ...[PRINT NAME], give consent to my participation in the research project

Title: Stakeholder Experiences and Perspectives of Paediatric Clinical Trials

In giving my consent I acknowledge that:

1. The procedures required for the project and the time involved have been explained to me, and any questions I have about the project have been answered to my satisfaction.

2. I have read the Participant Information Statement and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.

3. I understand that being in this study is completely voluntary – I am not under any obligation to consent.

4. I understand that my involvement is strictly confidential. I understand that any research data gathered from the results of the study may be published however no information about me will be used in any way that is identifiable.

5. I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher(s) or the University of Sydney now or in the future.

6. I understand that I can stop the interview at any time if I do not wish to continue, the audio recording will be erased and the information provided will not be included in the study.

7. I consent to:

- Audio-recording YES ☐ NO ☐
- Receiving Feedback YES ☐ NO ☐

If you answered YES to the "Receiving Feedback" question, please provide your details i.e. mailing address, email address.

Feedback Option

Address: **……**

……

Email: **……**

.....
Signature

.....
Please PRINT name

.....

Date

Appendix D4 - Participant (Professional stakeholders) demographics

Country:…… **State:**…….

Gender: □ Male □ Female

Age group: □ 20s □ 30s □ 40s □ 50s □ 60s □ 70s

Experience in trials in children (years): □ ≤2 □ 2-5 □ 6-10 □ 11-20 □ 21-30 □ >30

Current role(s) in trials

Clinical/investigating team
□ Investigator
□ Trial co-ordinator
□ Pharmacist
□ Paediatrician
□ Academic
□ Other:…….

Ethics/regulators
□ Bioethicist/ ethics committee member
□ Scientific Advisory committee member
□ Research Governance
□ Regulator/policy-makers
□ Other:……

Sponsor/industry/funding/bodies
□ Clinical research assistants
□ Monitors
□ Sponsor/industry
□ Other:……

Clinical trial speciality area(s)

□ Cardiology
□ Emergency
□ Endocrinology
□ Immunology and infectious disease
□ Intensive care
□ Neonates
□ Neonatology
□ Oncology
□ Psychological Medicine/Mental Health
□ Renal
□ Respiratory
□ Musculoskeletal/rheumatology
□ Other:……..

Main type of studies you have experience with: □ Investigator initiated □ Pharma sponsored □ Collaborative groups □ Funding bodies □ All types

Appendix E1 - Frequency of CONSORT domains in paediatric trial protocols (n=69)

Section/Topic	Item No	CONSORT Checklist item	Yes (%)	No (%)	Unclear (%)
Title and abstract	1a	Descriptive trial of the protocol	36 (52)	33 (48)	0
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	66 (96)	2(3)	1 (1)
	2b	Specific objectives or hypotheses	67 (97)	1 (1)	1 (1)
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	68 (97)	0	1 (1)
Participants	4a	Eligibility criteria for participants	62 (90)	3 (4)	4 (6)
	4b	Settings and locations of data collection	63 (91)	3 (4)	3 (4)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	58 (84)	4 (6)	7 (10)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	68 (99)	1 (1)	0
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	67 (97)	1 (1)	1 (1)
Harms or unintended effects	19	All important harms or unintended effects in each group[a]	56 (82)	8 (12)	4 (6)
Sample size	7a	How sample size was determined	56 (81)	6 (9)	7 (10)
	7b	When applicable, explanation of any interim analyses and stopping guidelines	50 (73)	18 (26)	1 (1)
Randomization:					
Sequence generation	8a	Method used to generate the random allocation sequence[a]	44 (85)	4 (8)	4 (8)
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	43 (86)	7 (10)	0
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	37 (76)	8 (16)	4 (6)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions[a]	42 (84)	3 (6)	5 (1)
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how[a]	34 (92)	0	3 (4)
	11b	If relevant, description of the similarity of interventions	50 (72)	5 (7)	0
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes[a]	58 (87)	6 (9)	3 (5)
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyzes	40 (58)	15 (22)	6 (9)
Other information					
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders[a]	67 (99)	0	1 (2)

[a]n is less than 69 as domain did not apply to some trials

Appendix E2 - Frequency of child-specific and other important domains in trial protocols (n=69)

Child-specific and other important domains	Yes (%)	No (%)	Unclear (%)
Background and objectives			
Indication of systematic review (where applicable)	33 (48)	13 (19)	23 (33)
Description of disease prevalence in children	60 (87)	9 (13)	0
Description of impact of the disease in children	52 (75)	17 (25)	0
Participants			
Participant timeline of enrolment, interventions, assessments and visits	53 (77)	16 (23)	0
Intervention			
Measurement of compliance of the therapeutic intervention[a]	44 (92)	1 (2)	3 (6)
Age, weight or body surface area adjustments of dose	43 (62)	26 (38	0
Threshold levels (maximum dose or therapeutic levels) for therapeutic intervention[a]	64 (94)	4 (6)	0
Safety data on the therapeutic interventions	63 (91)	5 (7)	1 (1)
Post-trial provision of successful interventions[a]	20 (39)	27 (53)	4 (8)
Outcomes			
Age and development specific outcomes	33 (48)	36 (52)	0
Description of continuous safety monitoring	60(87)	9(12)	0
Long-term safety monitoring[a]	8 (12)	59 (87)	1 (1.5)
Data Safety Monitoring Board included	45 (71)	20 (26)	4 (3)
Conditions when the protocol may be modified	37 (54)	31 (45)	1 (2)
Planned reporting of study results	52 (75)	17 (25)	0

[a]These items did not apply to certain trials

Appendix F1 - Interview guide

Interview guide*

1. Issues with clinical trials in children in (name of respondent's country)

a) In your opinion, what are positive aspects of doing trials in children in (name of respondent's country)?

b) On the other hand, what do you believe are the main concerns(s) with the conduct of trials in children in (name of respondent's country)? Can you describe these issues and its impact on the conduct of pediatric trials? *(recruitment, resources, ethics approval, operational issues, safety monitoring).*

c) Can you think of ways of addressing the challenges you mentioned with trials in children in (name of respondents country)? *(training, funding)*

d) In your view what are the different issues with investigator initiated, collaborative or pharma sponsored pediatric trials? How can these issues be addressed?

e) What is your view on registration and reporting of trials in children? Is there a need for paediatric specific registries or disease specific registries?

f) Do you feel that the trials conducted in (name of respondent's country) are meeting the needs of the children in the country? Why? *(number, quality, relevance).* Any suggestions on how this can be addressed or improved to meet the needs of children?

g) In an ideal world if you have unlimited resources what would be the one or two things you would change in trials in children in (name of respondents country).

h) Is there anything else you feel would be important to add about clinical trials in children in (name of respondent's country)?

2. Issues with clinical trials in children worldwide.

a) In your opinion what are some of the positive aspects of clinical trials in children that's occurring globally? (*advocacy*, *recruitment, poor study designs)*

b) What do you consider to be the international concerns or challenges with the conduct of trials in children? *(protocol design, ethical, regulatory, operational, recruitment and retention challenges, resources).*

c) In your view, what are the different issues (advantages or challenges) in trials in children in low-and middle- income countries compared to the wealthy nations?

d) Any suggestions or strategies on how the global challenges in trials in children can be overcome.

e) In an ideal world, if you have unlimited resources, what will be the one or two things you would change in trials in children?

* NB. This question guide includes questions relating to challenges and enablers in the respondent's country and globally. The complete interview guide is available on request from the authors.

Appendix F2 - Supplementary additional quotations

Sub-themes	Illustrative quotations
	Addressing pervasive inequities
Paucity of safety and efficacy data	We want to increase access of children and adolescents with relapsed malignancies which is not curable with current treatment. We want to seek access for these patients to more active compounds… to increase the number of phase 1 and phase 2 trials. (Researcher, paediatrician, academic sponsor, France)
	All diseases are understudied…all other fields outside paediatric oncology are lacking enough trials and qualitatively, good trials. (Researcher, paediatrician, academic, Canada)
	So there's just a mismatch based on where you can put the incentives and the fact that there are many older products…in neonatology in particular…that are off-label and are off-patent and are not subject to those incentives. (Researcher, IRB, regulator, US)
Knowledge disparities	In my experience…the parents who are more educated and understand the needs of the clinical trial better, tend to comply better than those who are less educated, who tend to get lost to follow-up and drop out. (Researcher, paediatrician, Nigeria)
	I think that language is somewhat of a barrier in that if you are dealing with children who come from particularly rural areas or places where literacy levels are low. (Researcher, paediatrician, South Africa)
Volatile environment	You have opened the Pandora's Box…I belong to a local organization. But there is politics. I also belong to International organization, with virtually non-existent politics…the local politics. It suffices to say it is filthy. (Researcher, Nigeria)
	We need to nominate or appoint certain staff from that lab to be part of the clinical trial. And sometimes other staff in the same labs that are not part of the clinical trial can see that the scientists being part of the trial being given some extra material or extra money. And try to make things difficult for them… I am not sure whether to call it envy or rivalry…is also a major logistical problem in conducting the trial. (Researcher, paediatrician, Nigeria)
	The ethos...research is not a paying thing. There is a driving force from the university to undertake the research…But it's not a system that incentivise. It's actually a stick tackle approach you don't do it, you don't get this. It's quite abrasive in ways. They are actually very harsh and rude...they actually destroy people rather than build on them…in that way actually young people don't want even to come into the research fold because they just know that the people and the politics behind it, is quite challenging. So I think that's a huge limitation in this space. (Researcher, IRB, regulator, South Africa)
Challenging double standards	The agency also registers the traditional drugs by alternative medicines practitioners. When we, orthodox doctors challenged this action, we were educated that toxicological tests on the drugs didn't show any toxicity or whatever. So, NAFDAC [National Agency for Food and Drug Administration and Control] is only interested in the safety according to them, but not interested in the efficacy and effectiveness. (Researcher, Nigeria)
	Families shouldn't be out of pocket...We have a problem that the current EU clinical trial regulation and our national trial regulation seems to suggest that it is illegal to pay children anything beyond those expenses and reimbursements. I think that's probably an unethical position and that there's a better way for the administrator to judge whether the proposed remunerations isn't an undue influence…in adult practice it seems fair to pay…we accept we pay people to take part in particular research projects. Yet we seem to be saying, we can't pay children and that seems a little bit odd… ethically it would be reasonable to pay. But it seems that legally, there is a serious question over the legality of paying. (Regulator, paediatrician, UK)
	But distinctly say that not for years, there's no standard of care because normally a person can't afford standard of care because you live in a poor population. That is not appropriate because you are now doing a study, the study has to give whatever is the standard of care for that particular disease whether it's something that the

Sub-themes	Illustrative quotations
	population would normally be going out and purchasing for themselves or be able to get at a hospital at a cost. You can't simply say, well they don't normally do anything and so we leave it at that. Earlier there were a lot more placebo trials. Now there are much fewer placebo trials because we've insisted at least the standard of care being given to the control. (Researcher, paediatrician, IRB, India)
Ensuring contextual relevance	Trials should only be done if they fulfil a local need and they address a local question and they build capacity among local people. They should not be coming in so-called developing countries simply because disease burdens are greatest so therefore you can get an answer quicker. (Researcher, paediatrician, DSMB, Papua New Guinea)
	We're not providing what would internationally be regarded as best clinical practice...there are certain studies where very expensive drugs are being used and it's unlikely that the study population where the study's being done would eventually get to benefit from the drug once it's licensed, just because it's too expensive. One example was a prophylaxis against respiratory syncytial virus where they get monoclonal antibodies for a group at risk like premature babies or babies with congenital heart disease. (Researcher, IRB, South Africa)
	Pharmaceutical companies are conducting trials in these low income countries because it's easier to get ethics approval and it's easy to conduct trials and is cheaper and it's not necessarily meeting the needs of the children in that area. (Researcher, paediatrician, IRB, Australia)
	I think there will be issues at times if you're conducting trials in health care settings where there may be a high degree of variability and the background clinical care that's provided. That it might be difficult to know whether the effects that you're seeing from the product that you're studying will be reproducible in a different setting. I think that cuts both ways, but one questions any time there's data that comes in from outside of the United States site would be, to what extent is it applicable to the US population. Not only from the standpoint of any changes…from pharmacogenomics differences or within the population, but also in the actual delivery of the background care to the patients that are enrolled. (Researcher, IRB, regulator, US)
Market driven forces	There's an attitude of people being used to do trials on medicines that don't become available within that country and people know about that. I think that's partly to do with the politics within those countries…I think there's reasonable case that medicine should be tested on a broad spectrum of humanity, if they get to be used in a board spectrum of humanity. So I can see why companies might want to do research in resource-poor countries because one day their medicines might be used there. I think also the value of infrastructure within well-resourced countries is that it does overcome the need for countries to go to less-resourced countries to actually do the recruitment. So in the UK we've had a progressive rise in a number of phase 3 studies being conducted on children in the UK, and a rise in the number of children being recruited to these studies in the UK. Which means there's less need for sponsors to find more challenging situations, more ethically ambivalent situations? (Researcher, regulator, industry consultant, UK)
	In terms of whether it meets children's needs, I think there's a real gap here both in the EU and the US because the legislative drivers for research in children are filling in the gaps from adults to children. These are driven to make sure that the medicines they sell to adults can be used in children. And that's a different perspective from developing medicines that children need. And that's been a big barrier and I think it's a result of the political pressures that were compromised when the medicines registration was set up. (Researcher, regulator, industry consultant, UK)
	We recruit from any country where there is a need for the drug in paediatrics and where our company has a footprint. We intend to make the drug available or market the drug in that country. If we are not going to go to that country to market that drug, we would not do research there. (Researcher, paediatrician, industry sponsor, US)
Industry sponsorship bias	There are trials done by academic institutions, trials involving drugs and devices or done in academic institutions outside the sponsorship by industry. But in those cases…the data from those studies cannot be used in a regulatory context…so if it's done by a pure academic then the people who regulate drugs licencing, may not be able to use the information. (Researcher, pharmacologist, US)
	A pragmatic study will only answer certain questions reliant upon you knowing quite a lot about the intervention and certainly in the UK there's a lot of funding for pragmatic studies and so people do them in many contexts when they're inappropriate. So a lot of people to avoid registration studies are actually doing quite poor

Sub-themes	Illustrative quotations
	quality studies in terms of internal validity and external validity. So there's that big mash in between the curiosity-driven investigator study that's generally poor and the studies which are leading to marketing authorization which are generally of high quality. (Researcher, regulator, industry consultant, UK)
	In terms of ethics there is a little higher moral ground from the collaborative research. Primary investigator driven research we always put patients first. (Researcher, IRB, regulator, South Africa)
Dissuaded by prohibitive costs	Small biotechnology is scraping through every single dollar they can get to be able to bring the product to market. It is very expensive to do that. If they are forced to provide the drug, that is still unproven post-initial clinical trial, then they might not physically have the funds to do that. Because besides providing the drug they have an obligation to monitor those patients. And it becomes a very big expense or potentially could be a big expense and that's typical for them not having the funding for that. (Industry sponsor, CRO, monitor, Australia)
	And in South Africa, we have some of the highest radiology prices in the world because, we don't know why, we just get exploited basically. So that pushes up the price of clinical trials involving oncology and radiology so it does become a bit of a money issue where they want to get paid more and more and more. (Industry CRA, monitor, South Africa)
	Some of the drugs are just not available in Australia or the drug companies won't let Australian sites participate because they don't want to be bothered with shipping drugs down here. So they stick with the sites in the Northern Hemisphere…and then compared to countries like India and China, the employment costs are more expensive as well. (Trial co-ordinator, trial center, Australia)
	It's so pricey to go and just go and audit a place and expect for the sponsor to pay for it. So at the moment, the ethics we're using there're not doing that. (Industry monitor, South Africa)
Contending with infrastructural barriers	
Overwhelming resource constraints	In terms of Nigeria, not all institutions have an ethics committee. Not all institutions have IRBs. Most of the teaching institutions do. So this is an issue if you want to start a clinical trial. (Researcher, paediatrician, Nigeria)
	Insufficient. We get a little bit of money from New South Wales Cancer Institute but it's more just politically. They couldn't be seen not to support paediatrics. So we get a little bit of funding but most of our study coordinators are funded through donated funds. And that's all the money we get. We get enough to cover probably one salary and this aren't enough? (Trial coordinator, trial centre, Australia)
	The general system of power in most of the developed countries where there has been a need to cut resources allocated to health care. That has meant that at all levels of health care and for all people working in the health care, any other time that they can freely allocate something they would like to do has been drastically, dramatically reduced to the extent that it has practically disappeared for instance in Finland. And that means that in the old times whether you call them bad or good times is subjective assessment, but it was for a paediatrician or a doctor treating children at a hospital or even in rehabilitatory care, you could allocate some of your time for doing research. (Researcher, paediatrician, IRB, Finland)
	I am employed by the university. If I had to get a grant and that grant goes to the university and I am then allowed to use it, but I don't have carte blanche to use it in any way I think it's the most appropriate. And if by some chance you have actually been efficient and ran the study well and you've got left over funds, the university takes it away. So you really don't have money to come up with the next study…It's a huge challenge. (Researcher, IRB, regulator, South Africa)
	The pharma company would prefer to get all samples frozen, send them to US or wherever and have them analysed there. Where it would have been actually better for a developing country to do everything local. But then again…the developing country hasn't got all the same assays they run, all the same machinery to do the sampling or to do the analysis. (Industry monitor, South Africa)

Sub-themes	Illustrative quotations
	The heavy administrative burden and increasing costs that really jeopardized or delayed the activation of these clinical trials in children with cancer across Europe. (Researcher, paediatrician, academic sponsor, France)
Dearth of pediatric trial expertise	Our work has shown that up to 90% of trials have either unclear or high risk bias…it's outrageous that we're doing research that may be high risk of bias or not even dealing with these issues when we have the knowledge how to do it. So I think that's an urgent agenda item that, we shouldn't be allowing people to do trials unless they have the know-how and show they know how to design and implement trials. (Researcher, paediatrician, research governance, Canada)
	Because the very basic aspects about conducting research is not a general curriculum in most of our academics or as a medical student, neither me nor anyone for that matter. It's really not part of academics, so people really are not exposed to research methodologies so there are deep flaws in the research methodologies. Because I am a firm believer in the dictum that bad science is bad ethics. (IRB, CRO, India)
	Lack of accountability. Because all of a sudden everybody gets MCC [Medicine Control Council] inspections, FDA inspections, they're running around like chickens without heads. They manage to pull it off for one or two inspections but meanwhile they are sort of crumbling and crumbling further. Eventually these types of government institutions implode because they just can't keep up with the demand of the pharmaceutical industry…if you make a doctor a manager you just kill them completely because that's not what they study to be and they shouldn't be expected to have business acumen. But we actually do need them to be business managers. So it's the doctors in private practice, who have a bit of business background, or MBA or whatever just even a financial accounting course to understand how things work better, they see the bigger picture. (Industry CRA, monitor, South Africa)
	Some of the issues haven't been answered that might be in the actual day-to-day running, particularly from investigator driven studies, quite a few issues may not have been addressed in the protocols. May not be as detailed as one would expect to ensure that they run equally across all sites, or some of the products provided may not have as much supporting information as we sometimes expect. (Pharmacist, IRB, Australia)
	And people don't necessarily know a lot about the details, other than wanting to do a randomised control trial. They know it should be random, but there's kind of a limit on the knowledge in a lot of cases. (Academic, methodologist, Canada)
	There are new clinicians, investigators but it is very hard to get well-trained people and most of them are not really familiar with how trials are conducted and it ends up being a lot of our own personal time and personal supervision. So it's actually a real big problem and we don't get dedicated time to do the work. (Researcher, paediatrician, industry sponsor, US)
Traversing logistical complexities	I think the other major challenge for research participants in South Africa is distances that they have to travel, particularly if they're not living in the city or they're living in informal settlements further away from the hospital. Because as you know most of these research studies happen in larger academic centers, whereas people live out in quite far off communities, and it becomes quite a costly exercise to travel. (Researcher, paediatrician, South Africa)
	Heterogeneity in terms of resources because patients are paying from their own pockets so that the quality of care and of the treatment is often not trial-based, but is often patient-based. Funding, time, the ability for the clinician, manpower. (Researcher, trial coordinator, India)
Navigating complex regulatory and ethical frameworks	
"Draconian" oversight	I suppose my main issue about the funding and research is that it is a frighteningly bleak one. I get upset when I see that public and private funds, funding for research are being spent on bureaucracy and applications to R and D [Research and Development] Departments to hospital trust. And really quite a significant amount of money is being spent even before you start to near recruit the first patient. And that is where I feel it's unethical. People are raising funds for research which then has to be spent on unreasonable bureaucracy. (Regulator, paediatrician, UK)
	Bio-banking, I think is a low risk enterprise for the most part, but is something people feel strongly about once an element of choice. Again, some research going on in that particular domain but that's going to remain a challenging one to not overburden investigators with tracking people down and getting consent while at the same time

Sub-themes	Illustrative quotations
	maintaining trust and the research enterprise, I think that's the main conflict there. (Regulator, IRB, governance, US)
	The other problem is that a lot of doctors don't like to do clinical research because it's incredibly laborious and has such admin issues and we want every't' crossed and every 'i' dotted. We want it perfect and it's getting worse so the GCP requirements are becoming more, they haven't changed, but people are requiring that investigators stick to it more. Time is a problem; capacity in terms of staff is a problem, qualified staff. (Industry CRA, monitor, South Africa)
	Too long and cumbersome. From the forms, from the processes, the number of hoops you have to go through, the level of complexity, it's just got to the point where I don't think it actually helps protect children or childhood experiences. It can sometimes overall hinder them, because less trials get done when you spend so much time getting one trial up. (Trial coordinator, IRB, government sponsor, Australia)
	I think their [Medicine Control Council] bureaucracy is inadequate to cope. (Researcher, IRB, South Africa)
	Perhaps the pendulum has swung to an ethical approach that puts undue limitations on some trials in some aspects and makes it very hard for researchers to conduct trials in industrialized countries. (Researcher, paediatrician, DSMB, Papua New Guinea)
Ambiguous requirements	People struggle…what kinds of incentives are appropriate. Sometimes pencils are. You know, people are just unsure of things to present to ethics committees. What's acceptable and what's not. At times is not necessarily consistent. (Trial coordinator, network, Canada)
	You have to give the insurance and you have to know how much you're going to be compensating for what kind of things. The rules right now are very vague. (Researcher, paediatrician, IRB, India)
	A bit of gray area is the use of consent and assent forms…But it seems at this stage to be ethics committees specific and then not even mandatory to use. So mandatory to write them but not to use them and it's just seems like an inefficient use of time at the moment. (Trial coordinator, trial center, Australia)
Fear of exploiting the vulnerable	So you can't go to a third world country and exploit the cheap labor and use those children for your clinical trial and then pack up and leave again. The supportive care and the sought of long term follow-up needs to be offered to those participants. (Trial coordinator, trial center, Australia)
	Actually, in the media, somehow it always gets projected like Indians are being used for international trials. So I think the last few years, Indian government has made it very difficult to do international trials in India. (Researcher, trial coordinator, India)
	You've got to be very careful not to exploit the vulnerable population, and children are deemed vulnerable population, because obviously they are not 18 yet and they don't really necessarily 100% understand what's going on...Because I don't think you can rely on governments in certain countries to be as sensitive to the needs of the children as you would want them to be. (Industry CRA, monitor, South Africa)
	It was a trial that was done on girls in Gujarat and that I thought was again a huge oversight because the children who were enrolled in the study were tribal girls who were studying in a boarding school. And we all know that children in India are a vulnerable population and tribal are an even more vulnerable population…it just didn't make sense. I mean you could do the study in a different population; you didn't have to go to this population. And unfortunately because there were a few deaths, it put the whole cervical cancer vaccine into jeopardy which was really quite ridiculous and I felt very careless of the researchers. If they did it in a better way they could have gotten the same results and in a properly conducted and ethical study. (Researcher, paediatrician, IRB, India)
Excessive paternalism and unwarranted exclusion	Lots of the things one does in a neonatal intensive care are (considered funded) not experimental but considered we haven't done it before. It's more problematic when you're trying to run or test already used drugs or therapies in some older groups in paediatrics. It is actually harder to convince an ethics committee 'why' children should be randomised to one treatment or another when they're both being used in clinical practice albeit not with any evidence base. (Trial coordinator, regulator, government sponsor, Australia)
	And so people are extremely defensive and they just don't want to really have no part, any kind of research, where even a little risk is involved. So we are now extremely risk-averse which is a big problem especially conducting clinical research in India and also though the paediatricians and clinicians are extremely good, because of this

Sub-themes	Illustrative quotations
	general, bad negative publicity and background that is prevailing…they are also not keen on taking up a lot of research because the caregivers and parents are also extremely apprehensive about participating or allowing their kids to participate in these research. (IRB, CRO, India)
Precariousness of coercion vs.volunteerism	A barrier in India is that often if the family is presented at trial by the doctors or the other people who treat patients. They often feel that there may be a compulsion to participate in the trial and even if you tell them no, that it is entirely voluntary and it's up to you there is a sort of feeling that they may have to participate. (Researcher, paediatrician, IRB, India)
	I have spoken to people in developing countries. And they say that they are so desperate for research and so desperate for funding that they are prepared to take any research. Because it puts funding, training and some help for those people in their country that might be suffering with that particular condition that will be helped by the study, even though it's not meeting sort of the overall needs of all children in that country. So, I mean, they are in such a desperate situation that they are more willing to accept studies which may not be the best study to be conducted in that country. (Researcher, paediatrician, IRB, Australia)
	I think that one needs to be careful that parents aren't enrolling their kids in the clinical trials in order to pocket the money. (Researcher, IRB, regulator, US)
	If we're paying a certain amount in the United States and a certain amount in whatever third world country-disadvantaged country. It isn't the money that's the issue, it's basically you don't want to be coercive. (Researcher, paediatrician, industry sponsor, US)
Respecting uniqueness of children	
Embracing paediatric research paradigms	Because you have to deal with childish behaviours and you have to deal with parents who are struggling with the concept that they have a sick child. If you're doing trials in sick children, so you need a lot more time and resources to manage a child on a study than an adult on a study. So I think that poses problems if funding bodies or drug companies think that budgets and performance metrics that are appropriate for adult studies, if they try and impose those onto paediatric studies, then it's a problem. (Trial coordinator, trial center, Australia)
	So from critically appraising the results and putting them into practice. Now I've moved into appraising and enhancing methods used in trials with kids, with the aim to make the trials more relevant, more valid and more efficient, i.e. faster results, more valid results that can inform decisions tomorrow or maybe next week. And exploring new methodologies that will do smarter job without putting children at risk if they participate. (Researcher, paediatrician, academic, Canada)
	The other challenge in paediatrics particularly when you get into the neonatal, infant and the young child stage is that if there are products that may have neurocognitive consequences, they are unknown. But potentially of concern is the length of trial you then need to do to see any of that, it's quite expensive and we would extend way past what would be considered a meaningful timeline for a product to be studied to get into the market given the constraints of patents and so on and so forth. (Researcher, IRB, regulator, US)
Considering child-appropriate approaches	We eventually found that the patients were lying and they weren't completing their diaries as they were supposed to and because at the end of study, if you look at their compliance with the study drug and it, turned out to be, less on the e-diary than normal with the actual device, because you can do the estimate on the device as well...They're kids! And I think they want to sleep late over holidays and they don't want to answer these things [e-diaries] that are prompting them to answer. And I think parents aren't always there to guide the children. (Industry monitor, South Africa)
	Another major challenge has been the fact that many of these children have lost their parents so their primary caregivers then are people who are usually not formally recognized as legal guardians. (Researcher, paediatrician, South Africa)
	You are enrolling somebody who may not be able to give consent and you are relying on a second or third party, i.e. parents to give permission. So the issues about ensuring they understand the proposal and then making sure that, if you are getting permission from the parents, you also are under our regulations, ensure that the child to the best of…his developmental capacity can understand what you propose to do …assent then to have the safeguard of recognizing if the child objects. Is that objection sufficiently significant to say well actually I don't think you should be a part of the trial anymore. (Regulator, paediatrician, UK)

Sub-themes	Illustrative quotations
	When it's appropriate to conduct, a phase I oncology trial in particular, in children, is an ethical challenge…the whole domain of whole genome sequencing and the management of incidental findings is a very hot topic right now. The retention of bio-specimens and how to engage children in consent for the ongoing use of those specimens once the kids become adults is an interesting issue. And I think the whole assent process still is challenging to try to make sure kids are given an adequate decision-making role in their participation and research. (Regulator, IRB, research governance, US)
Facilitating family-centered empowerment	When you are recruiting a kid, you are recruiting a whole family really, especially with the longitudinal studies where there's multiple visits. So there's a lot of loss to follow up which I know happens in the adult population, but I think happens even more so in kids. (Trial coordinator, network, Canada)
	We need to improve the input of families and parents and children in setting up priorities and in designing studies and then conducting studies. (Researcher, regulator, industry consultant, UK)
	Parents usually want to see that their children are treated well and recover from their illness so they do co-operate...I haven't seen major problems coming from parents of children who participated in the research. (Researcher, IRB, monitor, Nigeria)
Driving evidence-based child health	
Promoting research advocacy	I suppose there's a particular great need for us all to sign up to the idea that research isn't an optional extra, it should be a part of everyday care. And that's difficult for professionals and I think it's also difficult sometimes for families and children to understand.(Regulator, paediatrician, UK)
	Very clear top-down direction from the highest level of government that this is a priority and that priority is accompanied by token amounts of money that can be spent directly on children's research. That then has to be met by a level of committed management who share that focus, share that vision and can turn it into effective operational issues and then that has to meet with the enthusiasm of researchers…And I think you do need that business case, hard dollars and cents and how many people does it cost to run a network, how many trials can you get done, how many medicines can you study? I think that's the essential part. And the emotional and moral case is only a small part of it. You have to really play the same game as everyone else plays when they're helping politicians for money. (Researcher, regulator, industry consultant, UK)
	There would be 100 news against the trials which are going on. And there would be hardly one news which is for it…So media needs to be structured-needs to give a neutral perspective on this rather than over doing it. (Trial centre administrator, India)
	In Nigeria, before you enter a community there are some people you need to go to. You have the traditional rulers like the local, and then you have the chief local government chairman… the power and local stakeholders. They will help with mobilization. So there will be some organization ahead of time to let the people know and these are the things involved. So the people are already aware. We also have some special programs from outside Europe that dump on the people. The people now encourage a lot of active participation. When they realize the importance we need to coerce them with jobs, voluntary work and that will be. (Paediatrician, safety monitor, Nigeria)
	I would like to see a huge campaign with children, parents, researchers, the public, to explain why we research, what we see the benefits of research, how it's currently regulated to ensure that it is safe. So that we can all ultimately have a fair view of the place of research in health care and a fair view of its benefits and risks. That's utopia. (Regulator, paediatrician, UK)
Creating and seizing opportunities	The current clinical research, infrastructure, experience and process has immensely benefitted from a lot of best practices which has come from the western populations and countries. So, even now, I am sure even though our regulators and adults may not accept it, we still look up to a lot of well-accepted and respected processes, SOPs and guidelines and rules which are already being used in US, Europe or Australia or other countries. (IRB, CRO, India)
	We need to support the philanthropy approaches. But I guess I have a concern that those philanthropic approaches are isolated and not really taking advantage of the opportunities for high quality research now being developed in the ICH jurisdictions. So it would be helpful if there's a way to sort of reach out to those philanthropic

Sub-themes	Illustrative quotations
	developments and make sure they are being done to high quality. Because the host countries for research don't have the regulatory apparatus to ensure that. (Researcher, regulator, industry consultant, UK)
	We have a first-world infrastructure and have third-world burden of disease. So we actually have an ability to answer in detail difficult questions with the patient population rather than, spending time on animal models and things like that. We have the patients with the problem and we try and resolve those as part of the clinical practice which in time relates to clinical research. (Researcher, IRB, regulator, South Africa)
	In 2013 in the first nine months of that financial year, the NIHR [National Institute of Health Research] across all specialities children and adult were able to recruit 25 first global patients, that means in a commercial study opening across the international at the same time point; in 25 of those studies the first patient recruited was in England. And of those 25, 11 were in the children's network. So it shows that that's an international competitive metric. And I think that plus the sense of collaboration that has allowed investigators in this case, paediatricians or other children's health professionals, to work equitably and collaboratively, has allowed us to develop that work and taken away some of the academic tension and pressures that can sometimes get in the way there. And make it attractive to industry to undertake research studies of new medicines in children. (Researcher, research facility, network, UK)
Supporting best practice	In Europe, it is a rather good continent to implement clinical research; it's for sure because we have this longstanding networking experience and activity with all paediatric oncologists and hematologists across the Union. (Researcher, paediatrician, academic sponsor, France)
	That people have different jurisdictions and they want slightly different information so it's getting all the stakeholders together to agree on some common core data items and then the registries will want some additional information as will the ethics committees, as will the TGA [Therapeutic Goods Administration], but at least your common core data set could be entered just once. (Trial coordinator, IRB, government sponsor, Australia)
	Harmonization of terminology is needed; I think inter-operability of trial processes and databases are needed. I think that quite a lot of training is needed, but all of that needs to be done in an intelligent, pragmatic way that takes account of reality rather than having a one size fits all other regulatory design or ethical level. (Researcher, regulator, industry consultant, UK)
	There's a lot of work that needs to be done to optimize the design of clinical trials, particularly helping people make intelligent, justifiable choices about how to do their phase I studies, how to do their phase II studies, how to do their phase III studies. And there are issues about comparators, there are issues about Fujian extrapolation, there are issues about PK [pharmacokinetic] modeling, about population PK, about blood sampling, about the developing and optimization of formulations and testing of formulations. There's a whole strand of methodology that needs to be incorporated into research so that people designing their studies not in an abstract, academic way, but based upon the experiences of experts and of clinicians and networks that are built up share memory about these things. So there's quite a lot that can be done to improve the way clinical trials are operationalized. (Researcher, regulator, industry consultant, UK)
	The interaction of…global initiatives and country implementation. These are often a challenge. When countries don't have good health systems where there's mistrust between the academics and the health professionals, governments then go to international bodies to say what we should do. And that's become the problem because they may be advising incorrectly because they are coming from what's good for Zambia or Zimbabwe rather than what's good for South Africa, so I think there is that concern that WHO, UNICEF, all these organisations shouldn't have more say than people that working on the ground. They should be inputting into people on the ground exactly what they are doing. It's almost as though some of these programs are run internationally for South Africa. They are not even run by South Africa. (Researcher, IRB, regulator, South Africa)
Improving access to treatment	One reason companies don't put medicines into other markets is that they don't get paid what they think they deserve, or they can get the money without having to register the medicine. So people who feel they're not getting access to medicines need to review carefully what their reimbursement strategies are and to make sure that if they are going to reimburse then the agent does meet a proper need. And I think that health technology assessments are described not very early in drug developments because this demonstrating efficacy doesn't demonstrate value for money. And value for money studies is different from traditional drug development.

Sub-themes	Illustrative quotations
	(Researcher, regulator, industry consultant, UK)
	From Nigeria, cost is not really the issue a lot of time this is availability. Availability that is hampered by lack of experience and inability to acquire some of those products is really the problem… just because these products may be unavailable because we are poor. I think that we need to change that. (Researcher, IRB, monitor, Nigeria)
	So the collaboration between pharma and academic research needs to be really fine-tuned, improved, clearly defining together the best way to develop a drug and the best way to introduce these drugs into standard care. And finally the best way to follow surviving patients after having been exposed to these drugs on the long term. (Researcher, paediatrician, academic sponsor, France)
	The trials that I've been involved in have been run on limited, very lean budgets and that can have some benefits I see, in that if the trial itself is more integrated within, normal, structures and it's run in a way where the results are more sustainable. If you've got a heavily funded clinical trial, the interpretation and generalizability of those results can be limited because the funding for implementation of whatever the result is not always available. (Researcher, paediatrician, DSMB, Papua New Guinea)
	In paediatric oncology we have long standing record, have a strong way of conducting clinical trials, meaning that clinical research is integrated into care. And more than 50-60% of children with leukemia or malignant tumours participates into clinical trials, phase III, phase II and phase I. (Researcher, paediatrician, academic sponsor, France)
Prioritizing research productivity	The life of a child is important anywhere in the world whether in Nigeria or anywhere. Life is sacred, it is a gift from God and I think that all hands need to be on deck to ensure that these children's needs are met. We do realize now that the world is a global village. People in developed nations should not just sit back and that we have finished dealing with all the problems in our nation and we don't have any problems…somebody else has a problem in a developing nation, this should be a cause of concerns and I think we should all should try and join hands together.(Paediatrician, safety monitor, Nigeria)
	The problems of children in Nigeria are many and are valid. Nigeria has a lot of people from different backgrounds and their unique backgrounds are not uniform across the country. The epidemiology of disease is different from one part of country to another. I would like to see that we address our issues of children more with research than politics.(Researcher, IRB, monitor, Nigeria)
	Clinical trials could address the major disease burden issues and address the issues of equity and inequity. I think that's very important and not just focus on I would say, medical intervention but be broader than that. Should have a balanced focus on prevention and curative health services, to address some of neglected disease burdens. But not to forget that many of the poorest countries still are bedeviled by some old problems that still have not been resolved. And so much of the focus, I think, of clinical trials shouldn't be about necessarily finding some new treatment approach but actually be operational research on how to do things better in difficult contexts. (Researcher, paediatrician, DSMB, Papua New Guinea)
	We need to look at the use of our health data, that's our held records, our social care records, our demographics and again with public leadership, not just agreement, we need to find a responsible way of using what I would call big data, to help us perform better and quicker research. (Researcher, research facility, network, UK)
	Stop mass production of research but to have research more coordinated…I have articles saying 'yes' and articles saying 'no' and unless we don't stop this mad rush to publish or perish, we're going to end up with more confusion than actually answering questions. (Researcher, IRB, regulator, South Africa)
	Have a critical mass of investigators support the necessary changes so that they can lead to culture change, but culture change by itself is just a sociologic phenomenon. What we really want to look at is culture change that is supportive of new logistical implementation, operational and business practices. (Research institute, regulator, government sponsor, US)
	If it is a multinational collaborative effort it will have a much stronger research question. Ensuring that trials are done in a more rigorous manner and ensuring quality control. So obviously there is some funding for these things. (Researcher, IRB, India)