Research Update
Special Focus Issue: Pediatrics

CLINICAL INVESTIGATION

Standards for Research in Child Health: developing guidelines for the design, conduct and reporting of pediatric clinical trials

Allison C Needham*[,1], Martin Offringa[1]; for the StaR Child Health Group
[1]Child Health Evaluative Sciences (CHES), Hospital for Sick Children, University of Toronto, ON, Canada
*Author for correspondence:
Tel.: +1 416 813 7654 ext.302684
allison.needham@sickkids.ca

Standards for Research (StaR) in Child Health was founded in 2009 to address the paucity and limitations of pediatric clinical trials. This initiative brings together international experts who are committed to developing practical, evidence-based standards to enhance the quality, ethics and relevance of clinical research in child health. By employing a systematic 'knowledge to action' plan, StaR Child Health creates opportunities to develop the evidence base for treatment of children around the world. To date, six StaR standards have been published with additional tools and standards are currently under development. Broad acceptance of research quality standards in child health can ultimately advance healthcare provided to children across the globe and enhance health outcomes.

Keywords: clinical trials • evidence based • methodology • pediatric • StaR child health • trial design

We need more & better research in children

Historically, the perceived vulnerability of children has led to an environment of exclusion from clinical trials, resulting in up to 90% of medicines prescribed to children in hospitals without sufficient evidence base for dosing, safety or efficacy [1,2]. While providers rely on information extrapolated from adult trials, evidence has shown that this practice may be ineffective for children and may increase the risk of adverse drug reactions and suboptimal therapy [3]. Thus, this paucity of pediatric pharmaceutical research means that on a daily basis child healthcare providers must make decisions without age and developmental stage appropriate information on how their treatments will affect short-term and long-term health outcomes in their young patients. In recent years the scientific community, along with regulators, parents and funders have acknowledged that research in children is not only necessary, but also morally imperative to provide children with safe and effective treatments. This acknowledgement is reflected in the increase of registered trials. While an increase in the number of trials represents a culture-shift towards the inclusions of children in trials, research involving children continues to demonstrate substantially lower quantity, quality and relevance compared with research involving adults [4].

The current shortcomings of pediatric clinical trials stemming from particular methodological and practical challenges of conducting research in children have been highlighted [3,5]. Many of these methodological shortcomings are threats to scientific validity and impact the science that is used by decision-makers who determine children's access to new and existing therapies. Thus, research that is not conducted in the best or safest ways possible, pose a potential threat to the health of children across the globe. To address these potential concerns, clinical researchers, funders, medical ethical committees and journal editors now seek to evaluate research quality standards. Therefore, as the need to enhance high-quality research in children is more pronounced than ever, there is an urgent need for standardization

FUTURE SCIENCE part of fsg

of research protocols, research conduct and reporting standards for child health trials.

Standards for Research in Child Health

Founded in 2009, Standards for Research (StaR) in Child Health is an international grassroots organization formed by methodologists, clinicians, policymakers, funders, trialists and researchers with the unified purpose of addressing the scarcity and deficiency of pediatric clinical trials [6]. This initiative aims to improve the design, conduct and reporting of pediatric research through the development and dissemination of evidence-based standards. These evidence-based standards take into consideration the methodological issues pertaining to clinical research design that are unique to child health such as recruitment and consent, justification for age groups, outcome selection and measurement, calculating adequate sample size, among others. Methodological research is chosen as the primary activity as a result of the understanding that failure to consider the uniqueness of children in clinical trial design and conduct can lead to the introduction of harm to the child or result in data that is neither reliable nor applicable.

High-priority areas for research

After forming the executive group in April of 2009, StaR set out to conduct a systematic review of available guidelines for the design, conduct and reporting of research in children. This initial step supported by the WHO, revealed very few relevant guidelines [7]. Several gaps were identified including the appropriate stratification of groups by age or development, and the use of child-specific outcomes. Another significant finding of the review was that guidance focused on what to consider, but not the process of how it could be done. The reviewers recommended that to enhance the acceptability of research, guidelines should be developed using transparent methods with input from investigators, regulators, WHO and the pharmaceutical industry.

Box 1. Standards for Research in Child Health priority issues.

- Consent and recruitment
- Data-monitoring committees
- Adequate sample size
- Age groups for pediatric trials
- Risk of bias
- Global child health: trials in developing countries
- Selection, measurement, and reporting of pediatric outcomes
- Complex interventions
- Rare disease trials
- Appropriate comparators

In October 2009, on the eve of the 20th anniversary of the adoption of the United Nations Convention on the Rights of the Child adoption, StaR Child Health hosted its first summit in Amsterdam. This meeting convened in conjunction with WHO, involved approximately 180 participants including representation from the WHO, the US FDA and the European Medicines Agency. The aim was to discuss the challenges of conducting trials in low- and middle-income settings as well as ways to advance the research agenda toward more and better trials for children in all settings. Based on the results of the systematic review and a survey of leading child health methodologists and regulators, StaR identified high-priority issues in the design, conduct and reporting of pediatric clinical trials [6]. These priority topics included issues specific to children such as recruitment and consent, and generic issues such as data-monitoring committees. New high-priority topics have been identified and prioritized since the first systematic review was completed in 2009 (Box 1).

StaR Child Health process

Once high-priority areas have been identified, potential collaborators from around the world are consulted and invited to participate in a standard development group (SDG). SDGs are working groups that bring together experts and individuals interested in a given topic through invitation and subscription. SDGs systematically identify what is known, create a research agenda when gaps exist and translate information into practical guidance for end users. SDGs are led by conveners who report to the StaR steering committee and are responsible for identifying tasks for the group, setting timelines, coordinating activities and leading the preparation of reports. The draft reports from the SDGs are circulated for discussion among a larger group of researchers, regulators and representatives from pharmaceutical industry. In collaboration with the SDGs, the StaR executive committee has developed a plan for dissemination and translation of the guidance documents to ensure the effective uptake of these principles by child health researchers.

Progress

To date, StaR has hosted four global summits, as well as writing weekends and workshops, resulting in six priority issues that have been addressed and published in an open access supplement to *Pediatrics* [8]. Published standards address recruitment and consent, containing the risk of bias, data-monitoring committees, adequate sample sizes, valid measurement of relevant and standardized outcomes and appropriate age groups. Since writing the standards, StaR reconvened in 2013 at the 20th Cochrane Colloquium in Quebec City to

revisit the mission statement and determine a network strategy for the next 4–5 years. New standards are in progress along with tools to better facilitate the uptake and application of StaR guidance.

Future perspective

New research in the field of child health methodology is evolving as more and more researchers and stakeholders strive to fill the identified knowledge gaps. StaR Child Health looks forward to providing updated guidance in the topics covered by our six published standards. Furthermore, there are several high-priority topics in pediatric clinical research that could benefit from StaR guidelines that take an instructional approach, by detailing what to consider, and also how to do it.

StaR continues to examine the landscape for emergent dilemmas in child health research. An important area that has come under microscopic consideration is the topic of rare diseases. Although individually rare, the collective burden of these 7000 rare diseases affects 1 in 12 Canadians and their families [9]. Furthermore, 75% of rare diseases affect children, with 30% of these patients dying before the age of 5 years. These diseases are typically genetic, causing a life-long burden of chronic illness, disability, premature death and a vast social and economic impact for families as well as society [10]. At this time, more than 90% of rare diseases have no treatment; highlighting the need for more research as well as innovative approaches to research design in order to overcome the methodological challenges of investigating therapeutic effectiveness of potential treatments stuck in the development pipeline. These challenges include the complexity and heterogeneity of patients, low individual prevalence rates and the unclear role of biomarkers in selecting patients for treatments. As the specificity of genetic testing improves along with increased laboratory progress on potential therapies, the need for methodological guidance to bring these discoveries to patients is pronounced.

Directly relevant to the methodology behind rare diseases research in child health is the selection, measurement and reporting of outcomes. During the process of integrative study design, the selection and reporting of appropriate outcomes is of the utmost importance in determining the effectiveness of an intervention [11]. Very few studies use systematic methods to select the appropriate outcomes for clinical research in children, thereby reducing the utility of the trial by producing potential misleading information about benefits and harms of an intervention [12]. Also, most pediatric trials are underpowered with regard to finding significant differences in the primary outcome, partly due to the fact that the uncontrolled event rates and unknown distribution of the outcome parameters is unknown at the start of a trial [13]. Unfortunately, overcoming the problem of underpowered trials requires the synthesis of the evidence from different trials in systematic reviews. This synthesis is impaired by the use of broadly varying outcomes and outcome measurement instruments, in which the latter have rarely been evaluated for their clinometric properties such as being amenable to change. There are virtually no core sets of meaningful clinical outcomes in pediatrics and pediatric-validated outcome measurement instruments are nearly absent [11]. These deficiencies are among the major challenges in pediatric clinical research today. Planning and discussion among relevant stakeholders and potential collaborators is necessary in to order to develop the methodology needed to establish these child health relevant, disease specific, core outcome sets and to identify valid measurement outcome instruments. Similarly, although there are many promising new compounds in the pharmaceutical industry's pipeline, there are very few treatments available for the 6000–8000 rare diseases that have been identified. Strong methodological guidance from a multidisciplinary collaborative is required to produce evidence that can bring candidate treatments to the market in a timely manner. Methodological advances in both areas have the potential to improve of quality of life for children across the globe.

Conclusion

Research to support the effectiveness and safety of medications in young children can only be generated if high-quality randomized controlled trials are designed, conducted and reported appropriately. Recent years have seen a number of actions to encourage research involving children and help investigators cope with the many methodological, practical and ethical challenges of pediatric studies. These advances mean that it is no longer 'too difficult' to conduct trials with children. StaR Child Health is dedicated to improving child health across the globe by enabling better drugs for children through the development of guidance in pediatric clinical research.

Financial & competing interests disclosure

For parts of StaR's work, funding from Global Research in Pediatrics (www.grip-network.org/index.php/cms/en/home) was received. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- High-quality clinical research in children is necessary to support the safe and effective use of medicines in children.
- Standards for Research (STaR) in Child Health is an international collaboration that seeks to enhance the quality, ethics and relevance of clinical research in child health by promoting the use of evidence-based standards and guidance for the design, conduct and reporting of clinical trials with children.
- To date six priority issues have been addressed and published with open access in *Pediatrics*.
- A key objective of StaR is to update existing guidance, while developing new standards, and new tools to better facilitate the uptake and application of standards for design, conduct and reporting of pediatric clinical trials.

References

1 Conroy S, Choonara I, Impicciatore P *et al.* Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *BMJ* 320(7227), 79–82 (2000).

2 Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. Unapproved and off-label use of drugs in a children's hospital. *N. Engl. J. Med.* 343(15), 1125 (2000).

3 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.* 5(8), e172 (2008).

4 Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985–2004. *J. Clin. Epidemiol.* 60(2), 118–123 (2007).

5 Wittmeier KD, Craig J, Klassen TP, Offringa M. The mission of StaR Child Health is to improve the quality of the design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards. Introduction. *Pediatrics* 129(Suppl. 3), S111 (2012).

6 Klassen TP, Hartling L, Hamm M, van der Lee JH, Ursum J, Offringa M. StaR Child Health: an initiative for RCTs in children. *Lancet* 374(9698), 1310–1312 (2009).

7 Frakking FNJ, van der Lee JH, Klassen TP, Offringa M, for the StaR Child Health. Survey of current guidance for child health clinical trials. The StaR Child Health Project: Standards for Research in Children 1–37 (2009). www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf

8 Pediatrics (2012). http://pediatrics.aappublications.org/content/129/Supplement_3.toc

9 Canadian. About CORD (2011). www.corddonate.ca/aboutCord.aspx

10 European Organisation for Rare Diseases. What is a rare disease? (2009). www.eurordis.org/content/what-rare-disease

11 Sinha IP, Altman DG, Beresford MW *et al.* Standard 5: selection, measurement, and reporting of outcomes in clinical trials in children. *Pediatrics* 129(Suppl. 3), S146–S152 (2012).

12 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.* 5(4), e96 (2008).

13 van der Tweel I, Askie L, Vandermeer B *et al.* Standard 4: determining adequate sample sizes. *Pediatrics* 129(Suppl. 3), S138–S145 (2012).