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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **StaR Child Health: Developing Evidence-Based Guidance for the Design, Conduct, and Reporting of Pediatric Trials**

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*Pediatrics* 2012;129;S112

DOI: 10.1542/peds.2012-0055C

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American Academy of Pediatrics

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# StaR Child Health: Developing Evidence-Based Guidance for the Design, Conduct, and Reporting of Pediatric Trials

“Lack of research, poor research, and poorly reported research are violations of children’s human rights,” declared Dr Richard Horton in his plenary address to the audience of the first summit of Standards for Research in (StaR) Child Health.

StaR Child Health was founded in 2009 to address the paucity and shortcomings of pediatric clinical trials. This initiative involves international experts who are dedicated to developing practical, evidence-based standards to enhance the reliability and relevance of pediatric clinical research. Through a systematic “knowledge to action” plan, StaR Child Health will make efforts to improve and expand the evidence-base for child health across the world. This article introduces the StaR Child Health agenda, the 11 initial priority topics that have been identified, and methods used to address these issues.

Approximately 180 participants, including representatives from the World Health Organization (WHO), the US Food and Drug Administration, and the European Medicines Agency, gathered in Amsterdam for the first StaR Child Health summit in October 2009 (Table 1). The summit was held on the eve of the 20th anniversary of the adoption of the United Nations Convention on the Rights of the Child, which recognizes the right of all children “to the enjoyment of the highest attainable standard of health.”<sup>1</sup> One impediment to achieving this universal right is the paucity and well documented shortcomings of pediatric research and more specifically clinical trials.<sup>2</sup> It is recognized that the quantity, quality, and relevance of data involving children are substantially lower than for adults,<sup>3–5</sup> despite data demonstrating that inadequate testing of interventions in children can result in ineffective or harmful treatments being offered or beneficial treatments being withheld.<sup>6</sup>

The mission of StaR Child Health is to improve the design, conduct, and reporting of pediatric research through the development and dissemination of evidence-based standards. This involves a systematic “knowledge to action” process, which includes the following: identifying problems that need to be addressed; identifying and reviewing knowledge relevant to the problem; generating knowledge where gaps exist; adapting knowledge to the relevant context; assessing barriers to knowledge implementation; designing knowledge transfer strategies and promoting best practice; and evaluating knowledge uptake and the impact on practice.<sup>7</sup> The following sections describe the StaR Child Health mission and the initial 11 priority topics.

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## KEY WORDS

StaR Child Health, evidence-based, pediatric, clinical trials, methodology, reporting

## ABBREVIATIONS

DMC—data monitoring committee

SDG—standard development group

StaR Child Health—Standards for Research in Child Health

WHO—World Health Organization

Drs Hartling, Klassen, and Offringa wrote the first draft of the article; Drs Wittmeier, van der Lee, Caldwell, and Craig contributed to the writing of the article; Drs Hartling, van der Lee, Caldwell, Craig, Klassen, and Offringa participated in regular conference calls, identified the issues, and drafted the article; Drs Hartline, van der Lee, Caldwell, Craig, Klassen, and Offringa participated in identifying the evidence base for StaR Child Health standards; and Drs Wittmeier, Hartling, Caldwell, Craig, Klassen, and Offringa agree with the final version.

[www.pediatrics.org/cgi/doi/10.1542/peds.2012-0055C](http://www.pediatrics.org/cgi/doi/10.1542/peds.2012-0055C)

doi:10.1542/peds.2012-0055C

Accepted for publication Mar 23, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**TABLE 1** Chronology of Key Events for StaR Child Health

Date	Event
April 2009	StaR Child Health Executive Group assembled
October 2009	1st StaR Child Health Summit held in Amsterdam, Netherlands
September 2010	2nd StaR Child Health Summit held in Vancouver, Canada
February 2011	StaR Child Health SDGs meet in Amsterdam, Netherlands

## ADVANCING THE StaR CHILD HEALTH AGENDA

In April 2009, the StaR Child Health executive group was assembled, which involved leading experts in pediatric clinical research and methodology (participant list and affiliations are available at [www.starchildhealth.org](http://www.starchildhealth.org), accessed July 18, 2011). The first task was to conduct a systematic review of available guidelines for the design, conduct, and reporting of research in children. This step, sponsored by the WHO, revealed few relevant guidelines.<sup>8</sup> Critical topics such as the need to consider appropriate stratification according to age or key aspects of development and the use of child-specific outcomes are not discussed. Most importantly, guidance is predominantly aimed at what should be done but not how.

Based on the results of the systematic review, and a survey of leading child health methodologists and regulators, a list of priority issues regarding the design, conduct, and reporting of pediatric clinical trials was compiled (Fig 1).<sup>9</sup> These topics are being systematically addressed through standard development groups (SDGs), working groups that bring together experts and individuals interested in a given topic through invitation and subscription. A convener for each SDG reports to the StaR Child Health executive board and is responsible for identifying tasks for the group, setting timelines and deliverables, coordinating activities, and leading the preparation of reports. General deliverables for the working groups are as follows: a summary of the current evidence; a list of recommendations for the process of design,

conduct, and reporting of trials with children; identification of gaps leading to a research agenda; and a plan for dissemination and implementation of the findings and recommendations. The SDGs will undertake methodological research to advance the knowledge base as indicated. The draft reports from the SDGs are circulated for discussion among a larger group of researchers, regulators, and representatives from the pharmaceutical industry. In collaboration with the SDGs, the executive will develop a plan for dissemination and translation of the guidance documents. To date, 11 priority issues have been identified, and the salient issues for these initial 11 priority topics are described below.

## PRIORITY TOPICS FOR StaR CHILD HEALTH

### 1. Recruitment and Informed Consent: Providing Appropriate Information for Children and Families Eligible for Inclusion in a Trial

Recruiting children into clinical trials is influenced by multiple factors including parental factors (beliefs, knowledge), the child (condition, child's choices), the trial (use of placebo or other comparators, specific trial requirements), and doctors (treatment preferences, doctor's influences on parental consent).<sup>10</sup> Children's participation in trials can be enhanced by improving communication, education, and optimizing the risk-benefit ratio (eg, through use of appropriate comparator). Reaching agreement on how to best recruit children in an efficient and ethical manner is a prerequisite for adequate and timely

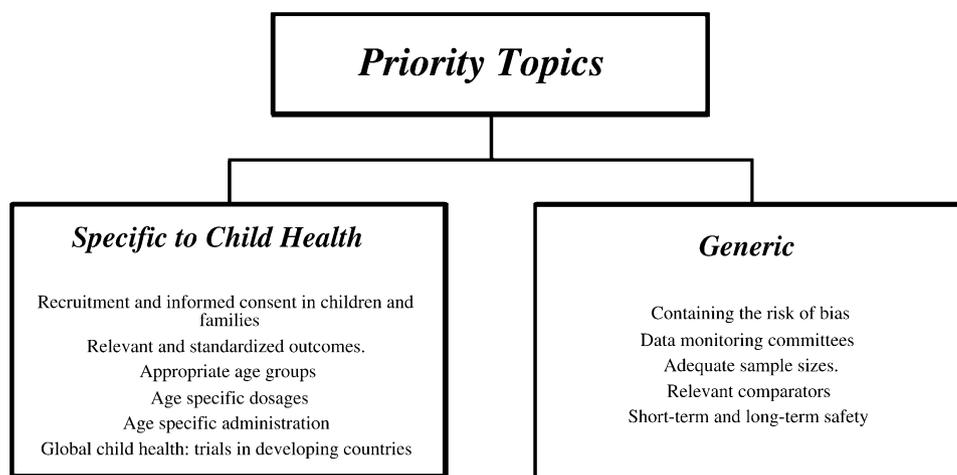
recruitment. This SDG will develop guidance regarding the following questions: (1) Who should give consent for children in research? (2) Which information is necessary to obtain consent? (3) How can we make sure that research in extra vulnerable children means equitable opportunity, not exploitation? (4) Is payment for research justified or unethical? (5) Can the child's clinician also be the investigator? (6) Who decides which eligible patients are invited to participate in a trial?

### 2. Containing the Risk of Bias

Trials with a high risk of bias tend to overestimate treatment effects.<sup>11</sup> Evaluations of pediatric trials have revealed the majority to be at high risk of bias.<sup>12,13</sup> Factors contributing to risk of bias need to be considered and minimized at all stages of the research process from trial conception to reporting. This SDG will address issues related to bias, including (1) sequence generation and allocation concealment, (2) blinding, (3) missing outcome data, (4) selective outcome reporting, and (5) other sources of bias. The above will be discussed in the context of trial registration<sup>14</sup> and in relation to existing guidelines for development and reporting of randomized controlled trials.

### 3. Data Monitoring Committees

There is consensus that data monitoring committees (DMCs) should be a standard consideration for trials with vulnerable populations such as children; however, guidance is needed to determine when a DMC is necessary. In a review of 739 pediatric trials performed until 2002, only 2% reported to have a DMC, whereas 71% reported an adverse event, and 20% reported a serious adverse event.<sup>15</sup> An analysis of pediatric trials published in 2007 revealed that 4.7% had a DMC.<sup>13</sup> Although an independent DMC may help ensure the safety of study participants,



**FIGURE 1** Priority issues regarding design, conduct, and reporting of pediatric clinical trials.

decisions made by DMCs regarding interim analysis and early stopping of clinical trials can have consequences for the scientific validity, results, and clinical impact of a trial.<sup>16–18</sup> Two recent systematic reviews revealed that only 17% of 648 recent pediatric trials reported on DMC activities, interim analysis, or early stopping.<sup>19,20</sup> Strict predefined statistical stopping “rules” were reported in only 10 of these 648 trials, and the validity of results from early stopped trials was threatened by their small sample sizes. This SDG will address the following questions: (1) What types of trials require DMCs? (2) What clinical and methodological (sub) specialties should be included in a DMC? (3) What is the scope of responsibilities of a DMC for a pediatric trial? (4) How should a DMC operate? (5) What details of the DMC should be reported in the study protocol, trial registration, and trial reports?

#### 4. Adequate Sample Sizes

Evidence demonstrates that pediatric trials are generally smaller than adult trials, more often single-center, and sample size calculations are rarely reported.<sup>21</sup> According to ethical principles, no unnecessary experimentation should be done. This principle encourages minimizing the number of subjects

included in a trial and results in more pilot studies to establish variance in outcome parameters, interim analyses, and other methods to make pediatric trials ostensibly more efficient than adult trials. Another pragmatic reason for smaller sample sizes in pediatric research is the relative scarcity of many medical conditions in children in developed countries. Guidance on this priority will provide the following: (1) methods to calculate optimal sample size, including the use of information from earlier studies and from meta-analysis; (2) methods to stop a trial when sufficient information has been collected for decision-making, including guidance on interim analyses and sequential designs, as well as the extent of evidence required to define clinical and regulatory actions; (3) methods to perform sample size calculations when there is insufficient information to make a priori estimates (eg, simulation and modeling techniques); and (4) novel approaches to conducting research when the number of available participants is small (eg, adaptive protocols, use of historical data).

#### 5. Valid Measurement of Relevant and Standardized Outcomes

A recent systematic review revealed that few studies address the appro-

priate choice of outcomes for clinical research with children.<sup>22</sup> A surrogate end point may be measured instead of the variable of interest for reasons of efficiency and practical considerations. There also can be various methods and tools for measuring the same outcome (eg, pain, behavior, and quality of life), often by using instruments that have not been validated in children. This heterogeneous approach presents a challenge when assessing the totality of evidence based on different trials (eg, in the context of meta-analysis). This SDG will address the use of relevant outcomes and standard approaches to measuring outcomes as essential factors to facilitate comparing and combining findings across trials and to estimate the relative effects on outcomes that matter to children and their families.<sup>22,23</sup> The Outcome Measures in Rheumatology network established in 1992 offers a precedent and model for developing core sets of outcomes to be included in trials.<sup>24</sup>

#### 6. Appropriate Age Groups for Pediatric Trials

Large variability exists in the age ranges and age subgroups of children considered appropriate to be included in recent pediatric trials and meta-analyses; the rationale for the selection

of particular age subgroups is often unclear. This variation impairs intertrial comparison and data synthesis of information about treatment effectiveness and safety. It also indicates a lack of knowledge of the legitimacy of age groups in existing guidance, which limits current research examining specific differences between and within age groups.

### 7. Age-Specific Dosages

Children often receive drug doses that are calculated on an individual basis, taking into account their gestational and postnatal age, weight, and/or body surface area. As there have been no pharmacokinetic studies performed in the pediatric or neonatal setting for many of the medicines that are used on a daily basis, dosing regimens for many medicines used in children are extrapolated from the recommendations for adults despite differences in drug metabolism and treatment response between adults and children.<sup>2,25</sup> A converted dosing regimen can result in a harmful overdose or a dosage too low to yield therapeutic benefit. This SDG will address generic methods to establish the optimal drug dosages in specific age groups and define situations in which pharmacokinetic and pharmacodynamic studies are mandatory to avoid under- or overdosing.

### 8. Age-Specific Administration

Appropriate dosage forms of medication are often not available for use in newborns, infants, and young children. The ability of the child to use different dosage forms varies with age, physical development, and the ability to coordinate swallowing, as well as psychological development and understanding.<sup>26</sup> However, the form of the drug needs to be considered a source of variation in drug delivery because the pharmacokinetics for liquid, melt, or topical skin patch formulation may vary. In pediatrics, palatability is a critical factor because any

additional discomfort, pain, or stress associated with the administration of medicinal products can reduce the tolerance or adherence to those products. Further, flavor preferences may vary geographically, leading to logistical and financial implications for industry and pharmacies. Finally, hospital and community pharmacies often need to prepare “in house” formulations when no specific pediatric formulation is available, which increases the risk of dosage error.<sup>27</sup> Guidance from this SDG will emphasize that medicines for children should require minimal or no fractioning or dilution steps to decrease risk of dosage errors. Further, the development of appropriate dosage forms of medication for the different age groups in a palatable form will be discussed as essential steps to make medicines safe, manageable, and acceptable for children.<sup>28</sup>

### 9. Relevant Comparators

Determining the appropriate comparator for an intervention is critical because trials provide estimates of relative effectiveness. “Standard treatment” and placebo controls are common comparators. However, standard treatment may involve an off-label or unlicensed drug, which itself does not have strong evidence to support its use. Further, clinicians and parents may not accept a placebo controlled study, which in turn may affect recruitment.<sup>10,29</sup> This is further complicated by the fact that placebo response may vary by age.<sup>30,31</sup> Guidance on this priority from the SDG will involve identifying when placebo is appropriate for which we must understand what constitutes a relevant comparator and what is acceptable as standard treatment.

### 10. Short-Term and Long-Term Participants’ Safety

Randomized trials are considered the gold standard to assess the efficacy of a therapeutic intervention<sup>32</sup>; however,

they are often relatively short in duration and may not be powered to detect rare but serious adverse effects. Cohort or postmarketing surveillance studies may be better suited to determine safety, depending on the baseline event rate of the adverse effects of interest. One of the main concerns for pediatric trials is that long-term effects may not be identified for many years.<sup>10</sup> This SDG will provide guidance on suitable options to identify and deal with potential hazards to protect children from harm.

### 11. Global Child Health: Ensuring Relevance and Appropriate Representation of All Children in Research

Special attention is needed to ensure the quality and safety of clinical research in developing countries where researchers face practical challenges implementing methodologically rigorous studies and the population can be particularly vulnerable to exploitation.<sup>33</sup> Specific considerations for research in developing countries are as follows: (1) the use of incentives or payment for participation, including the recruitment for trials of treatments that are not affordable for the community<sup>34</sup>; (2) issues of informed consent by families who may not understand the consent process or where it is culturally inappropriate to ask questions or refuse consent<sup>35</sup>; (3) limited accessibility to health care; (4) challenges with long-term follow-up; and (5) posttrial access to medicines for trial participants. To address some of the challenges, the WHO convened satellite meetings after the StaR Child Health Summits in 2009 and 2010 (<http://www.ifsrc.org/files/presentatie2010/SatelliteMtgSept12-10finalLB.pdf>, accessed July 18, 2011). Discussion topics included the following: improving the quality of trials in low and middle income countries; the role of pharmaceutical industries; the need for trained researchers on the ground; how

to give appropriate information to children and families and improve the informed consent and assent process in rural areas; and the absence of DMCs in many trials. This SDG will provide guidance for standards for research that are broadly applicable, culturally sensitive, and ethically responsible to the community where research is carried out.<sup>54</sup>

## THE StaR CHILD HEALTH VISION

In the past few hundred years, access to medical attention for children when they fell ill has improved remarkably (Fig 2). Only fairly recently, the large gap in evidence that exists, evidence to underpin clinical choices for safe and effective treatments, has come to the larger public's attention. It has motivated the emergence of dedicated research networks worldwide. This much needed research in sick children may improve if the guidelines developed through StaR Child Health are implemented in practice. This requires an integrated knowledge translation plan that involves numerous stakeholders. The network is aware of the many challenges surrounding the uptake and dissemination of the StaR Child Health guidance and will therefore not only coordinate efforts on the assessment of unmet needs within the priority topics but also ensure measures for uptake and dissemination. So far, representatives of a variety of stakeholder groups, including clinicians, researchers, methodologists, industry partners, regulators, and journal editors, participate in various activities of StaR Child Health. New opportunities for involvement will present as StaR Child Health identifies future priority areas and new SDGs are developed. After publication of the SDG guidance articles addressing the aforementioned priority areas, a general knowledge translation strategy will



**FIGURE 2**

StaR Child Health inspiration: "The Sick Child" by Dutch painter Gabriel Metsu, c. 1660. Oil on canvas, Rijksmuseum, Amsterdam. Reprinted with permission #43282.

be developed to support the SDG recommendations. This will occur in concert with other relevant initiatives such as Global Research in Pediatrics.<sup>56</sup> Further, StaR Child Health plans to adapt the Consolidated Standards of Reporting Trials Statement to include items specific to trials in children and produce a proposal for Consolidated Standards of Reporting Trials—Children.<sup>57</sup> Finally, the network seeks to create a StaR Child Health—WHO platform ([http://www.who.int/childmedicines/progress/Amsterdam\\_Meeting.pdf](http://www.who.int/childmedicines/progress/Amsterdam_Meeting.pdf), accessed August 1, 2011).

The vision for StaR Child Health is to become a virtual center that can provide resources and training related to the design, conduct, and reporting of clinical research with children. Associated activities include maintaining an ongoing research agenda; conducting empirical research to inform the design,

conduct, and reporting of clinical research in children; providing a repository of guidance documents and supporting materials; and engaging in knowledge transfer activities to optimize uptake and implementation. The overarching principle is that activities and recommendations be built on the best available evidence. StaR Child Health's initial goal is to create guidance for each of the topic areas described above. To this end, SDGs are currently compiling existing empirical evidence, identifying gaps, and setting a research agenda to provide a sound basis for guidance. StaR Child Health aims to evolve into a global child health research network dedicated to improving the design, conduct, and reporting of pediatric clinical trials and ultimately improving the quality of health care provided to children across the globe.

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*Pediatrics* 2012;129;S112

DOI: 10.1542/peds.2012-0055C

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