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Evidence-based guidelines for pediatric clinical trials: focus on StaR Child Health

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Abstract

Clinical trials in children are challenging and filled with important ethical considerations that differ from adults. Given difficulties associated with pediatric clinical trials, off-label prescribing is a common practice in pediatrics, which can lead to adverse safety events and efficacy failures. To overcome these consequences, in the past 15 years, legislation in the USA and Europe has provided incentives to industry and increased government funding to conduct pediatric trials. Pediatric trial networks have also been formed to decrease the knowledge gap. However, challenges to performing pediatric trials and lack of standardization and guidelines regarding studies in children still exist. Standards for Research (StaR) in Child Health, begun in 2009, aims to improve the design, conduct and reporting of pediatric trials. This organization uses a consensus guideline approach involving academic, government and industry stakeholders to identify and disseminate best practices for pediatric trials. Six out of 11 planned standards are currently published.

Keywords

clinical trials; guidelines; pediatrics

Existing pediatric clinical research guidelines

Standards for Research (StaR) Child Health was founded by a group of experts to improve pediatric clinical research methodology. In 2008, the current members of the StaR Child Health executive group noted a large evidence gap and lower quality of clinical research in children relative to adults and described the need for better pediatric clinical trial evidence [1]. In 2009, the StaR group conducted a systematic review of pediatric research guidelines and a survey of child health clinical researchers and regulators to identify and prioritize challenges related to the design, conduct and reporting of pediatric clinical trials. The systematic review was limited to a 10-year period (1999–2009) and to publications containing recommendations for pediatric clinical trials. They identified a total of 43 existing guidelines from the peer-reviewed literature, as well as from government, regulatory and scientific organization websites. Guideline quality was assessed using a modified version of the Appraisal of Guidelines Research and Evaluation instrument [2].

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The Appraisal of Guidelines Research and Evaluation instrument, designed to assess clinical practice guideline quality, was modified to retain only those items relevant to clinical research. The StaR group identified the following limitations of existing pediatric research guidelines: poor description of guideline development, lack of evidence supporting guideline recommendations and a lack of information on guideline implementation [101].

Standard development methods & results

The StaR group identified 11 priority topics requiring evidence-based guidance documents. Six topics specific to child health included recruitment and consent, outcome measures, appropriate age groups, age-specific dosage, age-specific medication administration, and pediatric trials in developing countries. The five priority topics not specific to child health included sample size, data-monitoring committees (DMCs), containing risk of bias, relevant comparators, and safety.

The most relevant concerns within each topic were identified. For recruitment and consent: individuals responsible for consent in pediatric studies; information needed to obtain consent; exploitation in extravulnerable children participating in clinical studies; justification and ethical considerations of payments made to pediatric research subjects as well as conflicts of interests generated by clinicians serving as investigators; and the decision-making process of eligible participants invited to participate in research. For outcome measures: relevant outcome measures and standard approaches to measure outcomes and to allow comparability and combination of study results across trials. For age-specific dosage and administration: methods to establish optimal drug dosages in specific age groups; pharmacokinetic (PK) and pharmacodynamic (PD) studies required to guide dosing and development of age-specific drug formulations. For pediatric trials in developing countries: development of applicable, culturally sensitive and ethically responsible standards for community-based research. The issues associated with topics not specific to child health included measures to decrease risk of bias in clinical research; need and responsibilities of DMC and identification of appropriate individuals involved in these committees; methods to assess appropriate sample sizes and incorporation of modeling and simulation in sample size calculations; appropriateness of placebo and relevant comparator use in clinical trials; and short- and long-term safety assessments in children partaking in research.

Priority areas and challenges identified by StaR Child Health are systematically assessed by experts on each topic through standard development groups (SDGs). The SDGs will summarize available evidence, identify research gaps and present recommendations regarding design, conduct and reporting of clinical trials involving children. The draft reports from the SDGs on each priority area are reviewed by a group of experts including researchers, regulators and representatives from the pharmaceutical industry, to develop a plan for dissemination and translation of the final guidance documents. To this end, the StaR group is pursuing collaborations with the Global Research in Pediatrics initiative and the WHO to increase the uptake and impact of the guidelines. In addition, the StaR group proposes to incorporate child-specific items in the Consolidated Standards of Reporting Trials statement, a set of recommendations for reporting clinical trials endorsed by many medical journals [3].

The StaR group has published six out of 11 planned standards [102]. Each contains recommendations for practice, which are summarized in Box 1. The recruitment and consent standard is focused on ethical considerations with the consent process and provides recommendations addressing child objection to research participation, equitable recruitment, compensation for participants and the need to differentiate research participation from clinical care. Standard 2, containing risk of bias, focuses on design and reporting practices

intended to improve the quality of evidence resulting from pediatric trials. Standard 3, DMC, provides straightforward recommendations regarding needs and scope in pediatric studies. The recommendations of the fourth standard, determining adequate sample sizes, emphasize *a priori* sample size determination and inclusion of statisticians during the study design phase. Standard 5, outcomes in children, underscores the need for population-specific clinical trial end points and standard 6, age groups for pediatric trials, highlights standardization of pediatric age groups used in clinical trials.

Discussion

Challenges in pediatric clinical research

Clinical research involves many ethical considerations to minimize risk to participants. In the case of children, special ethical considerations are required, which increases the complexity and reduces the feasibility of research studies in this population. Children lack decision-making capacity and are subject to the authority of adults, resulting in unique challenges to the informed consent process. Other limitations associated with conducting studies in children include the number of subjects required to ensure success of clinical trials; number of biological samples required to determine appropriate drug dosing; availability of age-specific safety findings and evaluations; identification of clinically relevant and feasible pediatric-specific end points; appropriate use of comparators in efficacy trials; standardization of clinical trial reporting and efficient routes for information dissemination. These limitations and challenges have resulted in a lack of evidence-based drug dosing and frequent unlicensed, or off-label, use of drugs in children that leads to adverse safety events and therapy failures. Several studies have shown 40–100% of hospitalized children are prescribed at least one off-label drug [4–6]. In addition, several interventions poorly evaluated in children have been adopted as standard-of-care and later shown to either lack benefit or cause harm [7–9]. Thus, safety is of particular concern in pediatric trials. The StaR standards on DMC (completed) and safety (in progress) address this topic. Most of the above challenges associated with pediatric research were identified within the topics of the StaR group and are being systematically addressed to generate standardized guidelines. This is particularly important in the setting of an increasing number of pediatric studies for existing treatments, in addition to regulatory incentives and mandates for pediatric studies of new drugs.

Pediatric research legislation

Historically, drug regulations in the USA resulted from several disasters primarily affecting children. Toxicity from diethylene glycol used in sulfanilamide that killed 107 individuals (mainly children) led to strengthening of the Food, Drug and Cosmetics Act of 1938 to require drugs to be approved as safe prior to being marketed. Similarly, birth defects caused by thalidomide and circulatory collapse caused by chloramphenicol lead to the Kefauver Harris Amendment of 1962, which required drug manufacturers to provide proof of effectiveness and safety of drugs before approval. Though central to the historical development of US drug regulation, children are considered vulnerable and are thus protected from participation in drug research.

Over the past 15 years, several pieces of legislation have been developed to increase the knowledge of pediatric therapeutics. In the USA, the FDA Modernization Act of 1997 incentivized the study of on-patent drugs. A continuation of this act, the Best Pharmaceuticals for Children Act (BPCA) in 2002 (reauthorized in 2007), established a mechanism to study off-patent drugs in children. In addition, the Pediatric Research Equity Act (PREA) in 2003 amended the Federal Food, Drug, and Cosmetic Act to authorize the US FDA to require sponsors to conduct certain research on drugs used in children. As of

April 2012, BPCA and PREA have resulted in 438 pediatric-labeling changes [103]. The most common therapeutic areas studied are antivirals, antibiotics and antihistamines (Table 1). In spite of this success, only ten of these studies included neonates and almost all of these were conducted in neonates at risk of or infected with HIV. This emphasizes the need to conduct drug trials in this vulnerable patient population. The continuity of BPCA and PREA is uncertain and is currently under review by the US Congress, as they require reauthorization every 5 years. Without reauthorization, the expiration date for these programs is 1 October 2012.

In 2007, the EMA adopted the Pediatric Regulation, which obligates drug manufacturers to prepare a pediatric investigation plan for all age ranges for drugs in development and provides industry incentives (6-month patent extension) to perform pediatric studies. The EU legislation provides more certainty than the US regulatory efforts to manufacturers because it does not require reauthorization. An analysis of the first 3 years of the EU pediatric regulation reveals little impact on the number of pediatric trials conducted as a result of this mechanism [10]. However, because the EMA requires sponsors to submit pediatric investigation plans during early drug development, many proposed studies may not yet be initiated. Therefore, the full impact of the Pediatric Regulation on the number of EU pediatric studies may not be detected for several years. In addition, only one company has thus far received the patent extension under this program [104].

There is also pediatric research legislation in other developed countries such as Canada, Australia and Japan. Canada has a voluntary 6-month patent extension mechanism for studies conducted for a pediatric indication. In Australia and Japan, there have been efforts to increase pediatric research, but legislative and regulatory reforms are lacking [11].

Pediatric research networks & initiatives

The StaR group is not a clinical trials network; however, their standards are timely because there are numerous new and existing pediatric research networks. The American Academy of Pediatrics website lists >80 active US/Canadian pediatric clinical research networks, of which a few will be illustrated (Table 2) [105]. The Children's Oncology Group (COG), established over 50 years ago, is the largest pediatric clinical trials organization, with nearly 100 active trials at any one time [106]. The standard medical care for children with cancer is to be enrolled in a COG study. Treatments are standardized and guidelines are generated through evidence-based research on a national level. As a result of these efforts, childhood cancer survival rates have risen from 10 to 80% over the past 50 years [12]. The Neonatal Research Network (NRN) is another group of 20 academic centers, established in 1986, specializing in conducting efficacy trials in premature infants. This network has completed over 20 randomized controlled trials to date [107]. Since its start, mortality has decreased substantially for low-birthweight neonates born at NRN institutions [13]. In fall 2010, the Pediatric Trials Network (PTN) was created to conduct pediatric trials for off-patent therapeutics in which PK, safety and/or efficacy data are lacking. The main focuses of the PTN are age-specific dosages and administration, use of modeling and simulation to determine sample sizes and relevant end points for pediatric trials, increased clinical trial efficiency, and feasibility and development of opportunistic study designs to broaden the reach of pediatric trials. Many of these areas were included in the StaR Child Health priority topics. Starting in 2011, the PTN expects to conduct more than 20 pediatric trials over 7 years [14]. One PTN study has been completed and six are enroling. Although there are guidelines from professional societies [15] and regulatory agencies focused on the conduct of pediatric studies [108,109], limitations of current networks include a lack of standardization of clinical trial design, conduct and reporting, which are concerns StaR Child Health aims to address.

As of 2011, the EMA identified 60 pediatric research networks in the EU. The 2007 Pediatric Rule mandated the formation of a European network of networks, investigators and centers, called the European Network of Pediatric Research at the EMA [16]. This organization is intended to enhance collaboration, build competencies and prevent duplicative effort among the networks. Networks had to document competency with regard to the following six quality criteria in order to join: research experience and ability, network organization and processes, scientific competencies and ability to provide expert advice, quality management, training and educational capacity to build competencies and public involvement. Eighteen of 32 that applied networks were accepted. It is too early to evaluate the effectiveness of this initiative. Another EU network, ERA-NET PrioMedChild, is a pediatric research network established in 2007 with funds from 11 EU member states. The purpose of this network is to foster transnational pediatric research and establish best practices. Seven studies in areas such as pharmacoeconomics, modeling and simulation, imaging and biomarkers are ongoing from this network. None of the projects are clinical trials, although one project aims to measure excipient exposure in neonates [110]. It is too early to evaluate this network as projects were funded in 2010.

The Global Research in Pediatrics Network (GRIP) is an EU-funded initiative aimed at harnessing the globally scattered pediatric research expertise by linking more than 1000 institutions [111]. The GRIP plans to develop guidelines for pediatric research, but has not published detailed information about specific guideline development plans. The GRIP also plans to a build pediatric clinical research infrastructure including research programs focused on neonatal research, pharmacoepidemiology and pediatric formulations as well as development of a pediatric clinical pharmacology training program (although there are other such programs in Europe). The StaR group plans to collaborate with the GRIP to find potential overlaps between the two initiatives and disseminate and implement completed guidelines.

PK/PD modeling & simulation

PK/PD modeling and simulation is an important area of clinical pharmacology pediatric research absent from the StaR Child Health priority topic list. Drug development in adults almost always involves PK and dose-ranging studies in healthy subjects prior to studies in patients with the medical condition the drug is intended to treat. Such studies in healthy children are impossible to conduct owing to ethical implications and therefore the dosing (PK) knowledge gap for most drugs used in children is exceedingly large. Direct (linear, bodyweight) extrapolation of adult data to children often fails to accurately reflect the most appropriate dose to use in this population owing to developmental changes characteristic of children. In addition, the pathophysiology and natural history of the adult disease should be similar to children in order to justify extrapolation. If the disease is similar between adults and children, mathematical models can be used to predict the most appropriate dose in children using data collected from adults. Simulations enable assessment of the likely drug exposure with given assumptions about body size and drug elimination pathways as well as developmental changes associated with these factors. Simulation studies can be used to assess whether the dosing regimen(s) proposed for children will result in drug concentrations found to be safe and effective in adults. In addition, modeling and simulation techniques can provide important insight into clinical trial design in children to optimize data collection and increase the likelihood of trial success. A critical example is the collection of sparse and optimal PK samples. Traditional PK studies involve intensive blood sampling in order to characterize drug disposition over time. This presents difficulties for pediatric studies. Parents may be unwilling to allow their child to participate in a study requiring frequent blood sampling or the number of PK blood samples may pose a safety risk to the subject (neonate). For these reasons, sparse sampling combined with population

PK analyses and optimal PK sampling design may be the only way to characterize drug PK in children. Regulatory agencies also support increasing the use of PK/PD modeling and simulation to support pediatric trial designs. The FDA set a goal, for 2020, to have all pediatric study designs submitted in response to a written request supported by PK/PD modeling and simulation [112].

Data sharing & selective reporting

The need to share patient-level clinical trial data between investigators is a topic increasingly discussed by the pediatric research community [17–19]. The advantages of clinical data sharing include evaluation of PK/PD models using data sets other than the ones used for model development [20], subgroup analyses of pediatric data enrolled in adult trials, meta-analyses of pediatric data and opportunities for interinstitution collaboration. A related topic to data sharing is selective reporting of clinical trial results. This practice involves publication bias of 'positive' trials, which limits the appropriate assessment of the literature and can lead to duplication of efforts and unnecessary enrollment of children in clinical trials. This is particularly important for the pediatric population given the ethical considerations and scarce resources to study drugs in children. Selective reporting of clinical trials can also hamper the ability of conducting systematic reviews of the pediatric literature. The StaR group should emphasize the need to avoid publication bias as well as consider the addition of data sharing as a priority topic for guideline development.

Expert commentary & five-year view

Pediatric clinical trials are difficult to conduct and are filled with challenges, resulting in an unacceptable knowledge gap regarding optimal drug dosing and study design in children. Some of these challenges are being addressed by legislative efforts in the USA and Europe as well as by pediatric clinical research networks. However, gaps still remain in standardization of pediatric trial design, conduct and reporting of results. StaR Child Health is one of the first comprehensive efforts to develop and disseminate best practices for pediatric research. Six of 11 planned standards are now published by this initiative. While the StaR standard development process is described with greater detail than previous pediatric research guidelines, clear differentiation between evidence-based and expert opinion recommendations is still required. The StaR group should consider inclusion of PK/PD modeling and simulation and clinical trial data sharing as additional priority topics for clinical trials planned in children. These practices will benefit the scientific community as pediatric research is increasingly being mandated by countries around the world. Over the next 5 years, the recommendations and standards generated by StaR Child Health should be prospectively evaluated to determine the most efficacious, safe, ethical and feasible approaches to conducting studies involving children.

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Box 1. Abbreviated recommendations from completed StaR Child Health standards

Standard 1: consent and recruitment

- Investigators must always obtain consent/assent
- Recognize a child's objection to research participation in the context of whether the child would object to the same procedure in a routine clinical care context
- Seek to approach all eligible patients
- Ensure that compensation does not induce families to take unnecessary risks
- Clearly differentiate clinical care from research participation

Standard 2: containing risk of bias

- Use appropriate randomization and blinding
- Prespecify all outcomes and analyses
- Calculate sample size requirements based on the primary outcome
- Document disposition of all participants
- Report on all outcomes and justify protocol changes
- Declare conflicts of interests and the role of sponsors in all aspects of the trial
- Prespecify how baseline imbalances will be addressed
- Register the trial before initiation
- Report protocol items and results in accordance with applicable guidelines, such as SPIRIT and CONSORT

Standard 3: DMC

- DMCs should exist for all pediatric trials with major clinical end points, possible early stopping and/or high safety risk
- Avoid including individuals with conflicts of interest to serve on the DMC
- Have a manual of procedures for the DMC signed off by relevant parties before trial initiation
- Describe DMC activities, analyses and recommendations in the study report

Standard 4: determining adequate sample sizes

- Always perform sample size calculations, in consultation with a statistician, to support the design of a randomized controlled trial
- Use standard methods for sample size calculation when information from the population of interest is available; otherwise, use alternative methods
- Fully describe all parameters for sample size calculation in the study report
- Avoid loss to follow-up

Standard 5: selection, measurement and reporting of outcomes in clinical trials in children

- Measure and report broadly accepted outcomes or describe why they were not measured

- Measure outcomes that are valid in the population of interest and report the results of all outcomes
- Document any changes to outcomes during the trial

Standard 6: age groups for pediatric trials

- Consider age range in all aspects of protocol design and the effect of developmental and psychosocial changes
- Consider use of the age groupings proposed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development
- Consider using validated predictive models when available
- Pool data with other studies of the same age group, if possible, in order to perform age-group specific analyses

DMC: Data-monitoring committee.

Data taken from [102].

Key issues

- Standards for Research (StaR) Child Health was created in 2009 and is developing standards for pediatric clinical research.
- Standards Development Groups consist of experts in 11 priority areas.
- The development of rigorous pediatric research guidelines are timely because legislative and other initiatives have increased the number of pediatric trials being conducted.
- StaR recommendations require clarification between evidence-based and expert opinion sources.
- The incorporation of PK/PD modeling and simulation for clinical pharmacology trials and clinical trial data sharing should be considered as future priority topics.
- Prospective evaluation of StaR Child Health guidelines will be necessary to strengthen the evidence base of recommendations.

Table 1

Top ten therapeutic categories from US pediatric-labeling changes.

Therapeutic category	n	Percentage
Antiviral	47	10.8
Antibiotic	21	4.8
Antihistamine	21	4.8
Antiasthmatic	19	4.4
Anti-inflammatory, topical	18	4.2
Anticonvulsant	16	3.7
Preventive vaccine	16	3.7
Antihypertensive	15	3.5
Antiulcerative	15	3.5
CNS stimulant	14	3.2

These are labeling changes submitted in response to legislative initiatives.
Data taken from [103].

Table 2

Selected pediatric research organizations and initiatives.

	StaR Child Health	COG	NRN	PrioMed Child	WHO (‘Make Medicines Child Size’)	PTN	GRIP	Enpr-EMA
Years	2009 to date	1955 to date	1986 to date	2007 to date	2007	2010–2017	2011–2015	2011
Countries	Global	Primarily USA	USA	EU	Global	USA	Global	EU, although some member networks have international collaborations
Funding source	Three current sponsors	US National Cancer Institute, philanthropy	US NICHD	11 EU member states	Gates Foundation and UNICEF	US NICHD	EU	EMA
Guideline development	Formal	–	–	Informal	–	–	Informal	Informal
Conducts studies	−	+	+	−	−	+	U	−
Number of studies planned or conducted	NA	>100 at any one time	Eight active, >20 completed	NA	NA	One complete, six enroling	U	NA
Members	Academic/medical, industry, regulatory, WHO	>220 institutions	20 academic/medical institutions	11 research agencies	WHO and partnerships	Academic/medical	Academic/medical, regulatory, industry	EMA, 18 research networks

+: An activity of the organization; −: Not an activity of the organization; COG: Children’s Oncology Group; Enpr-EMA: European Network of Pediatric Research at the EMA; GRIP: Global Research in Pediatrics Network; NA: Not applicable; NICHD: National Institute of Child Health and Human Development; NRN: Neonatal Research Network; PTN: Pediatric Trials Network; StaR: Standards for Research; U: Unknown; UNICEF: United Nations Children’s Fund.