STaR Child Health

Standards for
Research with Children

Hanneke van der Lee, MD, PhD

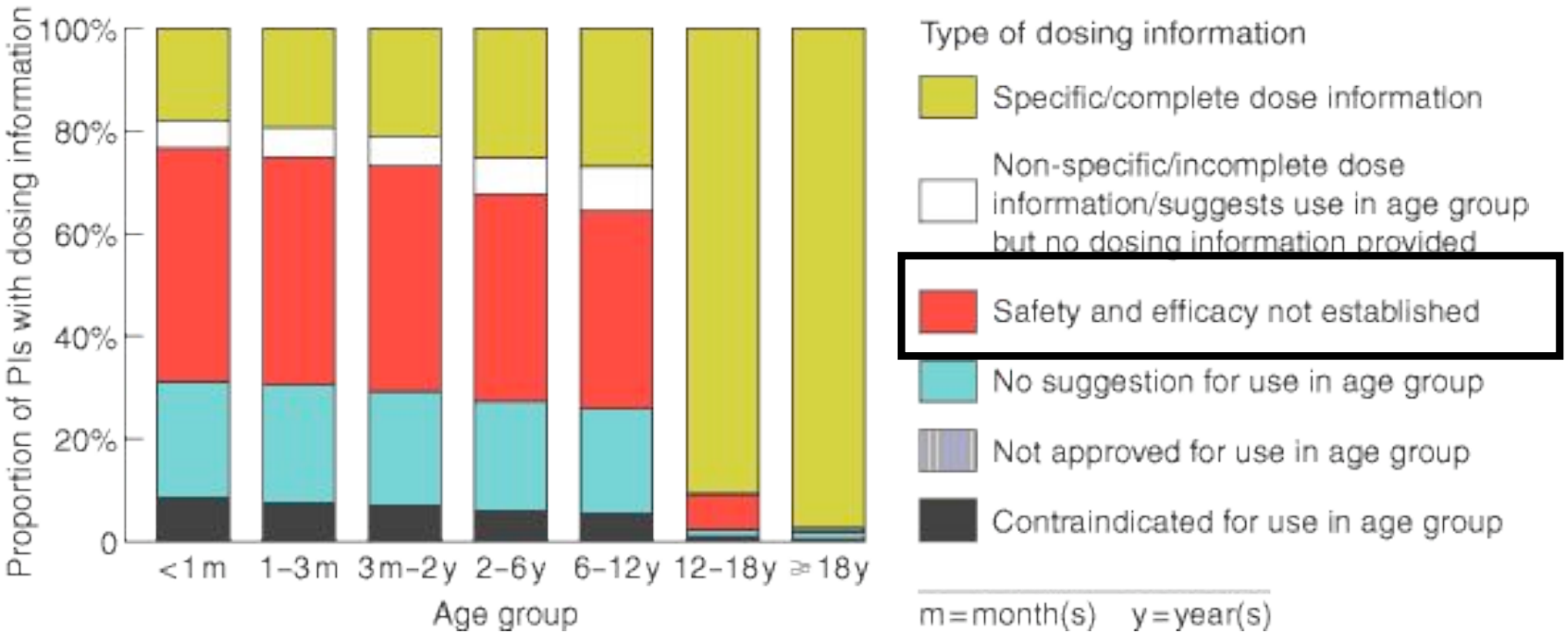
Outline

- Why
- Who
- What
- How

StaR Child Health?

Magnitude

'…no *adequate scientific basis* info for 80% of prescription medicines.'



Tan et al. MJA 2003

Why?

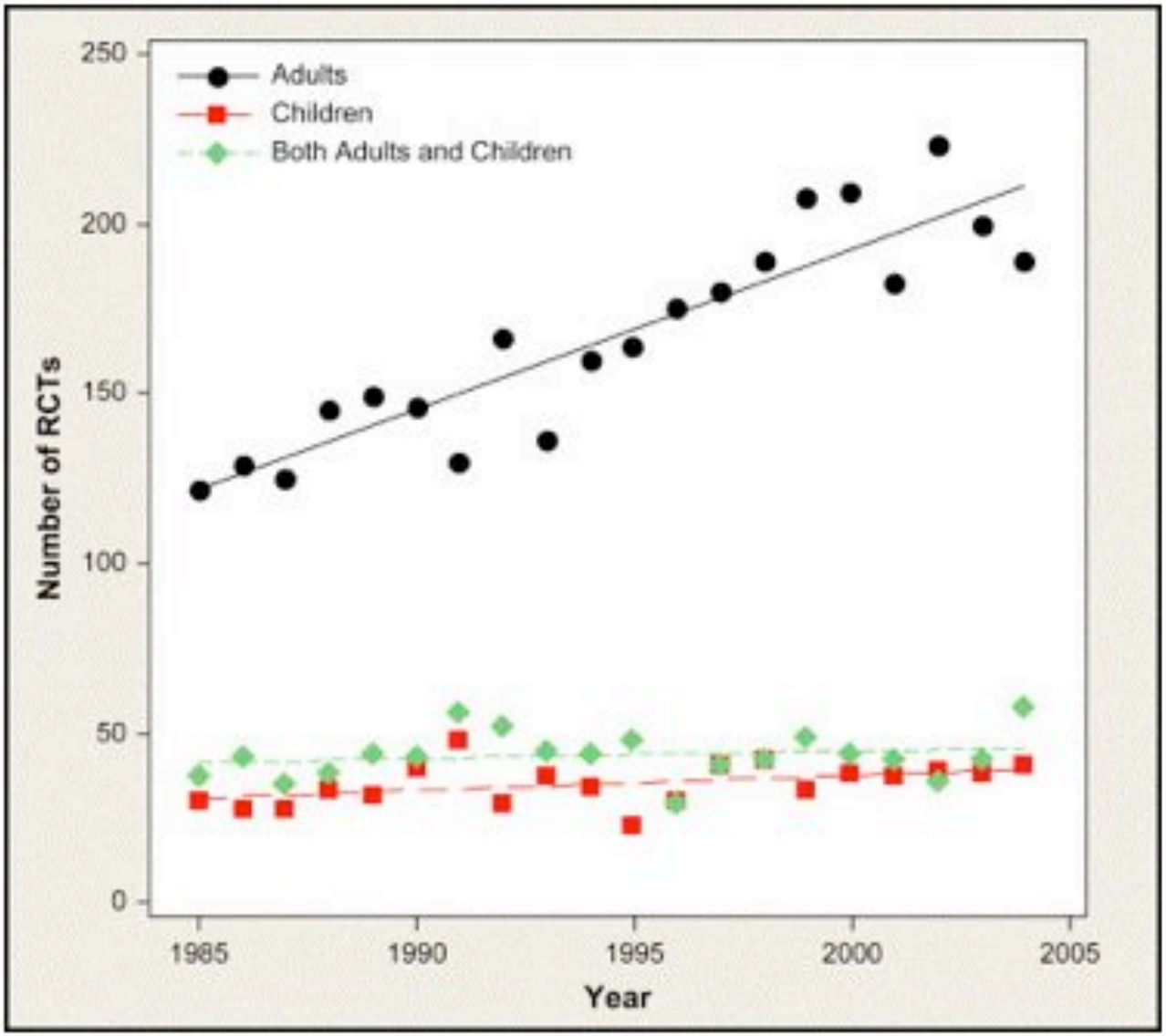


Fig. 2. Trends in publication of RCTs by age in five GMJs 1985–2004.

Cohen et al. J Clin Epidemiol 2007

Why?

STATE-OF-THE-ART REVIEW ARTICLE

State of the Evidence on Acute Asthma Management in Children: A Critical Appraisal of Systematic Reviews

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CONCLUSIONS. The methodologic quality of both the Cochrane and journal reviews on the management of acute asthma in children seems good, with Cochrane reviews being more rigorous. However, their usefulness for clinical practice is hampered by a lack of clear definitions of included populations, clinically important health outcomes, and separate reporting on children in mixed reviews. A major threat to these reviews' validity is the insufficient identification and handling of heterogeneity.

Pediatrics, 2006

Why?

BMC Pediatrics

BioMed Central

Research article

Open Access

Children in reviews: Methodological issues in child-relevant evidence syntheses

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Why?

Abstract

Background: The delivery of optimal medical care to children is dependent on the availability of child relevant research. Our objectives were to: i) systematically review and describe how children are handled in reviews of drug interventions published in the Cochrane Database of Systematic Reviews (CDSR); and ii) determine when effect sizes for the same drug interventions differ between children and adults.

Methods: We systematically identified all of the reviews relevant to child health in the CDSR 2002, Issue 4. Reviews were included if they investigated the efficacy or effectiveness of a drug intervention for a condition that occurs in both children and adults. Information was extracted on review characteristics including study methods, results, and conclusions.

Results: From 1496 systematic reviews, 408 (27%) were identified as relevant to both adult and child health; 52% (213) of these included data from children. No significant differences were found in effect sizes between adults and children for any of the drug interventions or conditions investigated. However, all of the comparisons lacked the power to detect a clinically significant difference and wide confidence intervals suggest important differences cannot be excluded. A large amount of data was unavailable due to inadequate reporting at the trial and systematic review level.

Conclusion: Overall, the findings of this study indicate there is a paucity of child-relevant and specific evidence generated from evidence syntheses of drug interventions. The results indicate a need for a higher standard of reporting for participant populations in studies of drug interventions.

Why?

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Comparative Effectiveness of Medical Interventions in Adults Versus Children

Despina G. Contopoulos-Ioannidis, MD, Maria S. Baltogianni, MD, and John P. A. Ioannidis, MD

Objective To estimate the comparative effectiveness of medical interventions in adults versus children.

Study design We identified from the Cochrane Database of Systematic Reviews (Issue 1, 2007) meta-analyses with data on at least 1 adult and 1 pediatric randomized trial with binary primary efficacy outcome. For each meta-analysis, we calculated the summary odds ratio of the adult trials and the pediatric trials, respectively; the relative odds ratio (ROR) of the adult versus pediatric odds ratios per meta-analysis; and the summary ROR across all meta-analyses. ROR <1 means that the experimental intervention is more unfavorable in children than adults.

Results Across 128 eligible meta-analyses (1051 adult and 343 pediatric trials), the summary ROR did not show a statistically significant difference between adults and children (0.96; 95% confidence intervals, 0.86 to 1.08). However, in all meta-analyses except for 1, the individual ROR's 95% confidence intervals could not exclude a relative difference in efficacy over 20%. In two-thirds, the relative difference in observed point estimates exceeded 50%. Nine statistically significant discrepancies were identified; 4 of them were also clinically important.

Conclusions Treatment effects are on average similar in adults and children, but available evidence leaves large uncertainty about their relative efficacy. Clinically important discrepancies may occur. *(J Pediatr 2010;157:322-30)*.

Reasons for insufficient number of pediatric trials

- Burden of disease relatively small
- Children comprise 20-25% of the population
- Diagnostic criteria difficult
- Outcome measurements difficult
- Ethical considerations
- Commercially less interesting

Why?

OPEN ACCESS Freely available online

PLoS MEDICINE

Perspective

Children Are Not Just Small Adults: The Urgent Need for High-Quality Trial Evidence in Children

Terry P. Klassen*, Lisa Hartling, Jonathan C. Craig, Martin Offringa

Children are often touted as being very important members of society because they represent our future. Optimizing their health outcomes has the potential for a huge impact on public health because children are at an early stage in the life trajectory. But it is often unclear how society allocates its resources or creates policies to ensure that it invests in children's health. The under-investment in pediatric clinical trials is a good example of how our resource allocation may be insufficient.

Over half of the pharmacological interventions we use for hospitalized children are off-label or unlicensed drugs [1,2]. The challenge for clinical care is that health care providers may fail to use medications that are indeed has not been adequately studied, or by medication that has demonstrated differences in pharmacokinetics and pharmacodynamics in children as compared to adults, it has been more difficult to demonstrate significant and important differences in treatment effects between adults and children. In an examination of Cochrane systematic reviews dealing with interventions for diseases occurring in both children and adults, we identified 408 reviews. Only 52% of these included data from children. We could find no significant differences in effect sizes between these two groups, because all of the comparisons lacked statistical power with wide confidence intervals, and hence it was not possible to rule out clinically important differences [3].

Linked Research Article

This Perspective discusses the following new study published in *PLoS Medicine*:

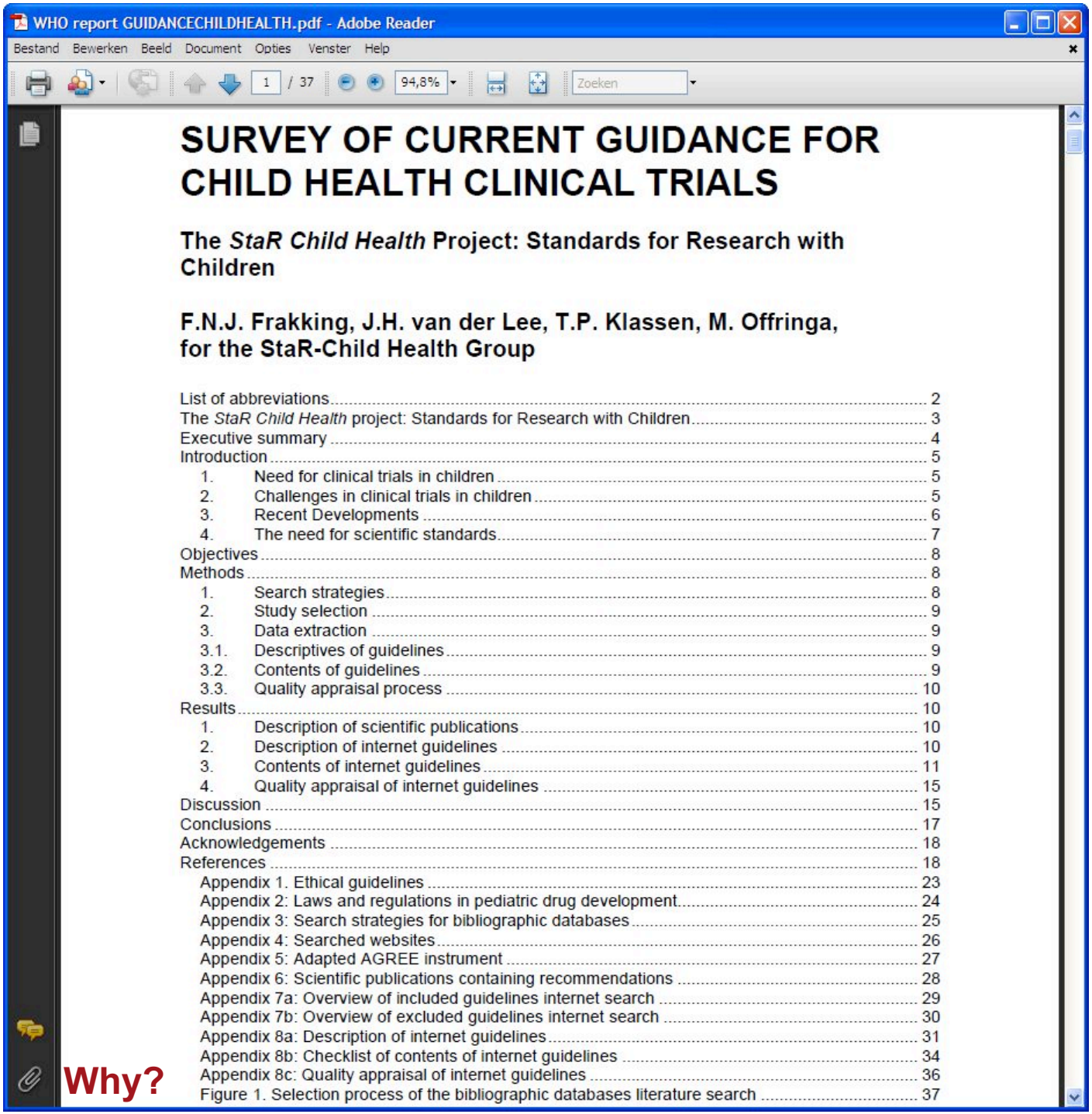
Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P (2008) Greater response to placebo in children than in adults: A systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med 5(8): e166. doi:10.1371/journal.pmed.0050166

In a systematic review of antiepileptic drugs, Philippe Ryvlin and colleagues find that children with drug-resistant partial epilepsy enrolled in trials seem to have a greater response to placebo than adults enrolled in such trials.

Why?

Why StaR Child Health?

- Lack of evidence for decision making
- Profound lack of trials in children
- Those that are performed are of low quality
  - We are left with *Bias* and *Uncertainty*
- Children are at risk of using ineffective medications that are not safe



SURVEY OF CURRENT GUIDANCE FOR CHILD HEALTH CLINICAL TRIALS

The *StaR Child Health* Project: Standards for Research with Children

F.N.J. Frakking, J.H. van der Lee, T.P. Klassen, M. Offringa, for the StaR-Child Health Group

Why?

make medicines child size

Guidance for child health clinical trials

- Methods of research guideline development were poorly described
- Empirical evidence for recommendations was scarce
- Most research guidelines are limited to “what one should aim to do” instead of “how to do it”

Frakking et al. 2009

Why?

StaR Child Health

www.starchildhealth.org

International Forum of Standards for Research in Children

Home

- About StaR Child Health
- Standards
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Welcome to

Standards for Research in Child Health

StaR Child Health is THE resource centre for pediatric clinical research design, conduct, and reporting.

StaR Child Health is a new initiative that seeks to improve the quality of design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards.

Find out how to get involved.

You can follow STaR Child Health on Twitter: http://twitter.com/StaRChildHealth

Last Updated on Friday, 27 August 2010 12:01

STANDARDS

Go directly to the Standards

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Meeting 3-4 Feb. 2011 Standard Development Groups

read more

Who is STaR Child Health ?

- An international group of motivated and informed methodologists, child health care providers, and decision makers
  - Assessing current evidence for guidance
  - Identifying the gaps in knowledge
  - Ensuring that evidence based standards are developed and utilized for research

Stakeholders

- National & International Research networks
- Pharmaceutical companies
- Funders
- EMA / FDA
- Trialists from (Developing) Countries
- WHO
- Medical Journals: Lancet, PLoS, Pediatrics, etc.
- Children and their families

StaR Child Health: an initiative for RCTs in children

With more than 550 000 trial reports on therapeutic interventions in adults available worldwide in the Cochrane central register of controlled trials, is more research required on the same interventions in children or can we extrapolate adult evidence to young people? Accumulating evidence shows that children are not simply little adults, and adapting adult evidence to children can result in ineffective or even unsafe medical care. The growing number of trials in children reflects this imperative to create a child-specific evidence base. StaR Child Health[1] was founded to ensure that this evidence base is methodologically strong and relevant.

About 2500 trials in child health are published every year with a total of 35 000 child-health trials since the first one in 1948.[2] The trials form an important basis for decision making and are often the essential building blocks for systematic reviews. Yet there remain several shortcomings with this existing evidence base for children.

Panel 1: **List of topics for StaR Child Health[10]**

- Adequate sample size
- Data-monitoring committees
- Age-specific doses and administration
- Relevant comparators
- Relevant and standardised outcomes
- Short-term and long-term participants' safety
- Appropriate information for children and families
- Risk of bias
- Trials in developing countries

First, most paediatric trials are at high or unclear risk of bias, yielding underestimates or more often overestimates of treatment effects and creating uncertainty around practice implications.[3] Second, despite the sizeable number of child-health trials, a survey of systematic reviews of randomised controlled trials (RCTs) dealing with interventions of relevance to adults and children showed that in over half of these interventions the effect of the intervention was not studied in children.[4] Furthermore, recent evidence shows that the number of adult RCTs in general medical journals increases at a ten-fold rate compared with paediatric RCTs.[5]

For drug therapy, there is an urgent need to increase the knowledge base in paediatrics. Legislative incentives have been implemented in Europe and the USA to encourage such investment by drug companies,[6] which has led to the establishment of national clinical research networks, such as in the Netherlands and the UK.[7,8]

Motivated by the increased focus on clinical research in children and the stark deficiencies in knowledge about optimum ways to deal with the methodological and practical challenges of research in children, the StaR Child Health initiative was created.[9] The initiative aims to enhance the design, conduct, and reporting of trials in children. The initiative brings together an international group of leading methodologists, clinicians, regulators, funders, and decision makers to systematically identify what is known, create a research agenda when gaps exist, and translate information into practical guidance

What?

Klassen et al, Lancet 2009

Standard Development Groups

- Adequate Sample sizes & Data Monitoring Committees
- Risk of Bias
- Recruitment and Informed Consent
- Relevant and standardised outcomes
- Relevant subgroups
- Age-specific dosages and administration
- Relevant comparators
- Short- and long-term participant's safety
- Special: Implementation of standards for research with children in developing countries

What?

Process

- Teams of experts around the world: high and low income countries
- Assemble and evaluate existing guidance and evidence
- Use consensus when evidence is lacking
- Identify gaps
- Prepare and maintain ***Standard for research with Children***

How?

Future

- Launch a new era in quality of child health clinical research
- Develop standards for research in child health to improve
  - design
  - conduct
  - reporting

  } Of trials with children
- Global Research in Pediatrics

How?

www.starchildhealth.org