

SUMMARY REPORT

CHALLENGES AND THE CONDUCT OF PEDIATRIC CLINICAL TRIALS IN LOW AND MIDDLE INCOME COUNTRIES

September 12, 2010

INTRODUCTION

The satellite meeting of The 2nd StaR Child Health Summit, (<http://starsummit2010.proreg.ca/>) held on September 12, 2010, was organized by the StaR Child Health, the Centre for International Child Health at BC Children's Hospital, and the University of British Columbia. The meeting was chaired by Dr. Stuart MacLeod, Professor of Pediatrics, University of British Columbia. Dr. MacLeod convened this session as a follow-up to two previous meetings. The first meeting, jointly sponsored by WHO and StaR Child Health, was held in Amsterdam on October 28, 2009 with the purpose of discussing the use of standards in pediatric clinical trials in developing countries (http://www.who.int/childmedicines/progress/Amsterdam_Meeting.pdf). A second meeting was then held in Copenhagen July 18, 2010 as a satellite to World Pharma 2010 (http://www.who.int/childmedicines/progress/UNICEF_formulations.pdf).

The September 12 meeting, the third in this series, was designed to continue the dialogue about establishing clinical trials standards for pediatric research in low and middle income countries. Full webcasts of this event can be found at "Challenges in Conduct of Paediatric Clinical Trials in Low and Middle Income settings" [Webcast A](#), [Webcast B](#), [Webcast C](#), [Webcast D](#), [Webcast E](#), [Webcast F](#), [Webcast G](#), [Webcast H](#), [Webcast I](#).

<http://phsa.mediasite.com/mediasite/Viewer/?peid=98604b2f75d7410896790dcfbb0e56b61d>

BACKGROUND

WHO sponsored the Amsterdam meeting in October, 2009 and has expressed continuing interest. Since then additional partners from academia, government, and the private sector have joined this discussion. A list of participants is attached (Appendix A).

MEETING SPONSORS

1. StaR Child Health
2. Child & Family Research Institute/BC Children's Hospital
3. Centre for International Child Health, BC Children's Hospital
4. Canadian Society for Pharmacology and Therapeutics
5. International Federation of Pharmaceutical Manufacturers' Association (IFPMA)
6. Canada's Research-Based Pharmaceutical Companies (Rx&D)
7. Maternal Infant Child & Youth Research Network of Canada (MICYRN)

MEETING OBJECTIVES

The objectives were designed to begin a broader discussion about the following agenda items. To further development of consensus guidelines on critical ethical issues in child health research:

1. To explore a charter to include; a code of conduct, a statement of patient rights, and agreement on community roles and responsibilities in child health clinical trials
2. To describe a process to improve the framework for pediatric trials in low and middle income countries
3. To discuss needs in training, skills development and capacity building
4. To define knowledge translation and exploitation (KTE) strategies
5. To better define the role of WHO in this continuing discussion

Due to the complexity of the issues it was recognized that it would not be possible to have an exhaustive discussion and meet all of the stated objectives in this one session.

ETHICAL ISSUES, STANDARDS OF INFORMED CONSENT, CODE OF CONDUCT, CONFLICT OF INTEREST

Presenters: Dr. Robert Nelson (Office of Pediatric Therapeutics, US FDA); Dr. Denise Avaré, Centre of Genomics & Policy, McGill University); Dr. Gitanjali Batmanabane (WHO, SEARO, New Delhi, India)

1 Dr. Nelson talked about three overarching themes relating to biomedical research, namely vulnerability, voluntary choice, and exploitation.

Most subjects in child health research projects have a diminished capacity to protect their own interests and therefore their ability to grant consent is ineffective. When talking about consent what added protections are added for children? including such questions as do parents need to protect? and what are the obligations of parents? and can a parent act as a proxy with respect to consent? The opinion of the speaker is that we need to protect children from non evidence-based interventions through research and development efforts.

a. Based on work done by Kenneth Kipnis (2003) Dr. Nelson described 7 types of vulnerability:

- i. Incapacitational (diminished legal competence)
- ii. Juridic (objective)
- iii. Deferential (subjective)
- iv. Social (attitudinal vulnerability that may hinder review and diminish protections)
- v. Situational (eg. emergency interventions where consent or assent may be impossible or invalid)
- vi. Medical (options may be limited)
- vii. Allocational (eg. varied ability to access care)

- b. **Voluntary Choice.** There should not be an undue influence or coercion involved in the choice of treatments, although forced choices do not always annul consent. The choice is still valid provided that it is not controlled by others. Even voluntary choices may be based on therapeutic misconceptions such as the assumption that any research intervention necessarily represents effective treatment. Patients and families may often have unreasonable expectations and these may not always be discouraged by the investigator. It should be noted that a patient (family) may make a voluntary choice but still be exploited.

- c. **Exploitation.** The central question should be whether or not the treatment offered represents a "good deal for everyone everywhere." There should be a focus on justice and determination of whether or not the intervention represents "fair" and "just" treatment of research subjects. Justice should be built into the protocol design. There should be access to the studied intervention provided through the healthcare system after the trial is complete. National authorities have a parallel duty to ensure compliance with good clinical practice, to provide adequate healthcare supports, and to offer oversight of any contracting processes. Research protocols need to be designed so that the risks are appropriate to the context and based on input from the country or countries in which the research is to be conducted. In order to avoid exploitation we need to attempt to build capacity in both the intervention and the control arms of the study. In low and middle income countries, the care provided needs to become closer to the general standard of care expected in developed countries. Simultaneously, while we are building research and development capacity in lower and middle income countries, ideally we should also be building capacity in the health care delivery system. The protocols need to be structured to ensure that participation in the research and development activity is a fair deal and a rational choice. Although we need data to make sound decisions it is paramount that an ethical approach be sensitive to the context and the environment where research will be undertaken and findings applied. There are also new technologies available, such as videos and talking books that may support obtaining informed consent in low literacy populations.

2 Dr. Batmanabane discussed some of the challenges faced by her colleagues working in Chattisgarh, India. The approach to informed consent within a clinical trial may be very difficult in a highly stressed healthcare system in which the length of the patient- physician contact may be extremely brief. This factor may compromise full assessment of risk and benefit, and will certainly limit communication with patients.

The ethics committees in some institutions may lack the knowledge and skills required to process clinical trial applications. Children are generally seen as a group with diminished autonomy and, in Indian centres, clinical trials in children are often rejected even if scientifically

sound, ethically acceptable, and addressing an issue which has important practice implications. Improved training is the prime way to support members of the ethics committees.

Furthermore, the pool of investigators is sometimes small. Investigators often double up as members of ethics or scientific committees and it is not uncommon for a person to review the protocol submitted by his/her teacher or superior. This situation may result in conflicts of interest between the members of ethics committees and the investigators.

Apart from regulatory trials, there are numerous studies (some are clinical trials) conducted in children as a part of the training for the medical postgraduate paediatrics program. Many such studies are repetitive and not necessarily scientifically sound or well vetted. There is potential for children to be unnecessarily exposed to risk (including radiological risks) in association with testing undertaken for the sake of completing a curriculum requirement.

Even though the national public health services may not be providing the approved and accepted treatment for a particular condition; when conducting clinical trials, the best accepted practice in a particular region should be used as a control. For example, in remote villages, the primary health centre may not have a stock of Oral Rehydration Salts (ORS) on hand for the treatment of diarrhoea. This situation should not result in a clinical trial of an anti-diarrhoeal medication being conducted in that village using placebo as a control group.

Issues such as getting assent from children are alien to eastern culture. Children are "expected" to agree to decisions taken by parents on their behalf. Hence getting assent may not be perceived as necessary by parents and even by investigators. Within some developing country settings, there may also be issues in the consent process associated with hierarchy of roles and responsibilities. Some senior clinicians may not fully understand their responsibility to inform patients and families and to accept independent review of research protocols.

The Clinical Trial Registry of India has now been in place since 2007. Approximately 100 clinical trials in children have been registered, however, the quality of information is often poor. The records do not necessarily get updated by the investigators and there is a need to have a monitoring system in place to assist investigators to complete the details required for the registry. A more robust Registry is in place in Sri Lanka and might provide a suitable template for adoption in India.

3 Dr. Denise Avard stated that there are both supra and micro analyses attached to the consent process. The aforementioned includes issues pertaining to appropriate standards, community of interest, degree of involvement of the public, variability in the guidelines, standards for sharing data, capacity building, access to health care services, and distinctions between public health and clinical trial research. The micro process is concerned with the quality of the consent, assent, and waiver process. The speaker pointed out that consent is a process and advised against complex consent forms that may in fact set up increasing barriers including an increase in cost. With all of the above it is necessary to consider the different developmental stages, not just a 0 to 18 years single continuum.

Dr. Avaré provided a Canadian document under development titled, "Children and Youth Research: Building Best Practices". The full document, titled "Best Practices for Research Involving Children and Adolescents: Genetic, Pharmaceutical, Longitudinal, and Palliative Care Research" can be accessed at (www.pediagen.org/resources/BestPractices.pdf).

The authors describe the best practices document as being composed of ten main guidelines to be considered by both researchers when designing research involving children and/or adolescents, and by REBs in the specific areas of genetic research, pharmaceutical research, longitudinal and palliative care research. Many of the guidelines should be viewed as interdependent.

While it is generally agreed that a code of conduct is needed to govern clinical trials in poor resource settings, the difficulty in achieving agreement on such a code is also understood. Any code of conduct must be in accord with local values in health professional practice.

All speakers emphasized the importance of capacity building for individuals serving on research ethics boards. This could include the development of a standardized curriculum for training of research ethics reviewers in a variety of settings. The importance of harmonized ethics frameworks was also highlighted.

TRIAL DESIGN CHALLENGES

Four speakers (Drs. Goldsmith, Simon Fraser University, Vancouver; Collet, Child and Family Research Institute, Vancouver; Ansermino, Child and Family Research Institute, Vancouver; and Wiens, School of Population and Public Health, Vancouver) presented case studies relating to their experience with clinical trials in developing country settings.

1 Dr. Goldsmith addressed issues pertaining to experimental design and, in particular, the difficulty in comparing active interventions with placebo. He made the case for comparison of new treatments with the next best alternative. In addition to arriving at an appropriate sample size, investigators should design studies that take context into consideration. The choices to be made amongst different outcome measurements should be made explicit in the study proposal. Dr. Goldsmith talked about the importance of studying quality improvement measures. In his view, this objective is preferable to studies of efficacy since clinicians usually know what is efficacious; however, there is often a gap between what is known and what is done in practice. Dr. Goldsmith stressed the importance of improving the ability to monitor studies and to develop strategies that will support organizations attempting to make a cultural shift in practice.

2 Dr. Collet reported on his experience with research studies in China. He described challenges related to poor documentation of events including adverse effects. The clinical trial environment in China often lacks standardized processes and templates to be used for data collection. Quality control procedures are frequently inadequate in the clinical trial setting, and there is limited infrastructure for research and inconsistency in following GCP guidelines. Dr. Collet pointed out that there are sometimes problems related to the separation in China

between Faculties of Medicine and Schools of Public Health. Improvements in medical care must be coordinated with changes in public health policy.

3 Dr. Mark Ansermino has been working on the development of a new technology, wireless pulse oximetry, for use in developing countries. This technology once developed will provide a means for assessing very sick children in environments where no secondary or tertiary medical care is available. The ability to measure and interpret oxygen levels and other indicators of cardiovascular performance at a distance will facilitate decision making about transfer of children to higher levels of care. Dr. Ansermino reviewed the types of cell phone technology available and spoke to the issues that must be addressed in moving this concept to the implementation stage.

4 Dr. Matt Wiens presented a pilot study on the measurement of adherence with anti-retroviral therapy by adolescent patients in Uganda. He employed an eCAP technology to explore the feasibility of conducting longterm adherence monitoring in a developing country. Thirty teenagers were followed for one year and Dr. Wiens was able to demonstrate that the eCAP technology is much more accurate than self-reported compliance or compliance measured by pill counts. His results demonstrated somewhat surprisingly that overall adherence was good even in what may be considered a population at high risk for non-compliance. There was agreement that further work on adherence measurement procedures is justified and that the eCAP technology shows promise for application even in low resource settings.

KNOWLEDGE TRANSLATION AND EXPLOITATION

Dr. Terry Klassen (Manitoba Institute of Child Health, Winnipeg) spoke to the importance of a carefully planned knowledge translation strategy in seeing that the promising results from clinical research are implemented in the form of practice change that will improve health outcomes. He described the Iterative Figure 8 KT loop as published by Dr. Hartling in *Academic Emergency Medicine* (2007, pps 968-977). The critically important knowledge translation loop takes evidence generated through clinical research and puts it through a sequence of exploring barriers to implementation, studying effectiveness, and promoting widespread dissemination. Dr. Klassen emphasized that the knowledge translation activity must itself be evaluated. He also pointed out that Dr. Hartling and her colleagues have further refined their earlier work and are now recommending a third component characterized as a prioritization and accountability loop (L. Hartling et al, *Economic Evaluation in Child Health*, editor W. Ungar, Oxford University Press, 2010). Dr. Klassen emphasized that patients and families should be seen as the main beneficiaries of the knowledge translation process, and they are placed at the centre of the latest Hartling knowledge translation model (See Appendix B).

Dr. Klassen stressed the problems associated with evaluating the impact of complementary interventions, several of which may be introduced simultaneously. He also acknowledged some of the real world impediments to assessing clinical effectiveness such as poor compliance with prescribed treatments. He indicated that StaR Child Health will continue to emphasize knowledge translation (KT) as a central objective and logical conclusion to all efforts of the improvement of clinical trial methodology.

NETWORKS IN PEDIATRIC CLINICAL TRIALS

Dr. Anne Junker (Child & Family Research Institute, Vancouver) spoke of recent efforts in Canada to develop networks to support optimal clinical trials methods. She emphasized the need to develop higher levels of standardization driving the clinical research enterprise. Dr. Junker described the success over the last three years in bringing together 17 Canadian pediatric centres into the Maternal, Infant, Child and Youth Research Network (<http://www.micyrn.ca/>).

The main issues facing child health research networks are related to: data management, finances, information technology, governance, operations, recruitment/retention, training, mentoring, and professional development. Dr. Junker stressed the existence of opportunities for greater links with pharmaceutical companies and other industry partners (eg. biotechnology companies) as well as with other international networks with complementary interests.

In the following discussion, it was noted that other countries have excellent functioning networks, such as The Medicines for Children Network in the Netherlands (http://www.mcrn.nl/index.php?option=com_content&view=article&id=3&Itemid=2) and the Pediatric Rheumatology International Trials Organization (PRINTO) based in Italy. PRINTO is a non-governmental international network founded by Alberto Martini and Nicolino Roperto in 1996, and initially included 14 European countries. It has now expanded to include 47 countries and more than 200 centres worldwide with a goal of fostering and coordinating the development of multi-center international clinical trials. In many ways, PRINTO would be an appropriate model for broader development of clinical research networks (http://www.printo.it/what_is.asp). Other examples of pediatric research networks are the German Paediatric Research Network (<http://www.paed-net.org/>) and The National Institute for Health Research Medicines for Children Research Network (<http://www.mcrn.org.uk/>).

A recent network beginning with its nucleus within the European Community is being funded under the 7th Framework Programme for Research (http://europa.eu/legislation_summaries/research_innovation/general_framework/i23022_en.htm). The funded network, Global Research in Pediatrics (GRIP), has a stated intention of developing an international training program with a standardized curriculum and has already reached out to colleagues in the United States, Canada and Japan with plans to develop a program for training of researchers from developing countries.

RECOMMENDATIONS

1. All participants agreed that the primary focus of clinical research in child health should be placed on addressing the gap between what we know and what we should do to improve child health outcomes. We must get to the essence of this challenge which is how best to disseminate evidence and research findings to bring about practice change.

2. It is recommended that WHO consider the development of an international asset map describing clinical research capacity worldwide. This could be part of a broader survey of the international environment for child health research collaboration.
3. Training/Mentoring. It is clear that the human resource base for the conduct of frontline child health research in low and middle income countries is inadequate. Investigators from developed countries must find ways of supporting the development of basic professional and research skills internationally. The program now proposed by the GRIP network may be a good model in this regard. Participants also reminded us of the earlier model provided by the International Clinical Epidemiology Network (INCLEN)(<http://www.inclen.org/0>) that successfully trained mid-career professionals from almost 30 developing country institutions in the period 1980 - 2000. Many former INCLEN fellows are now established clinical trialists.
4. Consideration should be given to exploring the potential of the clinical research training sabbaticals offered through the USA National Institutes of Health Clinical Center (<http://clinicalcenter.nih.gov/training/sabbatical/index.html>). This is open to international participants and fees are not charged but there would need to be funds to support travel and living costs of participants from resource-poor countries. Another possibility would be development of a clinical investigators' training institute that might operate internationally, and was specifically designed to address the situations more prevalent in resource-poor countries. The institute would support curriculum development, and provide other training resources through which investigators in low and middle income countries might be coached about pediatric trials. The institute would also contribute to the development of ethics standards suitable for use in an international template.
5. An integrated approach to the development of optimal drug therapies for children should be fostered. It is important to include interested investigators from a number of disciplines including pharmacy, nursing, and medicine. It is also important to include those with an interest in improved childhood therapy from a regulatory approach. Participants were reminded that international regulators with an interest in child health had met in Berne, Switzerland in 2008 and again more recently in Geneva in March, 2010. It was felt that involvement of regulators will serve to bring together investigators, research ethicists, and institutional review expertise. Centralized review of child health research studies would be advantageous. The International Conference of Drug Regulatory Authorities (ICDRA) should be encouraged with their current initiatives. It is important to establish new momentum that builds on the work in the 1990's on ICH E 11 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf).
6. There should be a shared understanding developed about principles and strategies for community engagement in studies that involve infants, young children and youth.
7. There is a need for new approach to partnerships. This would include matching institutions in developed countries with those in low income countries in order to

encourage capacity building. A change in mindset from a paternalistic to collaborative approach is necessary on the part of developed country institutions. There is potential for funding support from the private sector and from foundations and international philanthropies such as the Rockefeller Foundation, Wellcome Trust, and the Bill and Melinda Gates Foundation. It is agreed that WHO must play a critical role in providing global coordination for child health research that is properly prioritized.

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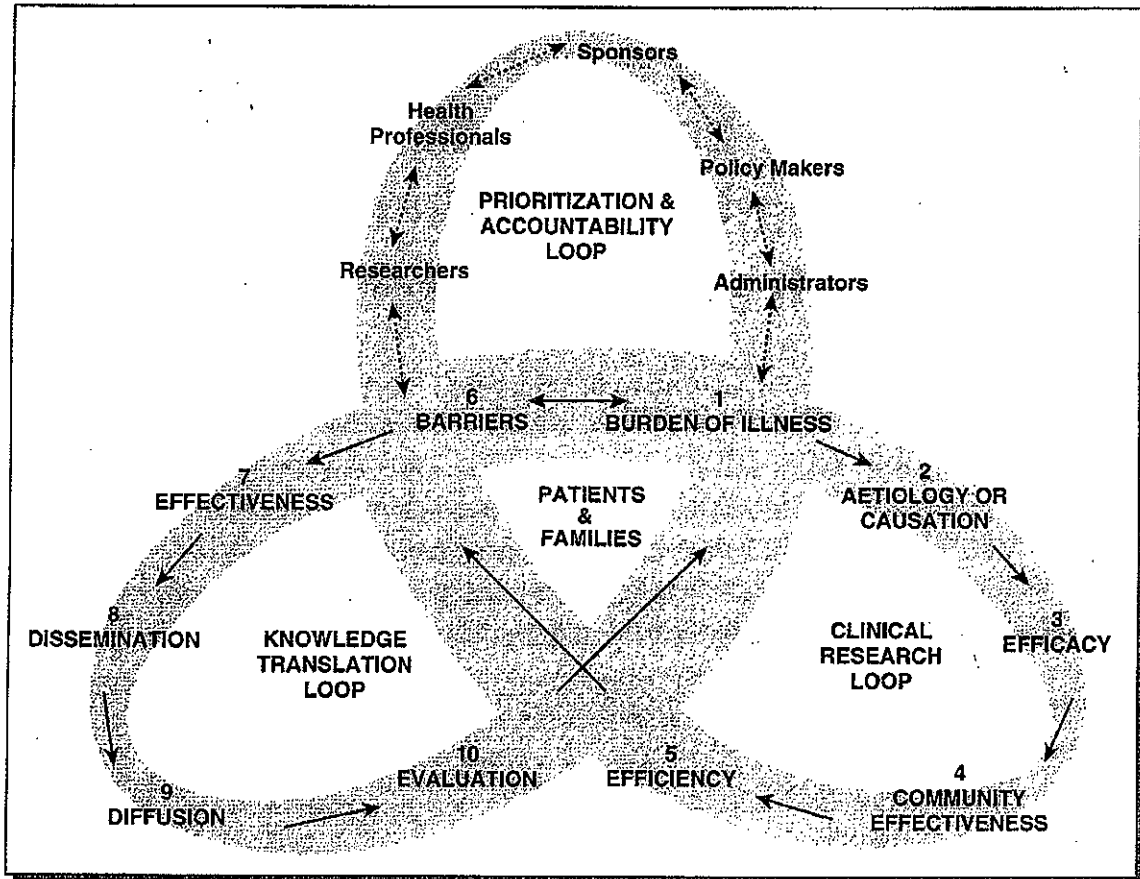


Fig. 14.1 Conceptual framework for generation and application of research in evidence-based decision-making.

LEGEND: (1) BURDEN OF ILLNESS: Determine health status using health status indicators; (2) AETIOLOGY OR CAUSATION: Identify and assess possible causes of burden of illness; (3) EFFICACY: Identify gaps in evidence through systematic reviews; evaluate treatment options through RCTs; (4) COMMUNITY EFFECTIVENESS: Assess benefit/harm ratio of potentially feasible interventions and estimate reduction of burden; (5) EFFICIENCY: Determine relationships between costs and effects of treatment options; (6) BARRIERS: Assess barriers to knowledge transfer/uptake; (7) EFFECTIVENESS: Identify gaps in KT evidence through systematic reviews; evaluate KT methods through cluster RCTs; (8) DISSEMINATION: Widespread dissemination of clinical and KT findings; (9) DIFFUSION: Natural diffusion of research in the 'real world' (non-research settings); (10) EVALUATION: Assess outcomes in 'real world'. RCT: randomized controlled trial; KT: knowledge translation.

Adapted from Hartling *et al.* [1].