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Meeting Report

WHO and StaR Child Health

Use of Standards in Paediatric Clinical Trials in Developing Countries Meeting

Amsterdam, The Netherlands

28 October 2009

This publication contains the Report of the WHO and StaR Child Health Paediatric Trials in Developing Countries Meeting and does not necessarily represent the decisions or policies of the World Health Organization

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Executive summary

In a one day meeting in Amsterdam various different aspects of current child health trials in developing countries were discussed. The quality of pediatric clinical trials in low and middle income countries can and should be improved in many aspects. There are question about how to give appropriate information to children and families, and on how to improve the informed consent and assent process. Data Safety Monitoring Boards are missing in many trials, or do not have specific expertise on pediatric trials. There is an urgent need for trained researchers on the ground. Funding for non-industrial studies and coercion from industry are a problem. Roles of local regulatory authority can be improved. Post-marketing strategies are lacking.

As regulators demand specific rules for pediatric clinical trials in a paediatric investigation plan and for post-marketing safety plans, scientific standards are needed, to minimize the risk of failed trials, to improve the provided research-information and to guarantee participants' safety. Trial registration of all child health trials is needed in order to have an overview of trials with children and to monitor publication of trial results.

The key recommended next steps from the group were:

- to develop strategies to improve reporting of paediatric clinical trials;
- to further develop standards for cluster randomized trials relevant and community participation in study design to ensure optimal results in studies of child health issues;
- to develop a knowledge translation and implementation strategy so that current standards for methodological aspects of trial design (e.g. considering risk of bias reduction) are implemented by all researchers;
- to develop guidance (a 'code of conduct' for research involving children for Industry and researchers that can be applied particularly in low and middle income country settings.

Suggestion on how these recommendations should be carried out are described in detail in the report.

Meeting background

StaR Child Health is a group of methodologists, clinicians and policy makers seeking to enhance the quality, ethics and reliability of pediatric clinical research by promoting the use of evidence-based standards or guidance for clinical studies with children. A recent systematic review of the current guidance for child health clinical trials[1] identified the need for the development of readily accessible, clear guidelines on how to design, conduct and report clinical drug trials in children in a scientifically and ethical way. The reviewers recommended that to enhance their acceptance, these guidelines should be developed using transparent methods with input from investigators, regulators, WHO and the pharmaceutical industry. This meeting was convened in conjunction with WHO in order to discuss the challenges of conducting clinical trials in children in low and middle income settings and to identify potential ways to move the research agenda forwards to facilitate an increase in the quantity and quality of relevant clinical trials in children in all settings.

Improving child health is a global health priority. The global mortality rate in children under five years remains a significant and inequitable problem. Medicines for children have long been a neglected area. The World Health Organization stipulates that children should be given medicines that have been appropriately evaluated for their use in paediatric populations, since the pharmacokinetics and pharmacodynamics of drugs in children are known to differ from those of adults. Most medicines for use in children were originally developed for adults, with little or no research performed specifically in paediatric populations. At the present time between 50 and 90% of daily prescriptions for sick children use "off label" medicines that have not been tested for safety and efficacy in this population[2]. The lack of data on the optimum target dose and therapeutic dose range for paediatric medicines and the unavailability of appropriate paediatric dosage forms result in children frequently being prescribed medicine doses that are inappropriate for their needs. To address this issue new legislation and incentives have recently been introduced by the European Union and United States of America Regulatory Agencies to encourage the pharmaceutical industry to investigate the pharmacological efficacy and safety of both new and existing medicines in children. These recent initiatives are expected to result in an increase in the number of paediatric clinical trials being undertaken in both developed and developing country settings. It is important that these clinical trials are of a high standard and relevant to the needs of the local pediatric population in different settings.

1 Frakking FN. et al. 2009. Survey of current guidance for child health clinical trials. The StaR Child Health Project: Standards for Research with Children. **Available at: http://www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf**

2 Pandolfini C. et al. 2005. A literature review on off-label drug use in children. European Journal of Pediatrics. 164(9): 552-558.

The meeting was opened by Louise Gunning, CEO of the Academic Medical Centre, Amsterdam. The need to raise awareness in the scientific arena to raise standards and quality of clinical trials in children was highlighted as a necessary and important endeavour. It was stated that the paediatric scientific community have a responsibility to help people make the right choices with regards to undertaking relevant research in children and using available funds for research appropriately and effectively.

Meeting objective

The objective of the meeting was to reach a consensus on the next steps for the promotion of quality research in children.

Summary of meeting discussions

The following presentations were made (copies of slides are available on request):

Professor H.P.S. Sachdev (India):
Carrying out research studies in children in low resource settings: current issues and problems

Professor Anita Zaidi (Pakistan):
Issues in clinical research on children in developing countries

Dr Martin Meremikwu (Nigeria):
Current issues and problems with carrying out research studies in children in a low resource setting

Dr Elizabeta. Zisovka (Macedonia):
Use of standards in trials in developing countries: perspective from middle income countries

Dr Yi Xiao Bao (China):
Clinical trials in children in China

Dr Gerard Goldfarb (IFPMA Pediatric Task Force):
Use of standards in pediatric trials in developing countries: Industry perspective and experience

Dr Martin Offringa (StaR Child Health):
Strategies to improve research: the role of scientific standards

Dr Skip Nelson (FDA) and Dr Agnes St Raymond (EMEA):
Strategies to improve research: the role of regulators

Dr Davina Ghersi (WHO):
Strategies to improve research: the role of clinical trial registration

Perspective and experiences from low income settings

In India there has been an increase in legislation as the regulatory processes and capacity have developed. However, at the present time the regulatory process is not oriented to children and there is a long lead time to get regulatory approval for research studies. There are many issues surrounding group (community) consent and individual consent and assent. At the community level it is not clear who is the most appropriate representative to provide consent for participation of the local community in a trial. The options range from local government, local leaders, small community groups to stakeholders and organizations working in the area. The need for alternatives to written consent at the community level was highlighted due to the presence of illiterate populations in low income settings. It was reported that obtaining consent and maintaining confidentiality for children taking part in trials was difficult due to extended family involvement and that the international community must be realistic about what constitutes inducement to take part in a trial. In many low resource settings, families are so poor that in order to maintain adequate follow-up in trials, the costs of taking part in a trial may need to be covered. Clear guidance needs to be developed to ensure exploitation of vulnerable populations does not occur. There was a call to make ICH guidelines simpler, so that general principles were described instead of dictating specifics which may not be attainable or appropriate in low resource settings. At the present time the main issues identified were the lack of capacity and dearth of expertise for undertaking paediatric research and confusion regarding stopping rules and plans for data analysis.

In Sri Lanka: 95% of adult trials are industry sponsored and there is pressure from senior academics for the Sri Lankan Drug Regulatory Authority to pass protocols for trials. Clinical Trials in children are not yet taking place in Sri Lanka and so it would be useful and timely to have new guidance for standards in clinical trials for children and a chance to build regulatory capacity ahead of possible proposals for clinical trials in children in Sri Lanka. In Pakistan, as well as low income countries, there is an increasing focus on the neonatal period and delivery of interventions at the community level. Many births take place at home and therefore neonates are not often assessable for inclusion in facility based trials. There is a need for the development of Good Clinical Practice (GCP) standards for home based interventions/trials. The issue of the most appropriate study design for a trial was raised. It was reported that in many resource poor countries pharmaceutical industry representatives directly approach academics and clinicians to participate in clinical trials in both adults and children and that the resultant trials are often only open label or observational studies.

In Nigeria, due to the collapse of the research infrastructure following the war, the only way of getting money for research was through industry. In recent years, research capacity has been improved via collaboration with WHO and the European and Developing Countries Clinical Trials Partnership (EDCTP). The regulatory process is getting stronger and a National Agency for Food and Drug Administration and Control (NAFDAC) has been constituted. There is a national Institutional Review Board (IRB) and national guidelines for ethical conduct exist. However, there is still a lack of awareness among local researchers for the need to obtain IRB approval. Industry led research is now conforming to GCP standards and their research is reported to be of a higher standard than some of the research undertaken by academics alone.

The lack of equipment for undertaking research in low income settings was highlighted. There is often no budget line in grant proposals for covering the costs of buying and maintaining essential equipment and resources required for running a clinical trial. Internet access, is often very expensive. Industry is an obvious source to provide funding for equipment for undertaking research and during industry sponsored trials they will often provide the required equipment for clinical trials. However, there are issues regarding conflict of interest and GCP guidelines are very strict about relationships with industry. In Malawi, it was reported that improvement in the regulatory authority made a major improvement to the standards of clinical research being undertaken in the country and also gave local ownership to the research.

Discussion

The discussion centered around the need for capacity building at both the regulatory and clinical level to ensure that research undertaken in these setting is ethical and relevant to the local paediatric population. In resource poor settings most of the research is done by regular clinicians. There is lack of human resource capacity to have separate roles for clinicians and trialists. There is often no dedicated staff for research and there is competition with non-governmental organizations (NGOs) for experienced/trained staff; with reports of attrition of staff, because NGOs pay better. It was highlighted that international standards for undertaking clinical trials in children need to be adaptable to the local context. It was reported that in many resource poor countries pharmaceutical industry representatives directly approach academics and clinicians to participate in clinical trials in both adults and children and that the resultant trials are often only open label or observational studies. It was reported that in some low resource settings the majority of clinical trials being undertaken are Industry sponsored trials and there are concerns that some doctors are being coerced into recruiting patients for these trials. The recruiting doctor will be given money for each patient recruited and the patient will get free treatment. Often these approaches by Industry are done privately and do not go through

IRB/regulatory approval. Regarding consent, there were a lot of open questions concerning the consent procedure: when to sign the consent; before or after the randomization? Signed at home or in the clinic? Must it be signed by one or both parents? At which age is a child able to sign the consent for itself? There was also a call for the development of further guidance regarding the appropriate consent procedures for cluster RCTs.

Needs identified:

- Regulatory and clinical research capacity building, including infrastructure and collaborating networks.
- Regulatory guidance for Institutional Review Boards in order to ensure high quality and relevant research is undertaken in paediatric populations in low resource settings.
- Guidance on suitable alternatives to written consent at community level, due to presence of illiterate populations in many resource poor settings and guidance for obtaining consent for participation in cluster randomized controlled trials.
- Explore ways in which Industry and Researchers can work together in a positive way. It was suggested that money from industry could be used to develop local capacity for relevant paediatric research.
- Guidance for the design and implementation of Cluster Randomized Controlled Trials.
- Development of a proactive research agenda. The questions addressed by industry are not necessarily the right questions for improving clinical practice and population health.
- Development of standards for Industry sponsored trials in low income settings to address the issue of incentives/coercion.

Perspective and experiences from middle income settings

In Macedonia there has been knowledge translation regarding what elements should be included in informed consent and assent, such as the provision of information, understanding of both parents and patients and that ethical standards should be no less than other European Union (EU) members. Out of 36 clinical trials reported for approval in Macedonia, only 3 have been designed specifically for children (enrolment age range of 2-17 years). All 3 trials were part of a multi-centre trial from the EU. It was highlighted that there was a general lack of research in the neonates and that many products go "off-label" before getting studied in this population. It was reported that funding is required for developing clinical research in Eastern

European countries. Capacity building for recruitment and conduct of clinical research and support for drug monitoring committees is required.

In China, there are about 3500 drugs, however almost nothing is registered and <2% have a child dosage formulation and there are few manufacturers of children's medicines. The infrastructure for research is being established through the training of investigators, setting up ethics committees and quality control mechanisms. There are however on-going issues with the relative lack of experience of investigators, monitoring capacity and statistics specialists and some institutional conditions need to be improved. In order to be able to undertake clinical trials hospitals have to apply for a certificate from the Chinese Food and Drug Administration (SFDA). However, this process involves training and education and it can take 2-4 years to get approval for certification. At the present time there are no special regulations for clinical trials in children and no special clinical research network exists. There has been co-operation with high income countries to take part in multi-centre trials. Most of the trials being undertaken are industry led.

Discussion

The discussion centered on how to develop a network for undertaking clinical trials in children in middle income countries and the development of model regulations for "risk" with regards to how much risk should a child be exposed to. There was a request to develop a training course for investigators which would include an examination and review process for building investigator capacity. It was highlighted that capacity building was not just doing GCP, but was about getting the right trials in the right place and would be a great opportunity for clinical trial network development.

Needs identified:

- Guidance on how to develop a research network.
- Development of model regulations for "risk" assessment (How much risk should a child be exposed to?).
- Development of a training course for investigators.

Industry perspective and experience

Industry is requesting the development of precise guidelines for conducting research in developing countries.

At the present time there are approximately 30000 on-going trials worldwide, with around 30% enrolling children. There are a low number of studies involving children in developing countries. Changes in regulations, such as the introduction of Paediatric investigation Plans (PIP) by the EMEA and increased awareness regarding the need for clinical trials in children will lead to an increase in the number of trials being undertaken.

Discussion

The discussion focused on how to facilitate a network between industry and research organizations and the need to establish a forum for discussion between industry and researchers/countries for capacity development. It was highlighted that tools for the code of conduct regarding marketing already exist (e.g. UK, USA) and that these need to be reviewed with regards to their applicability/adaptability to low and middle income settings. Industry expressed an interest to partner with WHO and researchers to develop research capacity.

Needs identified:

1. **Ethical**
   - Informed consent should be detailed in protocol. Process of informed consent should be documented. How it was obtained, from whom, consent/assent etc. Document and be transparent about practice and process.
   - There should be dual review of protocol (developed and developing countries) - no precise rule. Open issues: timing: parallel or sequential left to choice of sponsor. Harmonized standard for IRB would be useful. Transparency of process should be described.
   - Investigators: industry plays a role in GCP, investigators need GCP training. Industry can assist with building capacity.
   - Data safety monitoring board (DSMB): inclusion of members from host country or with expertise in the developing world. Justification should be given for not using DSMB.
   - Ethical Committees are instrumental, but not all are experienced with paediatric trials.
   - Industry should use same fundamental ethical and scientific standard.

2. **Post-study commitments.**
   - study must benefit patients and community. Open label extension until product made available locally.
   - must be detailed prior to the start of the study.

3. **Other**
   - Standard of care: need for a harmonized definition.
   - Further clarification/guidelines for paediatric clinical trials are warranted.
   - Industry has a role to play in building capacity.

Strategies to improve research

A) The role of scientific standards

Discussion

In developing countries the tools and environment for research are different, but the rights and needs of children are the same. There is a need to have rigorous research standards in place order to minimize risk for participants. It is necessary to develop an iterative process for preparing, appraisal and field testing of Standards for Research with Children. There is a need for the engagement of journals of affiliated professional associations and the International Paediatric Association (IPA), the main developing country professional umbrella association for the dissemination and uptake of standards for clinical research.

Needs identified:

- Create a larger platform for information dissemination: beyond journals and professional associations.
- Work towards an agreement between journals to make information on Standards for Research with Children available simultaneously, e.g. like what has happened for CONSORT.
- Identify the best ways of disseminating information to developing countries.

B) The role of regulators

Discussion

The scope of FDA is product development and not implementation of research of a global perspective. There may be some opportunity to offer pro bono work of FDA reviewers to regulatory authorities in low and middle income countries. Their scientific expertise could also be utilized to help design relevant trials for global initiatives. There is a need to build regulatory and scientific review capacity and to

develop a network of regulatory authorities sp that direct communication between regulatory authorities regarding clinical trials for children can take place.

The EMEA can exchange expertise in analysing data and offer training. Outline for training programme to help build capacity for paediatric trials. Set up interactive training programme (EMEA). Streamline standards for paediatric formulations. In order to raise the standard of reporting of clinical trials undertaken in children, the need to adapt/revise the CONSORT statement specifically for children was identified. The development of paediatric formulations needs to be prioritized.

Needs identified:

- Strategies for using regulatory expertise for pro-bono work.
- Develop a network of regulatory authorities so that there can be direct communication between regulatory authorities regarding clinical trials for children.
- Adaption/revision of CONSORT statement for children.
- Prioritization of the development of paediatric formulations.

C) The role of clinical trial registration

Discussion

The WHO International Clinical Trials Registry Platform is a country led initiative and involves a search portal through which affiliated clinical trial registries can be searched. WHO also supports countries to develop national clinical trials registries. At the present time the number of registered trials does not match the number of published trials and there is evidence that trials are not being registered in low and middle income countries. In high income countries, about 85% of paediatric trials are registered. There are issues with the quality of the trial information registered, often only minimal information is register and there is inadequate information about interventions and outcomes. Clinical trial registers offer the opportunity to build capacity for trial design and there is evidence to suggest that clinicians who participate in trials are more likely to follow best practice after the trial. Non-industry trials have not yet caught up with regards to registering trials. There is resistance from some sectors to register trials, as well as a lot of misunderstanding surrounding the need to register. The sponsor is responsible for registering trial. Location should be registered and country of recruitment listed . There is also a lack of understanding about randomization in many developing countries

Needs identified:

- Countries need to have enforceable policies in place for registration of clinical trials.
- Improve capacity to design rigorous trials. China example: RCT randomization process not adequate.
- Disclosure of data sets. Rights of the people to have independent evaluation of data.

Recommendations for improving the quality of clinical trials for children

Standards and guidance:

- **Regarding design**
  - Consider observational studies, cluster RCTs
  - How best to foster community participation in design
  - Specification of inclusion criteria taking into account all developmentally appropriate groups.

- **Regarding conduct**
  - Code of conduct – researchers
  - Code of conduct – industry
  - Cluster RCTs - children
  - Observational studies (PMS)
  - Recruitment/ informed consent/assent
  - Long and short term safety.

- **Regarding reporting**
  - CONSORT-C – develop core set of items to be added to current CONSORT Statement
  - Enhance reporting of negative study/stopped studies publication
  - Stimulate reporting on long and short term safety.

Implementation / knowledge translation:

- **Targeting researchers**
  - Capacity development with industry
  - Capacity development with academic, independent groups
  - Training and certification of investigators
  - Evaluate the role of existing networks.

- **Targeting regulators**
  - Regulatory networking
  - Ethics guidelines
  - Model regulation for conduct of pediatric trials.

- **Targeting journals**
  - Consensus through pediatric journal editors
  - Other Journals.

Next steps

Need identified	Action	Suggested lead organization and/or person
Set a relevant research agenda: identify of gap between health problems in developing countries and existing evidence on pharmacology and effects	Circulate results of recent EMEA and WHO prioritization exercise appraising this issue	WHO and EMEA
Create a WHO-StaR Child Health Platform	Establish ways of working together efficiently according to a coherent plan	WHO and StaR Child Health group
Improve reporting of paediatric clinical trials.	Establish CONSORT for children	Agnes St Raymond (EMEA); Sue Hill (WHO)
Develop a standard for Cluster RCTs and community participation in study design	1) Review of cluster RCTs in developing countries 2) Check if there is linkage between StaR Child Health and the Bellagio Study Group on Child Survival 3) Establish link with Centre for International Child Health (Trevor Duke's group)	WHO and StaR Child Health group
Develop a knowledge translation and implementation strategy	Identify strategic partnerships and undertake an inventory of all relevant WHO initiatives (TDR, CAH, Good Governance Program, Ethics)	WHO

Need identified	Action	Suggested lead organization and/or person
Code of conduct for research involving children for Industry	Identify if a relevant code of conduct already exists	WHO
Code of conduct for researchers	1)Inventory of what exists already 2) Identify ways of building relationship between researchers and industry 3)Develop implementation strategy	WHO and StaR Child Health Group
Specification of inclusion criteria for trials, taking into account all developmentally appropriate age sub-groups	This problem will be addressed by the Standard Development Group: advocacy and guidance on how to design trials	StaR Child Health (John van den Anker)
Safety in trials	WHO has prepared a guidance document on this - to be circulated	WHO
Involving the community, parents and children in trials recruitment	This problem will be addressed by the standard Development Group: relevant information and recruitment	StaR Child Health (Patrina Caldwell and Martin Offringa)

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