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Paediatric Regulators Network Meeting

Geneva, 15-17 February 2010

Review of Clinical Trial Ethical Standards for Inclusion of Children

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DISCUSSION PAPER

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Purpose

Identify gaps and inconsistencies in ethical guidelines for research in children

Methods

This discussion paper analyzed three reviews of ethical guidelines and 14 individual guidelines.

Three reviews of inclusion of children in ethical guidelines were examined: The Survey of Current Guidance for Child Health Clinical Trials,[1] Best Practices for Research Involving Children and Adolescents,[2] and the International Compilation of Human Research Protections, 2010 edition[3]. The Survey of Current Guidance reviewed approximately 22 guidelines. The Best Practices document reviewed and compared 8 international ethical guidelines and 2 Canadian guidelines listed in Annex 1. The International Compilation of Human Research Protections, 2010 edition, compiled by the Office for Human Research Protections, US Department of Health and Human Services[3] lists the approximately 1100 laws, regulations and guidelines that govern human subjects research in 96 countries, as well as standards from a number of international and regional organizations. Standards were collected in the following categories: 1) general, 2) drugs, 3) privacy/data protection, 4) human biological materials, 5) genetic research and 6) embryo, stem cells and cloning. Relevant key organizations, legislation, regulations and guidelines are given for each category. This discussion paper analyzes regulations and guidelines for the general and drug categories. The compilation excludes ethics codes of academic, medical or other professional organizations.

The main source for identifying international and country-specific ethical guidelines was the International Compilation of Human Research Protections, 2010 edition, compiled by the Office for Human Research Protections, US Department of Health and Human Services[3]. As shown in Table 1, a total of 14 specific guidelines were reviewed in detail: 2 international (WHO, CIOMS); 1 regional (EMEA), 1 consensus document (ICH), 12 from African countries, and 1 from India. Guidelines from Africa and India were selected as these are examples of guidelines from low and middle income countries. Each guideline was reviewed for all statements that mentioned children.

Findings

Table 1 summarizes the statement concerning children that were obtained from the reviewed guidelines. Major themes identified are described below.

Some ethical guidelines do not mention children at all. Only a few guidelines state that children should be included in research studies or that research in children is beneficial. For example, the Best Practices[2] review states that "The inclusion of children in research promotes their safety and well-being."

Of the guidelines that do mention children, almost all mention issues of vulnerability of children regarding informed consent and recommend special safeguards for consent and assent. Guidelines typically cover conditions under which consent is necessary, procedures for assent and dissent of the child, and waiver of consent.

Many guidelines note that research conducted in children must be justified and relevant to the health needs of children, that pain management and facilities must be appropriate to children, and that ethical review committees should contain paediatric expertise.

Although most guidelines give an upper age limit for the definition of a child, different ethical requirement for different ages of children are not mentioned. Neonates were rarely mentioned specifically and this was related to suggesting limits on collections of physical samples.

All the guidelines require assessment of the risk benefit ratio of the research to be conducted in children. However, there is virtually no guidance about how such an assessment should or could be different from the assessment of risk benefit ratios for adults. Should less risk be tolerated in children, or should more benefit be demanded? Should large (above minimal) risks ever be tolerated? For example, if a child has a fatal condition, should they get an experimental treatment that is a known risk? For example, the Indian guidelines state that children can be candidates for gene therapy studies, although other guidelines would prohibit this as being too high a risk.

A main area of discrepancy among the guidelines is whether studies should include healthy children, ie the stipulation that children should be included in research that has greater than minimal risk only if there is a direct benefit to the participant. A few guidelines allow inclusion of healthy children if the risks are negligible, or comparable to a risk to which the child would be exposed in ordinary life or routine medical care. However, these acceptable risks are not well defined. Other guidelines would allow inclusion of health children if the least vulnerable children (e.g. older children) are considered first. Some guidelines mention that slightly more than minimal risk is acceptable if the research has the prospect of major scientific or medical significance. For example, guidelines from Uganda state that if there is greater than minimal risk and the study entails no prospect of direct benefit to the individual child participant, it may not be conducted unless:

a. A minor increase over minimal risk;
b. The intervention or procedure presents experiences that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
c. The intervention or procedure is likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance; and
d. Adequate consent assent procedures.

Lastly, some guidelines (e.g., EMEA) define direct benefit to include prevention (i.e., vaccine testing), whereas others consider only therapeutic benefit to be a direct benefit.

Equipoise is demanded for studies in children, but it is difficult to judge a medicine's therapeutic value until it has been tested. This has been the same ethical argument used against randomized trials. Pharmacokinetic (PK) studies could be precluded by the criterion requiring direct benefit. The India guideline, in contrast, specifically states that PK studies should be conducted in children.

Another common criterion among the guidelines is that studies in children should always be carried out after the phase III clinical trials in adults. Studies in children were considered permissible without initial testing in adults only if the drug had a therapeutic value in a primary disease of the children. However, waiting for phase III study results from adults could unduly delay research in children and may be irrelevant to children as the efficacy and safety profile of a medicine may be quite different in adults and children.

Phase 4 studies of safety in children were generally considered permissible as long as they were not being conducted for marketing purposes.

An issue that was rarely addressed in the guidelines was payments (to participants, parents or providers) for inclusion of children (sick or healthy) in studies. The Best Practices review[3] has an extensive discussion of payment issues and defines four types of payment for participation in research: 1) reimbursement payment that compensates the parents and the child for their expenses incurred by their participation, such as transportation, meals and lodging; 2) compensation payment, which compensates the parents and the child for their time and inconvenience; 3) appreciation payment, a bonus to the child once the research is completed to thank him/her; and 4) incentive payment, which encourages the child to participate in research (e.g. enrolment).

The majority of guidelines that do mention payments allow reimbursement and compensation. The Ugandan guidelines, for example, prohibit incentive payments, stating that:

> "For all research involving children, there must be no financial or other inducements to participate for the parent, guardian or child, although reimbursements and a token for the child after completion of the study may be acceptable."

There is a lack of clarity differentiating between payments to parents and children. Some guidelines note that parents cannot be paid for their child's participation in research, although children can be paid. There is no consistency among the guidelines about whether appreciation payments should be disclosed to children. Nor is there consensus regarding the use of incentive payments to encourage the enrolment of children in research.

Conclusions

This discussion paper reviewing international and country-specific guidelines suggests a need for consistency in how issues related to children are included in guidelines for ethical research. Gaps and inconsistencies in the guidelines raise several questions for further discussion:

- Should guidelines contain a positive statement that research in children is necessary and beneficial to children?
- Can an acceptable risk benefit ratio for children be defined, including a clear distinction of how this might differ from an acceptable ratio in adults?
- Can studies of diagnostic tests or preventive interventions be considered to directly benefit participating children?
- Should the timing of clinical trials in children, relative to studies conducted in adults, be reconsidered?
- What is the best way to conduct ethical PK studies in children, particularly healthy children?
- What is the best way to conduct ethical tests for safety in children, particularly healthy children?
- Can more specific guidance regarding payments to children and parents or guardians be developed?

References

1. Survey of Current Guidance for Child Health Clinical Trials. The StaR Child Health Project: Standards for Research with Children. Prepared by FNJ Frakking, JH van der Lee, TP Klassen, M Offringa for the StaR-Child Health Group. September, 2009.

2. Best Practices for Research Involving Children and Adolescents: Genetic, Pharmaceutical, Longitudinal Studies and Palliative Care Research. Prepared by Julie Samuel, Lee Black, Denise Avard, Bartha Maria Knoppers. Centre de recherche en droit public (CRDP), Université de Montréal, September 10th 2009.

3. International Compilation of Human Research Protections, 2009 edition, compiled by the Office for Human Research Protections, US Department of Health and Human Services. Final Version.

TABLE 1:
Summary of Ethical guidelines relevant to inclusion of children in research

Source	Reference	Date	Comments on inclusion of children
International			
WHO World Health Organization	Handbook for Good Clinical Research Practice	2002	• Consent/assent in a vulnerable population • Justify that the research must be done
	Guidelines for Ethics Review Committees	2000	• No mention of children
CIOMS Council of International Organizations of Medical Sciences	Guidelines for Ethical Research	2002	• Children should be included in studies. Participation of children is "indispensible" • Consent/assent in vulnerable populations • Justify that the research must be done • Research must be relevant to health needs of children • Risk benefit assessment necessary • Children should never be included in phase 1 or 2 vaccine trials EXCEPT "may be permissible after studies in adults have shown some therapeutic or preventive effect. For example, a Phase II vaccine trial seeking evidence of immunogenicity in infants may be justified when a vaccine has shown evidence of preventing or slowing progression of an infectious disease in adults, or Phase I research with children may be appropriate because the disease to be treated does not occur in adults or is manifested differently in children"

Source	Reference	Date	Comments on inclusion of children
Regional			
EMEA European Medicines Agency	Ethical considerations for clinical trials on medicinal products conducted with the paediatric population	2008	• Trials are necessary in children • Same ethical principles apply as in adults • Preference given to including older children • Child is up to 18yo • Consent/assent in vulnerable populations • Ethics committee should have paediatric expertise • For RCTs, must have equipoise • Uncontrolled studies to be avoided • Use of placebos should be carefully considered • Pain control and facilities child specific • Studies with direct benefit permissible… Benefit can be defined as progress in treatment, diagnosis, or prevention for the child or the group of children affected. • Risk benefit ratio to be acceptable • Healthy children should not be enrolled. Exceptions: palatability testing, prevention trials or paediatric vaccine trials • Sampling from neonates minimized • There must be no inducement to enter a trial, either for the parents, legal representatives or children. Parents/legal representative can only be compensated for their time and expenses.
ICH International Conference on Harmonization	ICH harmonized tripartite guideline: Clinical investigation of medicinal products in the pediatric population E11	2000	• Safety studies should normally not be done in children • Sampling from neonates minimized • Review committee should have paediatric expertise • Consent and assent • Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)/legal guardian or the study participant. Reimbursement and subsistence costs may be covered in the context of a pediatric clinical study. Any compensation should be reviewed by the IRB/IEC.

Source	Reference	Date	Comments on inclusion of children
Country level			
India	Good clinical practice guidelines	2001	• Consenting a vulnerable population
	Ethical guidelines for biomedical research	2006	• Limits on collection of samples (blood, etc) • Consent / assent in a vulnerable population • Justify that the research must be done • Research must be relevant to health needs of children • For drugs, studies must be carried out AFTER phase III in adults or earlier if drug has value in primary disease of children • Risk benefit ratio must be assessed • Studies must be done in settings where child can obtain adequate physical and psychological support • Pharmacokinetic studies should be done in children • Include children in Phase IV studies • Children for vaccine studies must be chosen carefully to be representative • Children should not be genetically screened at request of parents • Children can be candidates for gene therapy
Africa			
Botswana	Not available online		
Egypt	Professional Ethics Regs	2003	• No mention of children
Ethiopia	Not available online		
Gambia	Not available online		
Kenya	Guidelines for ethical conduct of research	2004	• If a potential drug might be used in children, then children should be included in studies • May be appropriate to include children only after safety assessed in adults • Consent / assent in a vulnerable population • Justify that the research must be done • Research must be relevant to health needs

Source	Reference	Date	Comments on inclusion of children
			of children • Risk benefit must be assessed • Children should never be included in phase 1 or 2 vaccine trials EXCEPT for infants "in the case of a vaccine that has shown evidence of preventing or slowing progression from asymptomatic HIV infection to disease in adults." • Drug studies: Children not to be involved in Phase1, may be in Phase 2 if already tested in adults • Phase 3 and 4 ok to include children
Malawi	n/a online		
Nigeria	National Code of Health Research Ethics	2006	• Children should not be excluded, particularly from studies that can advance their health and well being. However specific safeguards should be included to protect the vulnerable, appropriate to degree of risk. • Review Committee shall include or co-opt one or more individuals who are knowledgeable about and experienced in working with these research participants
South Africa	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	2006	• Child defined as under 21 • Strong justification needed, research must be relevant to children • No greater than minimal risk; or • The research interventions present more than minimal risk but hold out the prospect of direct benefit for the participant. • Consent / assent in a vulnerable population • Neonates: The collection of even small blood samples additional to those required for diagnostic purposes, or the handling of a low birth-weight infant to make observations will demand careful scrutiny.
Sudan	Not available online		
Tanzania	Guidelines on Ethics for health research in Tanzania	2001	• No mention of children

Source	Reference	Date	Comments on inclusion of children
Uganda	National Guidelines for Research Involving Humans as Research Participants	2006	• Greater than minimal risk and the prospect of direct benefit to the child may be conducted if: • risk benefit ratio acceptable • consent assent procedures • greater than minimal risk and entails no prospect of direct benefit to the individual child participant may not be conducted unless: a. a minor increase over minimal risk; b. The intervention or procedure presents experiences that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; c. The intervention or procedure is likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance; and d. Adequate consent assent procedures. • For all research involving children, there must be no financial or other inducements to participate for the parent, guardian or child, although reimbursements and a token for the child after completion of the study may be acceptable. • Review Committee shall include or co-opt one or more individuals who are knowledgeable about and experienced in working with these research participants
Zimbabwe	Guidelines for Clinical Researchers and Ethics committees Medical Research Council of Zimbabwe, Guidelines for Researchers and Ethics Review of Committees	2004	• Consenting vulnerable populations • Justify that the research must be done in children • Research must be relevant to health needs of children • Risk benefit must be assessed

Annex 1:
Guidelines included in Best Practices for Research Involving Children and Adolescents: Genetic, Pharmaceutical, Longitudinal Studies and Palliative Care Research[2]

1. National Council on Bioethics in Human Research (NCBHR), Report on Research Involving Children, (Ottawa: July 1993).

2. Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (1998, with 2000, 2002 and 2005 amendments) at 5.4 [CIHR, Tri-Council Policy Statement].

3. Interagency Advisory Panel on Research Ethics, Draft 2nd Edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, (Ottawa: 2008), online: <http://www.pre.ethics.gc.ca/english/pdf/newsandevents/TCPS_Dec_4_en.pdf> s. 4.5(b) [Interagency Advisory Panel on Research Ethics, Draft 2nd ed. of Tri-Council Policy Statement].

4. World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, (Seoul: 2008). World Medical Association (WMA), Code of Ethics of the World Medical Association, (1964) online: <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1816102&blobtype=pdf>.

5. Canadian Medical Association (CMA), CMA Code of Ethics, (2004), online: <http://www.cma.ca>. American Medical Association (AMA), Code of Medical Ethics, (2008).

6. Council for International Organization of Medical Sciences (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects, (Geneva: 2002) Guideline 14 [CIOMS, Guidelines 2002]

7. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Clinical Investigation of Medicinal Products in the Pediatric Population E11 (20th July 2000), s. 2.6.3 [ICH, Clinical Investigation E11].

8. European Medicines Agency (EMEA), Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (Recommendations of the Ad Hoc Group for the Development of Implementing Guidelines for Directive 2001/20/EC Relating To Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use), (2008), online: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf>, s. 15 [EMEA, Ethical Considerations for Clinical Trials].

9. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 2296 Stat. 111; Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408.

10. American Academy of Pediatrics, "Guidelines for the Ethical Conduct of Studies To Evaluate Drugs in Pediatric Populations," (1995) 95(2) Pediatrics 286 [American Academy of Pediatrics, "Guidelines"]; Children's Project on Palliative/Hospice Services (ChiPPS), "A Call for Change: Recommendation To Improve the Care of Children Living with Life Threatening Conditions," (2001), online: National Hospice and Palliative Care Organization <http://www.nhpco.org/files/public/ChiPPSCallforChange.pdf>.