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Ethical Challenges of Clinical Research in Children

Protection from Risks vs. Access to Benefits

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General Considerations

The twin studies in Birkenau and other 'research projects' during the Nazi regime in Germany resulted in the Nuremberg Principles of Research Ethics [1]. The major aim of the Nuremberg code was protection of the vulnerable subjects. However, the first principle ('the voluntary consent of the human subject is absolutely essential') makes paediatric research virtually impossible. Despite the Nuremberg code, in the 1950s and early 1960s a number of studies were performed on institutionalised children: at Willowbrook State School, New York, mentally retarded children were infected with the hepatitis virus to study the natural history of the disease. This is 1 of the 22 research projects Beecher [2] reported as being unethical.

In the 1970s special attention was paid to the vulnerability of the child. Protection from risks generated by research was prominent: The World Medical Association Declaration of Helsinki 1964 (last amend-

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ment Tokyo, 2004) [3] provides the ethical principles for medical research involving human subjects. Special attention is paid to the 'legally incompetent minor' who should 'not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons'.

Another landmark in ethical guidelines is the Belmont report of 1979 [4]: it summarizes the basic ethical principles identified by The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. Those 3 basic ethical principles are respect for persons, beneficence and justice. Respect for persons means protection of those with diminished autonomy. Children clearly belong to the group of persons that requires extensive protection.

It is obvious that ethical guidelines are essential, but the exclusion of children from research resulted in Shirkey's statement in 1963 that children are becoming 'therapeutic orphans' [5]. The Convention on the Rights of the Child, adopted by the United Nations General Assembly in 1989, stipulates that 'Children have the right to the highest attainable level of health' [6]. Children should be protected from risks but must have access to benefits from research. Medical research involving children is essential for the improvement of care [7]. In the 1970s, Ramsey [■■■■■■] was definitely opposed to non-therapeutic research or research without direct benefit to the child. Nowadays, the majority of paediatric researchers are convinced that the distinction between therapeutic and non-therapeutic research is artificial. The aim of a research project is to obtain generalised knowledge of vital importance.

Placebo-Controlled Clinical Trials in Children

The issue of testing medications in children still presents a dilemma. We should remember some of the tragedies from the past, especially those connected with sulfanilamide-treated deaths [8] and the epidemic of birth defects associated with thalidomide which were the cause of most of the changes regarding law and regulations that govern the testing and marketing of new drugs [9, 10]. However, the testing of medications for safety and efficacy has mainly benefited adults (who offer larger cohorts and definitely take more medications than children),

while medications used by children are rarely tested on them and even more – unapproved or unlicensed and ‘off-label’ drugs are often used in children’s hospitals [11]. Also, a considerable number of drugs prescribed in general practice are not licensed for use in children or are prescribed off label and the absolute number of children using such drugs is much higher than in a clinical care setting. This situation is highly unsatisfactory and efforts should be made to improve it [12]. On the other hand, since 1997 there has been an astounding progress in the amount of the paediatric clinical trials and it is likely that today tens of thousands of children are participating in studies of medications that are funded by industry or by the governments [10]. Recent and very important instruments are the documents issued by the 1990 funded International Conferences of Harmonization (ICH).¹ The first principle of ICH states: ‘Clinical trials should be conducted in accordance with the ethical principles that have the origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable requirements.’²

Current Issues

Despite legislative obstacles other obstacles also exist which may seem difficult to solve – the ethical issues, off-label prescribing practice, investment and clinical doability/feasibility [13]. Under the regulations children are considered a vulnerable group and as such require additional protection as research subjects and there are recent papers developed within the Working group of Ethics, Confederation of European Specialists in Paediatrics/European Academy of Paediatrics (CESP/EAP) dealing with these issues [14–20]. Despite the additional regulations for children they may not be adequately protected in practice [14]. Because of possible different explanations of what is the risk and what

¹ All these documents can be found at the ICH website at: www.ich.org.

² A revised version of the Declaration of Helsinki was issued in October 2000 and it remains a vital expression of medical ethics whose aims deserve unanimous support. Section 29 in particular states that ‘The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not preclude the use of placebo or no treatment in studies where no proven prophylactic, diagnostic or therapeutic method exists.’ See this and other relevant documents at the EMEA website at: <http://www.emea.eu.int/>.

Table 1. Classification of paediatric research [adapted from ref. 3]

Category	Requirements for approval by the institutional review board
Research not involving greater than minimal risk	adequate provisions for soliciting the assent of children and the permission of their parents or representatives
Research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects	risk justified by anticipated benefit to subjects; ratio of anticipated benefit to risk is at least as favourable as that for available alternative
Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalisable knowledge about the subject's disorder or condition	risk represents minor increase over minimal risk; intervention or procedure presents experiences reasonably commensurate with those inherent in subjects' actual or expected medical, dental, psychological, social, or educational situations; research likely to yield generalisable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of it
Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children	institutional review board of the Department of Health and Human Services, after consultation with panel experts, must find that the research presents a reasonable opportunity to meet criteria and will be conducted in accord with sound ethical principles

are the benefits of all research involving children (and especially what are the differences of such studies with regard to the studies in adults) some federal regulations were proposed in the USA which apply to research conducted or funded by the Department of Health and Human services or regulated by FDA (table 1) [10, 21]. However, as has already been stated, focusing only on national instruments such as these regulations will not provide sufficient protection for all our children and an international ethical framework supported by international sharing of data would be an ideal model [22].

Pros and Cons of Placebo-Controlled Trials in Children

The use of placebo has been considered by many as non-realistic and unjustified. Strict interpretation of a revised version of Declaration of Helsinki (see footnote ²) would appear to rule out those randomised-controlled trials (RCTs) that use a placebo (that is a dummy treatment administered to control group children) whenever licensed therapeutic method already exists, and thus preferring active controls. However, although the efficacy of some new medicinal products can be satisfactory demonstrated without the use of placebo, for others judicious use of placebo remains essential to demonstrate the efficacy and safety of the product. There are many groups of therapeutic agents where placebo controls are justified and even mandatory: analgesics, many psychopharmacological drugs, antihypertensives, antiarrhythmics and many drugs used in primary prevention. There are number of conditions which should be taken into account when considering use of placebo-controlled trials. It is essential that the use of placebo does not pose a risk of serious discomfort, irreversible harm or death to the child or that existing therapy improves survival or decreases serious morbidity. Also, the child included in the trial (and his/her legal representative) must receive and understand appropriate information on the trial and give informed written consent/assent [15–17, 20]. The child's (and his/her representative's) right is to withdraw at any time but still receive conventional treatment and this should strictly be respected. In all EU (and other foreign countries) similar ethical and Good Clinical Practice standards should be applied for trials performed. These aspects should fall within the responsibilities of ethics committees reviewing protocols of clinical trials in children.³ Forbidding placebo-controlled trials in therapeutic areas where there are proven prophylactic, diagnostic or therapeutic methods would preclude obtaining reliable scientific evidence for the evaluation of the benefits and risks of new medicinal products, and be contrary to public health interest as there is a need for both new products and alternatives to existing medicinal products.

³ 'The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the Helsinki Declaration' and 'A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.' See: EMEA/17424/01.

Ethical Considerations on Randomised-Controlled Paediatric Trials

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external evidence from systematic research [27]. Best available external clinical evidence means clinically relevant research, often from the basic sciences of medicine, the power of prognostic markers, precision of diagnostic tests and the efficacy and safety of therapeutic, rehabilitative and preventive regimens. In the health sciences there are various study designs and regarding their impact they are classified as meta-analyses, RCTs, cohort studies, case-control studies, case reports, non-systematic reviews and cost-effectiveness analyses. To find out about the accuracy of a diagnostic test we need to find proper cross-sectional studies of patients on randomised trials, for a question of prognosis we need proper follow-up studies, when asking questions about therapy we should try to avoid the non-experimental approaches since they may lead to false-positive conclusions about efficacy.

Recently, it has been proven that RCTs are the second-cited study design and are therefore the preferable way of research studies [23]. The majority of other studies have a similar impact, while case reports do not bare many citations if any. On the other hand, it has been stated that the proportion of most frequently cited articles funded by industry is significantly ($p = 0.001$) increasing over time and is sometimes even exclusive [24]. This implies that the future research (also in the paediatric field of research) will be mostly focused on the industry-funded RCTs. There were some doubts about the properly designed RCTs in certain conditions as some trials could be too small and too poorly designed to be able to detect or to refute reliably realistically modest but clinically important benefits or hazards of treatment, and that limited funding for research and unfamiliarity with issues of consent may be important obstacles [25]. The methodological concerns can also be a major reason for the acceptance or refusal of certain studies and the validity of a test can be one of its most important contributes as well as there may be demanding high levels of proof before funding is approved. However, even in common disorders there can be embarrassingly few data and this would

create a catch-22 situation [26]. In paediatrics, we lack long-term population studies to demonstrate the balance of benefits versus side effects. It is rather unlikely to set up a long-term RCT with placebo controls because not many parents want to risk their child being in the placebo arm. To emulate the success of certain fields, such as paediatric oncology (where in many countries most children are in some kind of study even if simply an observational one), requires an infrastructure as well as willpower and enormous resources [26].

However, some questions about therapy do not require RCTs or cannot wait for the trials to be conducted and if this is so, we must follow the trail to the next best external evidence and work from there [27, 33]. There are probably few childhood syndromes for which there are sufficient numbers of participants on which to perform RCT [30]. As the result of the increase in good paediatric studies, the investigators and instructional review boards may gain paediatric expertise as well and we should hope that the increased participation of children in clinical trials based on good clinical practice recommendations [15–19] will continue.

Finally, we should be aware that in cases where there is a limited number of evaluable subjects (which is frequently the case in paediatrics) the importance of collecting maximum information from the cases observed becomes essential, especially if the only data available consist of a series of isolated clinical information. Standardised analysis of information from various sources and on the basis of objective criteria would be of potential interest in the absence of other methods of evaluation.

Conclusion

We hope that in the future the major obstacles regarding the problems in paediatric drug development (limitation of the size, limitation of those willing to participate, either as placebo or healthy controls, limitation of doctors willing to take part in clinical trials, limitations by too strict criteria – for inclusion or exclusion) will soon be removed and that paediatricians will not be forced to adopt extraordinary measures to insure that their patients are not harmed by treatments that have not been adequately studied in children [32]. Finally, most important is the recognition of all different parties involved that it is in the interest of chil-

dren to evaluate medicinal products with scientifically proven methods, if possible by paediatric placebo-controlled trials, which should only be justified when their design, enrolment and conduct ensure that they really address the best interests of the children-participants with a view to their health and a concern of their dignity.

References

- 1 The Nuremberg Code: www.ushmm.org/research/doctors/codeptx.htm
- 2 Beecher HK: Ethics and clinical research. *N Engl J Med* 1966;274:1354–1360.
- 3 The World Medical Association Declaration of Helsinki 1964: www.wma.net/e/policy/b3.htm
- 4 The Belmont Report: <http://ohsr.od.nih.gov/guidelines/belmont.html>
- 5 Shirkey HC: Editorial comment: therapeutic orphans. *J Pediatr* 1968;119:119–120.
- 6 General Assembly of the United Nations: Convention on the Rights of the Child, 20 November 1989. www.unicef.org/crc/crc.htm
- 7 Sauer PJJ: Research in children. A report of the Ethics Working Group of CESP. *Eur J Pediatr* 2002;161:1–5.
- 8 Anon: Elixir of sulfonamide-massengil: chemical, pharmacologic, pathologic and necropsy reports. Preliminary toxicity reports on diethylene glycol and sulfonamide. *JAMA* 1937;109:1531–1539.
- 9 Kauffman RE: Drug safety, testing, and availability for children. *Child Legal Rights J* 1998;18:27–34.
- 10 Steinbrook R: Testing medications in children. *N Engl J Med* 2002;347:1462–1470.
- 11 't Jong GW, Vulto AG, de Hoog M, Schimmel KJM, Tibbole D, van den Anker JN: Unapproved and off-label use of drugs in a children's hospital. *N Engl J Med* 2000;343:1125.
- 12 't Jong GW, Eland IA, Stukenboom CJM, van den Anker JN, Stricker BHCh: Unlicensed and off label prescriptions of drugs to children: population based cohort study. *BMJ* 2002;324:1313–1314.
- 13 Ramet J: What the paediatricians need – the launch of paediatric research in Europe. *Eur J Pediatr* 2005;164:263–265.
- 14 Kurz R, Gill D, Mjones S: Ethics in the daily medical care of children. Statement of the Ethics WG of the CESP. *Eur J Pediatr* 2006;165:83–86.
- 15 Gill D, et al: Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics WG of the CESP. *Eur J Pediatr* 2004;163:53–57.
- 16 Gill D, Ethics Working Group of the Confederation of European Specialists in Paediatrics: Guidelines for informed consent in biomedical research involving paediatric populations as research participants. *Eur J Pediatr* 2003;162:455–458.
- 17 Kurz R, Gill D: Practical and ethical issues in paediatric clinical trials. *Appl Clin Trials* 2002;11:60–63.
- 18 Sauer PJJ: Research in children. *Eur J Pediatr* 2002;161:1–5.
- 19 Kurz R, Crawley FP: The Clinical Trial Directive's ethical impact on research into diseases that cause incapacity and diseases of children: perspectives from non-commercially funded research in hospitals. *Int J Pharm Med* 2003;17:7–9.

- 20 De Lourdes Levy M, Larcher V, Kurz R, et al: Informed consent/assent in children. *Eur J Pediatr* 2003;162:629–633.
- 21 Steinbrook R: Improving protection for research subject. *N Engl J Med* 2002;346:1838.
- 22 Crawley FP, Kurz R, Nakamura H: Testing medications in Children (reply). *N Engl J Med* 2003;348:763.
- 23 Patsopoulos NA, Analatos AA, Ioannidis JP: Relative citation impact of various study designs in the health sciences. *JAMA* 2005;293:2362–2366.
- 24 Patsopoulos NA, Analatos AA, Ioannidis JP: Origin and funding of the most frequently cited papers in medicine: database analysis. *BMJ* 2006;332:1061–1064.
- 25 Dickinson K, Bunn F, Wentz R, Edwards P, Roberts I: Size and quality of randomized controlled trials in head injury: review of published studies. *BMJ* 2000;320:1308–1311.
- 26 Baxter P: Evidence based medicine (editorial). *DMCN* 2004;46:723.
- 27 Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS: Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312:71–72.
- 28 Smith GCS, Pell JP: Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003;327:1459–1461.
- 29 Black D: The limitations of evidence. *J R Coll Physicians Lond* 1998;32:23–26.
- 30 Ferrie CD, Livingstone JH: Epilepsy and evidence-based medicine: a vote of confidence in expert opinion from the National Institute of Clinical Excellence? *DMCN* 2005;47:204–206.
- 31 National Institute for Clinical Excellence (Issue date: April 2004, review date: December 2006).
- 32 Groopman J: The Pediatric Gap. *New Yorker* 2005;80:32–37.
- 33 Draft Guideline on Clinical Trails in Small Populations, CHMP/EWP/83561/2005.