Editorial

Ethics of research in children

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Prior to World War II, research was largely an unregulated aspect of treatment[1]. The Nuremberg trials after the war revealed horrifying research performed by German doctors on captives. In the light of this, the Nuremberg Code was drawn up, regulating research[1]. At its heart is the voluntary consent of research participants. A problem with making such consent a requirement of all research is that it makes research on young children impossible[1]. In 1964, the World Medical Association drew up the Helsinki declaration. This modified the Nuremberg code in various ways, one of which was to permit research on children subject to strict control. One of the controls it recommended was that all healthcare research proposals should be submitted to an independent research committee[1]. Reputed journals now insist that the research they publish has been subject to ethical review[1].

Research is essential to advance knowledge about children's health and development[2]. However, research involving children should only be contemplated where the question posed is important to children, families or community, the proposed study is based on sound scientific concepts, information available from research on other subjects does not answer the question posed in relation to children and the study method is appropriate for children and is likely to result in a valid conclusion and subsequent publication of new information[2].

There is a relative paucity of good medical research in children[3]. In one review, there were only 249 randomised, controlled trials in children published in one paediatric journal over a 15 year period, and even out of these a large percentage were underpowered[3]. Furthermore, children have not reaped the benefits of pharmaceutical advances to the same extent as adults, rendering them "therapeutic orphans"[3]. Many medications, that are widely used in children, are rarely first tested on children[3]. Without paediatric studies, labelling cannot include guidance about dosage and side effects. Seventy per cent of the current medications lack sufficient data in children[3].

Research in children should only be undertaken where the study is to take place in circumstances and in an environment that provide for the physical, emotional and psychological safety of the child and the family[2]. Furthermore, informed consent must be given by the parent or guardian and also by the child when the child is of sufficient maturity and capacity to give consent[2]. Such consent must be given after a clear and understandable explanation of the reasons for the research, the likely benefits, especially to the child, the procedures to be undertaken, any complications associated with the procedures, the time likely to be taken, any costs likely to be incurred and the protection of confidentiality and privacy throughout the research activity[2]. It should be clearly stated that participation in the research is wholly voluntary and that non-participation in or subsequent withdrawal from the research will not affect the care and treatment that the child would otherwise receive[2]. In the process of obtaining consent, adequate time must be allowed for the child and family to ask questions about the research and to receive answers[2].

Although full disclosure of information during the procedure of obtaining consent is the ethical ideal, a particular study may necessitate withholding certain information or deception[4]. Whenever withholding information or deception is judged to be essential to the conduct of the study, the investigator should satisfy an ethical review committee that such judgment is correct[4].

The investigator should keep in confidence all information obtained about research participants. The participants' identity should be concealed in written and verbal reports of the results, as well as in informal discussion with students and colleagues[4]. The general principle underlying confidentiality in research is that data generated can only be used for the purposes for which the participants or their proxies gave consent[1]. This principle is subject to certain limitations. Confidentiality can be breached where this can be justified in the public interest, or when required by law or as a matter of child protection[1]. For example, an interviewer who unearthed evidence of child abuse would be expected to pass it on to other authorities, even though the child or his proxy did not give consent for interview information to be used in that way[1].

To gain access to institutional records, the investigator should obtain permission from responsible authorities in charge of records[4]. Anonymity of the information should be preserved and no information used other than that for which permission was obtained[4].

In considering whether the research proposal is justified, the risks to the child must be balanced against the likely benefit to the child or children in general, the family and the community, bearing in mind the nature of the condition being studied and the hazards of current therapy[2]. These risks include not only physical discomfort and inconveniences, but also psychological concerns like fright, separation from parents, and unfamiliar surroundings[3]. Another important consideration is the effect on growth and development, a risk that may persist for a longer period[3].

Research in children that does not offer direct benefit has generated substantial controversy[3]. Such research would not necessarily be unethical if the question asked was sufficiently important and relevant to children generally, families or the community[2]. Special care is required in these circumstances to minimise invasive procedures and any risks associated with the procedures[2]. A substantial risk of serious harm would render the research unethical except in special circumstances, usually life-threatening situations[2].

When research procedures result in undesirable consequences for the participant that were previously unforeseen, the investigator should immediately employ appropriate measures to correct these consequences and should redesign the procedures if they are to be included in subsequent studies[4].

Children (and parents or guardians) may be paid for inconvenience and time spent and should be reimbursed for expenses incurred in connection with their participation in research; they may also receive free medical services[5]. However, the payments should not be so large or the medical services so extensive as to induce prospective children to consent to participate in the research against their better judgment ("undue inducement")[5]. All payments, reimbursements and medical services to be provided to research subjects should be approved by an ethical review committee[5].

All proposals to conduct research involving children must be submitted for review and approval to one or more independent ethical review committees before the research is begun[2]. In reviewing the ethical soundness of research, ethical review committees consider three main criteria: scientific validity, the welfare of participants, and respect for the dignity and rights of participants[1]. 'Research which duplicates other work unnecessarily or which is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical'. The thought behind this statement is that invalid research wastes resources[1]. Ethical review committees must recognise, respect and take into account the cultural differences that exist in the community and the special needs that these differences may require[6]. When dealing with research in children, ethical review committees have an additional responsibility to act as advocates for the interests and needs of children who are often not in a position to speak for themselves[6]. Ethical review committees dealing with issues relating to children must include members or have access to people with experience and knowledge of children and child development[6].

There is an obligation to conduct research ethically and to report it honestly. Honest reporting begins with revealing the existence of all clinical studies, even those reflecting unfavourably on a research sponsor's product[7]. Unfortunately, selective reporting of trials does occur, and it distorts the body of evidence available for clinical decision-making[7]. Researchers (and journal editors) are generally enthusiastic about the publication of trials showing either a large effect of a new treatment (positive trials) or equivalence of two approaches to treatment (non-inferiority trials) but are less enthusiastic about trials that show that a new treatment is inferior to standard treatment (negative trials) and even less about trials that are inconclusive[7]. Trial results that place financial interests at risk are particularly likely to remain unpublished. The interests of the sponsor or authors notwithstanding, anyone should be able to learn of any trial's existence and its important characteristics[7].

International Committee of Medical Journal Editors (ICMJE) proposed a comprehensive clinical trials registration process as a solution to the problem of selective awareness[7]. Commencing July 1, 2005, the ICMJE member journals require, as a condition of consideration for publication, registration of a clinical trial in a public trials registry at or before the onset of patient enrollment. For this purpose, the ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome[7]. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g. phase I trials), are exempt[7].

The ICMJE requires authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration

data, and the registry should be electronically searchable[7]. An acceptable registry must include at minimum the following information: a unique identifying number, a statement of the intervention (or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete), target number of subjects, funding source, and contact information for the principal investigator[7].

The World Health Organization (WHO) has supported the call for mandatory trial registration by establishing the International Clinical Trials Registry Platform (ICTRP)[8].

The Sri Lanka Medical Association (SLMA) has taken the initiative to establish the Sri Lanka Clinical Trials Registry (SLCTR), which will provide a facility for registration of trials conducted in Sri Lanka or overseas, and for collaborative research between Sri Lankan and foreign researchers[9]. Any trial designed to test the efficacy of a health care intervention in human participants requires registration. Trials starting recruitment of subjects after 1st November 2006 were required to apply for prospective registration. Trials that have commenced recruitment before this date were allowed to apply for retrospective registration[9]. The SLCTR is an internet-based registry, with free access to researchers, clinicians, and the public. Trial registration can be done on-line (http://www.slctr.lk/application.asp) or by completing an application form available at the SLMA Office[9]. All trials should obtain approval from a recognized ethics review committee before enrolment of subjects. The principal investigator or person responsible for registration of the trial is requested to provide a brief progress report at 6 months, one year, and every year thereafter until completion of the trial[9]. Several trials have already been registered, the details of which are available at the SLCTR website (http://www.slctr.lk/).

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