Introduction

While human experimentation dates back thousands of years, the planned use of humans in medical research is much more recent. One of the first examples was Edmund Jenner’s study of the use of cowpox to immunise against smallpox in 1796. His first subject was a fourteen-year-old boy called James Phipps. Whether Jenner’s research would be permissible today is doubtful. In fact, in the latter half of this century the ethics of involving children in health research has given rise to vigorous debate, because of children’s vulnerability and lack of competence to give legally effective consent (Nicholson, 1986).

The Nuremburg Code, promulgated in 1947 to prevent the kind of inhuman experiments conducted in the Nazi concentration camps, made voluntary consent of the research participant absolutely essential, thus effectively precluding the involvement of children entirely. While research with children did not cease altogether, the limitations imposed were severe. In the United Kingdom, for instance, it was thought that parents could not lawfully agree to their child’s participation in health research if it was of no therapeutic benefit to that child and carried some risk of harm (Report of Medical Research Council, 1964). As almost all medical procedures carry some risk of harm, this view had the effect of preventing all non-therapeutic research with children. Even research intended to be of benefit to the child participants had to be considered particularly carefully.

By the mid-seventies it became apparent that if medical treatment of children was to advance, the existing restrictions, particularly those related to non-therapeutic research with children, would have to be lifted (Nicholson, 1986, p. 7). The question since then has been the extent to which health research with children should be permitted. A variety of answers have been proffered in different countries in the form of Guidelines and Codes. New Zealand has not considered this issue in depth, particularly those related to non-therapeutic research with children. Even research intended to be of benefit to the child participants had to be considered particularly carefully.

Should Children be Involved in Health Research?

The answer to this question is unequivocally in the affirmative. There are sound reasons why children should be involved in health research. First of all, they are not small adults; they have additional and unique sets of interests. They frequently suffer from disease processes which are peculiar to their age group. Their anatomy, physiology, metabolism, responses and reactions are different.

We argue that the involvement of children in health research is essential for the promotion of their well-being and for the good of society generally, but that special conditions must be imposed. We also consider whether children are competent to give legally effective consent to participate in health research and, in the absence of such competence, whether their parents or guardians may consent on their behalf.

It will become apparent that the answers to these issues are neither ethically nor legally clear-cut. Considerable controversy continues to surround them. We would therefore strongly recommend wide-ranging consultation before guidelines regulating the conduct of health research with children in New Zealand are adopted.
from adults. There is a need for systematic investigation into their normal development, the aetiology of childhood disease and the means of diagnosing, assessing and treating such diseases.

Treatments which are effective and safe in adults are not necessarily safe and effective in children. The exclusion of children from research creates uncertainty which may adversely affect their well-being. The American Academy of Pediatrics noted recently that eighty-one per cent of drugs listed in the Physicians' Desk Reference, a widely used drug formulary in the USA, included a disclaimer for use with children or lacked appropriate dose information (Kauffman et al, 1995). The studies required to produce this sort of information had not been done. This leaves the prescriber with the unenviable choice of either denying the child potentially beneficial therapy or risking an unforeseen toxic effect due to the different physiology of childhood.

The current international view therefore is that research with children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner. In fact, to exclude children from participating in scientifically and ethically sound research may be to deny them a basic human right, as it may impede the promotion of their health and well-being. It may also be a breach of Article 24 of the United Nations Convention on the Rights of the Child 1989, which New Zealand ratified in 1993. So, the debate has shifted and is now centred on the type of research which may be conducted on children and the special conditions which should apply to such research.

Several organisations have adopted guidelines for this purpose. The Council for International Organizations of Medical Sciences (CIOMS) has given careful consideration to the involvement of children in its International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993). So too has the British Paediatric Association (BPA) in its Guidelines for the Ethical Conduct of Medical Research Involving Children (1992). To these may be added the Council of Europe's recent convention (the European Convention, 1996) and the US Code of Federal Regulations on the Protection of Human Subjects, 1991, para 46).

All of these guidelines permit the involvement of children provided the research can not equally well be done on adults and that the purpose of the research is to obtain knowledge relevant to the health needs of children. Of course, the normal ethical principles applicable to all health research apply equally to children: the principle of respect for the rights of the individual, the obligation to protect the individual from undue risk and the requirement of fairness in distributing the burdens and benefits of research (American Academy of Pediatrics, 1995; CIOMS, 1993). The guidelines also require research proposals to be submitted to independent ethics committees for rigorous scientific and ethical review (Health Research Council, 1994; Ministry of Health, 1996).

The BPA Guidelines further specify that each project should:

- have an identifiable prospect of benefit to children;
- be well designed and well conducted;
- not simply duplicate earlier work;
- not be undertaken primarily for financial or professional advantage;
- involve a statistically appropriate number of participants and

eventually be properly reported (BPA, 1992, p. 4).

Risk assessment in therapeutic and non-therapeutic research

Most guidelines draw a distinction between therapeutic and non-therapeutic research. The former is intended to be of direct benefit to the research participants, whereas the latter is not. The purpose of non-therapeutic research is to produce generalisable knowledge which will be beneficial to children generally or to a specific class of children, but not necessarily to the research participants. While this distinction is not always easy to draw, and its merits are questionable, its significance lies in the different degrees of ethically permissible risk to child participants (Nicholson, 1986, pp. 26-31).

Risk is a qualitative description of all the hazards to which a child would not have been exposed but for participating in the research project. It refers to both the probability of a harm resulting from an activity and its magnitude. It includes not only the risk of physical harm, but also the psychological and emotional hazards to the child participant and his or her family. Children's responses are often unpredictable and change as they mature, so that generalisations about risk will alter with age. Hence the recommendation from the BPA (1992, p. 6) that, where possible, preference should be given to older children over younger ones.

Matters which need consideration in assessing risk include the degree of invasiveness of the research procedures and the severity of potential harm associated with those procedures. This assessment should not be confined to physical interventions. Psychological and behavioural research can be just as invasive. Are the adverse effects immediate or not evident until years later? Are they brief or long lasting? Researchers may underestimate a high risk of pain, or the fear of pain, if the effects are brief, whereas children or their parents may consider that the transient pain is not justified by the benefits that the study may bring. Injections and venepunctures are obvious examples. As Professor Hull said in his introduction to the BPA Guidelines:

It is clear that ... there is only a minimal risk of physical harm when blood is taken from a child by an experienced venesector. The problem is that children do not always see it like that. The use of needles to take blood upsets many children and a few are very frightened indeed by the prospect of blood sampling or an injection. Children who are admitted to hospital often perceive needles as more unpleasant than an operation (BPA, 1992, p. 3).

Some potential harms may not be immediately obvious, for example with research into serious genetic disorders which present in adult life. Pre-symptomatic diagnosis in childhood, while possibly beneficial, may also be very harmful and may affect the child's opportunities and freedom of choice in early life. This prompted the Council of Europe to include in its Convention that predictive genetic tests should be carried out only for health purposes and should be accompanied by appropriate counselling (Council of Europe, 1996, Article 12).

Special care also needs to be exercised in risk identification in chronically ill or vulnerable children, because they may already be exposed to such a degree of risk that adding to it by involving them in research may be unacceptable. Children in institutions or attached to specialist clinics are particularly vulnerable in this respect.
Risk should never be assessed in isolation. It has to be balanced against the potential benefits of the research to the participants and to society as a whole. The general ethical principle that the potential benefit of the research should outweigh the potential risks applies equally to children. But with children additional care has to be taken, because of their vulnerability and their inability to consent (Evans & Evans, 1997). CIOMS Guideline 5 (1993) requires in therapeutic research that the benefits to the child participants must clearly outweigh the risks of harm and that the therapeutic interventions must be at least as advantageous to the child as any available alternative. In other words, the risk-benefit assessment of the research procedure has to compare very favourably with the risk-benefit assessment of the standard treatment for the particular child.

Much greater caution is usually expressed in relation to non-therapeutic research, though the earlier view that children should not be exposed to non-therapeutic research at all seems to have been replaced by qualified support. The Declaration of Helsinki of 1964 does not prohibit such research. Nor do the BPA Guidelines:

The attempt to protect children absolutely from the potential harms of research denies any of them the potential benefits. We therefore support the premise that research that is of no intended benefit to the child subject is not necessarily unethical or illegal (1992, p. 7).

They all impose a limit on the level of risk permissible in non-therapeutic research, but the level varies. The BPA Guidelines are the most restrictive. They permit at most ‘minimal’ risk in non-therapeutic research. This includes procedures such as questioning, observing and measuring children, collecting a urine sample (but not by aspiration), and using blood from a sample that has been taken as part of treatment. It excludes injections or venepunctures, because many children fear needles. Such procedures are deemed to be ‘low’ risk, rather than minimal risk, and are permitted only in therapeutic research (BPA, 1992, p. 9).

The CIOMS Guidelines are less restrictive. They permit procedures with a ‘low’ risk of harm, i.e. a risk which is ‘no more likely and not greater than the risk attached to routine medical or psychological examination of such children’ (CIOMS, 1993, p. 21). Vene-punctures would be acceptable under these guidelines, as they would in terms of the US Federal Regulations (1991, paras 46.102 and 46.404) and the European Convention (Council of Europe, 1996, Article 17(2)(ii); Directorate of Legal Affairs, 1997, para 111), though the latter two use the term minimal risk rather than low risk in this context. In fact, the US Regulations even permit ‘a minor increase over minimal risk’ if the research is of vital importance (1991, para 46.406).

The BPA Guidelines are therefore considerably more restrictive than the other guidelines and concern was expressed at the time of their adoption that they would discourage important research which could benefit children. We share that concern and would advocate the approach adopted by CIOMS. While we do not wish to minimise the pain or fear engendered in children by some procedures, we believe that if the research has the potential to be of significant benefit to children generally and meets all the other ethical requirements, it would be to their detriment if such research were prevented because of brief pain which otherwise carried low risk of harm. Besides, some of these discomforts can be relieved by the use of experienced personnel or the application of a topical anaesthetic cream, such as Emla® (2.5 per cent lidocaine, 2.5 per cent prilocaine cream).

Of particular importance in the context of non-therapeutic research is the use of placebos or untreated control groups in drug trials and other active intervention trials. If the degree of permissible risk is too strict, such trials would be excluded to the detriment of children. Many childhood diseases which are now under control, would not be if it had not been for randomized controlled epidemiological trials. The American Academy of Pediatrics supports such trials in children but only in certain cases, such as when there is no commonly used therapy, or the standard therapy is of questionable efficacy or has common undesirable side effects (Kauffmann et al., 1995).

Whatever the nature of the research, every project must have clear and unambiguous information about the risks and benefits of the research and, where appropriate, the standard treatment. They must also follow a consent process which ensures that everyone’s participation is based on voluntary and informed agreement.

Consent Issues

Voluntary informed consent by research participants is a fundamental prerequisite to the conduct of all health research. It was the corner stone of the Nuremberg Code reflecting the ethical principle of respect for persons. Section 10 of the New Zealand Bill of Rights Act (1990) gives legal effect to this principle. It provides:

Every person has the right not to be subjected to medical or scientific experimentation without that person’s consent.

If children are to participate in health research, two questions arise in relation to this section: first, are children competent to give legally effective consent and, second, if they lack that competence, may their parents or guardians consent on their behalf? Space does not permit a detailed analysis of these two questions, so what follows is of necessity quite superficial.

Are children competent to give legally effective consent?

The answer to this question depends in the first instance on the age of the child. Children in New Zealand attain majority at the age of 20 (Section 4, Age of Majority Act, 1970). From that age onwards such capacity as they may have lacked solely by virtue of their age ceases. However, children below the age of 20 have the capacity to consent to a wide range of activities, including medical treatment. Section 25 of the Guardianship Act (1968) provides that:

the consent of a child of or over the age of 16 years to any donation of blood by him, or to any medical, surgical or dental procedure to be carried out on him for his benefit by a person professionally qualified to carry it out, shall have the same effect as if he were of full age.

As therapeutic research is intended to be of direct benefit to the research participant, we would argue that children of 16 and over should be entitled to give legally effective consent to their participation in such research. However, section 25 cannot be applied in the context of non-therapeutic research, as such research is not intended to benefit the participants and thus does not meet an essential condition of the section.

The common law, by contrast, does not make legal capacity age specific.
It evolves gradually as the child grows older and parental rights dwindle correspondingly (Hewer v Bryant [1969] All ER 578 at 582). The House of Lords in England held that children below the age of sixteen can legally consent to medical treatment if they have sufficient understanding and intelligence to know what it involves, but only if it is in their best interests (Gillick v West Norfolk and Wisbech Area Health Authority [1985] 3 All ER 402, 409-413). It is unclear whether this test applies in New Zealand but if it does the child’s right to consent would still be confined to therapeutic research, for it is only then that it could be argued that participation may be in the child’s best interests. Even then the test may not be satisfied, because therapeutic benefit and the best interest test do not necessarily coincide. A research study may be intended to benefit children, but the uncertainty which is inherent in all research often precludes an accurate assessment of the risks and benefits. It may be impossible to determine whether participation is in a child’s best interests (McLern, 1992).

So, while we would argue that children may legally consent to participate in therapeutic research from the age of 16, and possibly before that age, it seems that they would not have that right in respect of non-therapeutic research until they attain the age of majority. Common sense suggests that this distinction is inappropriate and at odds with reality. Sixteen-year-olds should be able to consent to non-therapeutic research, provided the risk is within permissible levels and clearly outweighed by the potential benefits of the research.

Whatever the required standard of competence for legally effective consent, there will always be children who will lack that competence, but whose participation in research will nonetheless be desirable. The question in that case is whether their parents or guardians have the right to consent on their behalf.

Do parents or guardians have the right to consent on behalf of their children?

Parents and guardians generally have the right to make decisions on behalf of their children and commonly do so in all areas of their child’s life. Most often the authorised activity will be of benefit to the child, but sometimes it will not. Parents may, for example, permit their child to play rugby, even though the child may well incur an injury.

Whether parents can authorise their child’s participation in health research depends again on section 10 of the New Zealand Bill of Rights Act, quoted above. The section is very specific in requiring the consent of the person who is to be subjected to the experimentation. It appears to preclude proxy consent. If that is the case, the scope of section 10 will depend on the meaning given to the words ‘medical or scientific experimentation’. They are not defined and could be interpreted in a number of different ways.

First, they could be given a very broad meaning to include all health research, whether of therapeutic benefit to the participants or not and irrespective of the level of risk involved. The effect of section 10 would then be to prevent all health research with children who lacked the required competence to consent, no matter how beneficial or harmless. It seems unlikely that the legislature could have intended such a drastic result, given the need for research in children and the state’s responsibility to promote the well-being and best interests of children (for example, s4 Children, Young Persons and their Families Act, 1989; s23 Guardianship Act 1968).

A second interpretation, and one which has some international support, limits the meaning of the words to non-therapeutic health research. McCance, for example, defined a medical experiment in the fifties as: anything done to a patient, which is not generally accepted as being for his direct therapeutic benefit or as contributing to the diagnosis of his disease (McCance, 1950, cited by Katz, 1972, p. 825).

If this interpretation were adopted section 10 would prevent children who lacked competence to consent from participating in health research which was of no direct benefit to them, irrespective of the risk involved.

Given the prevailing international standpoint that both therapeutic and non-therapeutic health research are essential to promote the well-being of children, and are ethically permissible subject to certain conditions, this second interpretation would also be detrimental to the future health of children in New Zealand.

The third interpretation of ‘experiment’, and in our view the preferred one, is considerably narrower and would include any research in which the pursuit of scientific knowledge is undertaken without regard to the interests of the research participants. This interpretation would permit research which complies with current national and international research guidelines, all of which require that concern for the interests of the research participant must always prevail over the interests of science and society (Ministry of Health, Helsinki, 1989, Principles 4 and 5; Council of Europe, 1996, Article 2; National Standard for Ethics Committees, 1996, p. 17; Health Research Council Guidelines, 1994, 6.3.2.2). The importance of the research objective must be in proportion to the inherent risk to the participant. This interpretation would capture the more sinister forms of experimentation, such as those which took place in Nazi Germany, and it would prevent research which is in breach of current national and international guidelines.

With the exception of the Nuremburg Code, all the ethical guidelines referred to above permit the involvement of children in therapeutic and non-therapeutic health research on the basis of proxy consent if the children are unable to decide for themselves. These guidelines are given indirect legal authority by Right 3 of the Code of Health and Disability Services Consumers’ Rights 1996. According to these guidelines parents and guardians may authorise their child’s participation in health research, provided the risks are within the permissible limits and are outweighed by the potential benefits of the research. If the research does not meet these conditions, proxy consent cannot legitimise a child’s participation.

Consent or assent of the child

The guidelines also stipulate that the child’s consent or assent be sought to the extent of the child’s capabilities and that, by analogy, a child’s refusal

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1 Auckland Health Services v Liu unreported, High Court Auckland, 1996, MB12/96 held that section 25 Guardianship Act implied that children below the age of 16 were not competent to consent to medical treatment: p. 7. Yet Right 7 of the Code of Health and Disability Services Consumers’ Rights 1996, promulgated under the Health and Disability Commissioner Act 1994, appears to suggest the contrary.
be respected unless the child would receive therapy for which there is no medically acceptable alternative (CIOMS, 1993). This requirement appears to accord with the provisions of Right 7 of the Code of Rights. The child is thus given a very real role in the consent process and has a power of veto. The exception to this right of veto is based on the best interests test and is therefore a justifiable limitation on the child's rights only in the case of therapeutic research (Evans, 1997).

Conclusion

We believe the conditions laid down in the CIOMS Guidelines and others referred to in this paper are sensible and provide proper protection for children participating in research. We would recommend the introduction of guidelines in keeping with the CIOMS Guidelines. However, we acknowledge that section 10 of the Bill of Rights Act may preclude this. This section may be interpreted to prevent proxy consent and thus preclude children from participating in health research unless they are competent to provide legally effective consent.

We also acknowledge the legitimate criticism, levelled by Sheila McLean (1992), at the failure of both national and international ethical guidelines to provide a justification for the use of proxy consent in medical research. The two tests which are traditionally used to justify proxy consent are the 'best interests' test and the 'substituted judgment' test. She argues convincingly that neither test provides a completely satisfactory basis for proxy consent in therapeutic research, and that they are both wholly inappropriate in the context of non-therapeutic research. Yet, proxy consent to the participation of children in both therapeutic and non-therapeutic research is routinely accepted and included in most international guidelines.

The Health Research Council of New Zealand is conscious of the need to formulate guidelines for research with children and has plans to do so in the near future. It is envisaged that they will be broadly similar to those adopted elsewhere, but given the legal and ethical uncertainties outlined above, we strongly recommend wide-ranging consultation with researchers, ethics committees, children's organisations, Maori consultative groups and other relevant parties.

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