Review of Legal Instruments and Codes on Medical Experimentation with Children

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Introduction

Medical research with children has been the subject of ongoing debate.[1] The reason for controversy is clear. As with research on adults, one must strike a balance between two goals—promoting the health of children through advances in scientific knowledge and protecting child research subjects from exploitation and harm. However, because of their age and relative immaturity, children cannot protect their own interests as well as adult subjects can. Yet as they progress toward adulthood, increasing care must be taken to involve children in decisions that affect them, even to the extent of allowing them to make choices that may have serious and long-term consequences.

This unique convergence of concerns has led many governments and professional organizations to develop legal or administrative instruments that treat pediatric research differently from research with adult subjects. The distinction may be examined with respect to four specific criteria: 1) when is it permissible to conduct pediatric research, 2) who decides whether a particular child can be a research subject, 3) what kinds of research can be conducted, and 4) the composition of committees that evaluate research protocols from an ethical standpoint. The purpose of this paper is to review an extensive array of legal instruments and codes to examine how they deal with these central issues.[2]

Selection of Children as Research Subjects

Prohibition of Research on Children

Documents that extend a blanket prohibition on pediatric research appear to be extremely rare, which reflects a general appreciation of the essential role that research plays in the improvement of medical care. In the case of therapeutic research, which tests experimental treatments, the benefits may accrue to the research participant. In the case of nontherapeutic research, which is not designed to promote the well-being of the research subject, the benefits flow to society in general. In both cases, though, the impetus behind the research activity is the same—to enable physicians to better combat disease and disorders.

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Regulations governing drug trials recently adopted by Tunisia, however, take a highly restrictive stance. The regulations provide that

> Medical or scientific experimentation on medicaments intended for use in human medicine may be undertaken only on persons who have reached the age of majority and enjoy all their mental faculties and legal capacities. No experimentation may be performed on minors.[3]

Criterion of Necessity

Out of a recognition of the benefits of medical research, it is uncommon to find any jurisdictions that have extended a comprehensive prohibition such as Tunisia's. This, however, does not mean that experiments can be conducted under any circumstances. To protect the child, many guidelines take the view that pediatric research is only permissible when the knowledge sought cannot be obtained in any other fashion; that is, similar studies on adults could not yield the same information, usually because the research relates to pediatric disease. For example, the guidelines issued by the British Paediatric Association (BPA) state that "research should only be done on children if comparable research on adults could not answer the same question."[4] Similarly, the American Medical Association (AMA) has stated that "minors . . . may be used as subjects only if . . . the nature of the investigation is such that mentally competent adults would not be suitable subjects."[5] Provisions to the same effect can be found in many other guidelines[6] and regulations.[7] The same recommendation was made in a Canadian report.[8]

The criterion of necessity seems to be a refinement of a general principle on research with human subjects: experiments should only be conducted when other means cannot yield the required information. The *Nuremberg Code* states that "the experiment should be such as to yield fruitful results . . . unprocurable by other methods."[9] In the case of adults, this means that laboratory and animal studies are inadequate; for children, this additionally implies that research with adults is insufficient.

Selecting among Children

Most documents merely indicate when children should be used in medical research but are silent on the matter of which children should be used. The BPA and the Council for International Organizations of Medical Sciences (CIOMS) guidelines are unique, however, in that they both recommend that preference be given to the selection of older rather than younger children.[10] The two differ, though, in that the CIOMS guidelines state that "older children *who are capable of informed consent* should be selected before younger children [italics added]," whereas the BPA guidelines merely provide, "When a choice of age groups is possible, older children should be involved in preference to younger ones." The rationale behind the CIOMS policy is clear; legally competent persons are in a better position to protect their own interests than are incompetent persons. Although no reasons are provided in the BPA document, a similar idea, i.e., that older children can better protect their interests than younger ones, is no doubt the motivation for its policy. Nonetheless, some research can only be conducted on very young children.

Decision to Participate: Who Decides?

Consent and the Child

Consent is a vital element of medical research with adults. Based on the principle of autonomy, it signifies an acceptance by the participant of the risks inherent in the particular research activity. However, whereas adults are presumed to be autonomous, it is not always clear that children are. This fact brings into question the ability of children to decide for themselves on their participation in experiments, i.e., their capacity to give a valid consent. To compensate for this decisional incapacity, it is generally recognized that in matters that affect the well-being of children, parental/guardian involvement in decision making is crucial. At issue, though, is the extent of the child's involvement in making these decisions.

Parental Consent

A few guidelines are highly protectionist. They take the view that children are incompetent to make decisions for themselves, and they therefore cannot be involved in making those decisions in any way at all. These documents make no reference to children's involvement; rather, they only set down a requirement that the researcher obtain the necessary approval from an appropriate guardian. For example, the AMA guidelines state that consent must be "given by a legally authorized representative of the subject."[11] Similarly, the European Commission has stated that a child should only be enrolled in a drug trial with "the agreement of a legally valid representative."[12] The European Charter of the Rights of the Child states that no child may be involved in research "without due authorization by his parents or the persons responsible for him."[13]

Assent of a Legal Minor

Solely relying on parental consent is based on an all-or-nothing view of a child's ability to make an informed and intelligent choice. In fact, children's capacity to consent probably develops as they grow older. In this light, capacity should not be viewed as being either present or absent but as a developing quality along a continuum of understanding. Thus, as the National Council on Bioethics in Human Research (Canada) has argued, although "children's vulnerability requires protection, their maturation requires nurture. The 'protective stance' is merged with one which recognizes the increasing achievement of adult independence by the majority of children."[14]

In recognition of the autonomy of the child, various guidelines give sufficiently mature children the right to be involved in the decision to participate in a research study, while preserving an important parental role. For example, the U.S. regulations require a child's "assent" in addition to parental "permission."[15] The assent must be the "child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent." Whether children are capable of giving assent depends on an assessment of the "ages, maturity, and psychological state of the children involved." Such an evaluation will be made for each child in the trial; as a result, the assent of none, some, or all may be required. Along the same lines, a preliminary draft of the *Bioethics Convention* being prepared under the auspices of the Council of Europe

provides that "the consent of minors shall be regarded as an increasingly determining factor in proportion to their age and capacity for discernment."[16] Similar provisions can be found in other guidelines,[17] reports,[18] and legal instruments.[19] A variety of terminology is used; thus, guidelines variously refer to parental "permission,"[20] "consent,"[21] and "proxy consent,"[22] as well as children's "assent"[23] and "consent."[24]

The double requirement of child assent and parental consent recognizes two competing values. By making a child's assent necessary, recognition is given to the autonomy of children who are mature enough to be involved in the decision to participate in research. However, by making this assent insufficient, the codes acknowledge that children are not always as autonomous as adults and thus need protection.

As an exception, the U.S. regulations[25] permit research solely on the basis of parental consent, without children's assent if 1) the research involves no more than minimal risk, 2) the lack of assent will not adversely affect the welfare and rights of the children, and 3) the research could not be carried out if assent were required.

Children's Refusal

Although a child's ability to assent is dependent on age and level of maturity, a few guidelines specify that a child's refusal to participate should be respected at any age. For example, the Medical Research Council of Canada (MRCC) code states that "a child whose consent or assent to participate in research is questionable, may nevertheless have the power to decline invasive involvement with conclusive effect."[26] Similarly, the Royal College of Psychiatrists (UK) guidelines state that parental consent "should not override the child's refusal."[27] The Medical Research Council (UK) (MRC) document[28] and a French law[29] contain similar provisions. One may argue that these provisions recognize the autonomy of the child. However, it is arguable that the emphasis is not so much on a child's reasoned refusal as on an unwillingness to force a child to do anything that might upset him/her. If autonomy were the guiding principle, then the same age requirements would apply to both assent and objections; they clearly do not. Concern not for autonomy but for the psychological well-being of the child may be the rationale behind these provisions. Moreover, an unwilling participant may distort the scientific validity of the results, especially in research where the cooperation of the subject is essential.

The CIOMS guidelines, however, take the view that the child's unwillingness to participate should be balanced against the possible benefit to the child. Thus, although they allow for a child's refusal to be respected, this refusal may be overridden if "according to the research protocol, the child would receive therapy for which there is no medically-acceptable alternative."[30]

United Kingdom Provisions

The above guidelines show respect for the autonomy of legal minors. In contrast, some bodies in the United Kingdom have issued codes that seek to limit the independence of minors who are legally competent to consent to treatment. For example, the MRC document states that when a child under 16 is legally competent to consent (as evidenced by their degree of maturity, etc.) to treatment and hence

therapeutic research it is nonetheless "usually wise to complement this with the approval of his parents or guardian."[31] Children who are over 16 have the power to give a legally valid consent to therapeutic research. Nevertheless, although the MRC acknowledges that "such consent does not in law demand a parallel consent from a parent or guardian," there may be circumstances in which "it may be thought to be a matter of good professional practice to seek the child's permission to explain the research proposal to parents and, if they object, to give these objections considerable weight." Unfortunately, it is left unspecified how a parent's objection would be weighed against a child's consent. For nontherapeutic procedures, the guidelines recognize that although a sufficiently mature child may consent to the procedure, "the prudent course of conduct would be to seek the consent of a parent or guardian."

Along the same lines, the Royal College of Physicians (RCP) guidelines state that for children under 16 "even if . . . a child is capable of giving legally valid consent, we advise that the approval of a parent or guardian should still be obtained."[32] For children over 16, "it may be also desirable to obtain parental consent." These guidelines also provide that the objections of a parent or guardian should always be respected, even for legally competent children. The Department of Health (UK) guidelines also state that, for legally competent children over 16 (but under 18), "generally parental consent should also be required."[33] However, an exception is allowed in situations where it is in the child's best interests that the parents not be informed. What those circumstances are is left unspecified. For children under 16 who are legally competent to give consent, "it would however be unacceptable not to have consent of the parent or guardian."

The United Kingdom codes run counter to a general trend granting increased recognition to the autonomy of children. In contrast to these guidelines, the BPA document states that if children are sufficiently mature to understand the procedure that is proposed, then only their consent is required.[34] In defence of these restrictive provisions, one may argue that whereas children of sufficient maturity may have a moral claim to greater control over treatment decisions, no such claim can be made regarding their participation in medical research. In response, it must be pointed out that the research/treatment distinction is untenable for therapeutic research. Moreover, if children are judged by an objective standard to be sufficiently capable to make certain life decisions for themselves, involving their parents without their agreement does not show respect for children as persons.

The MRC, Department of Health (UK), and RCP guidelines are consistent with a recent trend in the English courts, which have limited the autonomy of children with respect to informed consent. For example, in *Re W (A minor)*,[35] the Court of Appeal held that although a minor who had reached the age of 16 had the right to consent to medical treatment, a parent or the courts may override the refusal of consent given by a competent minor.

Permissible Kinds of Research Activity

Therapeutic vs. Nontherapeutic Research

Most guidelines draw a distinction between therapeutic and nontherapeutic research. In therapeutic research, the procedure performed is of potential benefit to the research subject. Conventionally, the procedure is administered to patients in the hope that the treatment will alleviate/cure their medical condition. Nonther-

apeutic research, in contrast, offers no such possibility of benefit to the research subject. Such an experiment may be designed to derive knowledge of a basic nature, for example, the elucidation of the digestive functioning of a normal human body. In other cases, such as for Phase I drug trials, the aim is to examine the effect on healthy people of medication that will later be used in therapeutic trials. Although nontherapeutic research does not benefit research participants, the knowledge it produces is of enormous importance and can be said to benefit society as a whole. In summary, the distinction between therapeutic and nontherapeutic research relates to who primarily benefits; the research subject or society.

Therapeutic Research: Risk–Benefit Analysis

The permissibility of therapeutic research, because it is in essence a form of medical treatment, is relatively uncontroversial. With the exception of the Tunisian regulations,[36] no legal instruments or codes prohibit therapeutic research. However, it is standard practice to require that therapeutic research only be conducted when the benefits of the proposed treatment outweigh its risks. This principle extends to research with all subjects, both adults and children. For example, the U.S. regulations state that research on adults may only take place when the "risks to subjects are reasonable in relation to anticipated benefits."[37] The *Declaration of Helsinki IV* states that "every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefit to the subject or to others."[38]

Levine[39] noted that the ethical principle of beneficence, i.e., to do no harm and to maximize possible benefits and minimize possible harms, is the philosophical basis for a favorable balance of risks and benefits. Thus, risk–benefit analysis is an additional level of protection beyond the requirement for informed consent because it limits the range of treatments that the subject may consent to. Because risk–benefit analysis is such an integral part of therapeutic research, it is only mentioned in a few general guidelines[40] and regulations[41] in their sections on pediatric research.

The BPA document has taken an interesting approach to risk–benefit analysis with children. It explicitly recognizes that the risks and benefits faced by children are different from those faced by adults, because "potentially with many decades ahead of them, they are likely to experience, in their development and education, the most lasting benefits or harms from research."[42] A Canadian report[43] suggested that risk–benefit analysis must be specific to the type of child. For example, one must distinguish the level of acceptable harm for infants from that for older children.

Codes usually require that a comparison be made between the proposed therapy and the standard treatment for the disease, if any, to assess whether the former is at least as advantageous as the latter. If this calculation were not performed, children could be denied a better treatment, thereby violating the principle of beneficence that underlies comparisons of risks and benefits. For example, the CIOMS guidelines state that

> interventions intended to provide direct diagnostic, therapeutic, or preventative benefit for the individual child-subject must be justified by the expectation that they will be at least as advantageous to the individual child-subject, considering both risks and benefits, as any available alternative.[44]

Because most guidelines are addressed to researchers and to research ethics committees, one may reasonably assume that the risk–benefit calculation is to be performed by them. The MRC document, however, states that a child's "inclusion should be subject to his parents' or guardians' judgement that the benefits likely to accrue to him outweigh the possible risks of harm."[45] One way to explain this provision is that consent and/or permission, by its very nature, involves a weighing of potential risks and benefits. The MRC guidelines, on this interpretation, merely restate what is implicit in requiring parental permission. However, what they do seem to omit is a consideration of risks and benefits by a body of informed and experienced professionals who are emotionally distanced from the situation at hand. Thus understood, review by committee provides an additional level of protection beyond parental permission.

Although all that is usually required for therapeutic research to proceed is a favorable risk–benefit ratio, some documents look directly at the magnitude and/or probability of the risks and benefits arising from the procedure. The Council of Europe, for example, stated that a "legally incapacitated person may not undergo medical research unless it is expected to produce a direct and significant benefit to his health."[46] On a plain reading, this provision would seem to exclude therapeutic research that does not offer a substantial benefit to child subjects, even if the benefits outweighed the risks. A Canadian report, in contrast, focused on risks, recommending that therapeutic research that has the potential of producing a "substantial probability" of a "substantial magnitude" of harm is not normally permissible.[47] However, an exception is allowed when "the benefit . . . could be seen as *substantially* outweighing the substantial probability of substantial harm [italics added]." As an example, the report suggested that "innovative attempts at life-saving interventions" could be allowed.

In this regard, the French law governing medical research merits special attention because its consent procedures for therapeutic research depend on the magnitude of the risk faced by the child. If the procedure does not involve "any serious foreseeable risk,"[48] parental/guardian consent is adequate. However, "in other cases," i.e., when the risk is greater, the parent/guardian must be authorized by the "Family Council or the judge supervising guardianship." Given the potentially serious ramifications of pursuing risky therapy, required third-party agreement serves as an additional check to protect the child. Moreover, as the British Medical Association noted, parents who volunteer their children for research are often emotionally vulnerable.[49] Involving a third party can help them to clarify their reasons, thereby ensuring that their decision is a considered one.

Nontherapeutic Research

Nontherapeutic procedures, unlike therapeutic procedures, do not benefit the research subject. With adults, codes generally take the view that as long as the benefits of the research outweigh the risks to the subject, then the experiment may proceed. The safeguard here is the requirement for consent. Faced with the prospect of involvement in an activity that offers them no benefit, people will only take on a level of risk acceptable to them.

The difficulty with children is that they may not be autonomous enough to accept these risks themselves. Whether through proxy consent or a combination of assent and consent, a parent or guardian is usually involved. The question is what standard of conduct is expected from those who authorize research on

children? Considerable support can be found for the view that parents must always act in their children's best interests. If this is the case, however, then the permissibility of nontherapeutic pediatric research, which by definition is not in the interest of the subject, is called into question.

Historically, a small minority of documents have dealt with this conundrum by banning nontherapeutic research on children entirely. An early example is a directive issued in 1900 by the Prussian Minister of Religious, Educational, and Medical Affairs, which may be in fact the first published regulation governing medical research. The directive states that "medical interventions for purposes other than diagnosis, therapy, and immunization are absolutely prohibited, even though all other legal and ethical requirements for performing such interventions are fulfilled if . . . the person in question is a minor or is not fully competent on other grounds."[50] The prohibition on nontherapeutic research with child subjects is complete.

Closer to the present, the *Nuremberg Code*, which governs nontherapeutic research, provides that "the voluntary consent of the human subject is absolutely essential. This means that the person involved should have the legal capacity to give consent."[51] Clearly, this language is intended to exclude legal incompetents from nontherapeutic procedures, and such a prohibition no doubt extends to children. A similar provision is found in Article 7 of the *International Covenant on Civil and Political Rights*,[52] which states that "no one shall be subjected without his free consent to medical or scientific experimentation." This article was undoubtedly inspired by the *Nuremberg Code*.[53]

A more recent example of a similar measure can be found in the pharmaceuticals research rules issued by Pakistan. Rule 7 states that "studies on children shall not be undertaken unless there is a possibility of benefit to them."[54] If "them" is taken to refer to the children involved in the experiments, as is likely, the Pakistani regulations would also seem to ban nontherapeutic drug trials.

The overwhelming majority of legal instruments and codes, however, do not adopt a restrictive approach to nontherapeutic research. In effect, they attempt to satisfy the best interests standard by only allowing nontherapeutic research when it is not against the interests of the child. This goal is met by limiting the risks inherent in the procedure in contrast to the balancing of risks and benefits seen in therapeutic research. In most cases, this means that only nontherapeutic activity carrying "minimal"[55,56] risk is permissible. Other documents refer to risk that is only "negligible"[57] or "low,"[58] whereas one report suggests that the experiment "not involve any serious risks."[59]

Some attempt has been made to define the content of these words. This is sometimes rather ambiguous. For example, the Department of Health (UK) guidelines describe a minimal risk as "one so insignificant as to be negligible."[60] However, some codes set the level of acceptable risk as risks of harm faced by children in their daily lives. For example, the MRCC guidelines state that "parents should not expose children to greater risks, for the sake of pure medical research, than the children take in their everyday lives."[61] In contrast, the CIOMS document defines the threshold of acceptable risk as "the risk attached to routine medical or psychological examination of such children."[62] Some documents, such as the MRC guidelines and the U.S. Federal Regulations, combine both definitions.[63]

On occasion, specific examples are given of procedures that fall into the acceptable category. Thus, the MRC document additionally provides that "procedures involving negligible risk would include the observation of behaviour, noninvasive

physical monitoring, developmental assessments and physical examination, changes in diet and obtaining blood and urine specimens."[64] Similarly, the BPA has stated that "procedures with minimal risk include collecting a single urine sample (but not by aspiration), or using blood from a sample that has been taken as part of treatment."[65]

It may be argued that "minimal risk" may be too restrictive a ceiling on nontherapeutic research. Some guidelines have responded to this fear by allowing an increase in the acceptable level of risk in exceptional circumstances, for example, when the aims of the research are extremely important or, in other words, the benefits of the research outweigh the risks. Thus, although the major mode of regulating nontherapeutic research seems to involve the setting of limits on the degree of risk, some codes nonetheless include risk–benefit analysis as an additional requirement. The CIOMS guidelines, for example, allow such an increase when "an ethical review committee is persuaded that the object of the research is sufficiently important."[66] Similarly, the Council of Europe has stated that the "risks should not be disproportionate to . . . the importance of the aims pursued by the research."[67]

The U.S. regulations, along the same lines, set a number of requirements, including that the risk must only represent "a minor increase over minimal risk" and that "the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' order or condition," which implicitly involves the weighing of risk and benefit.[68] Like the U.S. regulations, a Canadian report recommends that risk–benefit analysis be performed for nontherapeutic research when there is a greater than a negligible probability of negligible harm.[69]

In recent years, there has been some debate in Canada and the United Kingdom over the permissibility of venipuncture during nontherapeutic research. At issue is whether it poses too great a risk of harm to children. Venipuncture, when performed properly, does not pose a great threat of long-term physical harm. However, the short-term pain can be great. Moreover, given children's strong dislike of the procedure, the potential exists for psychological harm to the child.

The MRCC guidelines contain provisions that have been interpreted as prohibiting venipuncture. Although they provide that parents "may permit others to handle their children in ways that would otherwise constitute a technical and minor legal assault," nonetheless, research where "pain or discomfort beyond carefully defined limits would be liable to occur" is not acceptable.[70] Given that venipuncture is a routine procedure, Canadian researchers expressed concern that the MRCC guidelines were too stringent.[71] To respond to criticism of venipuncture, a recent Canadian report[72] reviews some methods whereby the psychological distress of venipuncture can be significantly reduced.

The BPA guidelines, however, have taken the view that venipuncture may not always constitute a low risk procedure and is therefore not always permissible.[73] The document states that "many children fear needles and to them low rather than minimal risks are often incurred by injection and venipuncture." The idea here is that when a child is very upset by the prospect of venipuncture, researchers should "accept this as genuine dissent from being involved." Conversely, when the child does not object, "the perspective which governs the situation is not that of the adult researcher, but that of the child subject." Protecting the child from

psychological harm seems to be the goal of these provisions. Moreover, by taking a subjective approach, the BPA seems to be basing its stance on a respect for children as persons; "the issue is no different from an adult's refusal to join a research project because of an extreme dislike to venipuncture."

Given the parental duty to act in their children's best interests, the issue of how children are to be enrolled in nontherapeutic research is an important one. No guidelines suggest that procedures for consent and/or assent should be any different. Nonetheless, fears may be raised that the lack of any benefit to research subjects in these situations creates the need for new safeguards. For example, the Law Reform Commission of Canada[74] has recommended that not only parental consent but also the consent "of an independent third party" be obtained. Examples of a third party are a judge, an ombudsman, or the child's lawyer.

Research Ethics Committees

In contrast to these issues, the question of the composition of research ethics committees, which review proposals for pediatric research, has received little attention. At issue is whether committees should have members with expertise in pediatric medicine or whether the same committees that review proposals for research with adults should be used.

A report by the Institute of Medical Ethics in London[75] gives a glimpse of what the situation was in the U.K. in 1982. According to the report, 118 (68%) of the committees had no pediatrician at all. This in itself is inconclusive because these committees may never come across proposals for pediatric research. However, of these 118 committees, 18 reviewed four or more proposals for pediatric research during 1981 and 1982.

Nicholson and his colleagues argued that there

> has been ample illustration . . . of the special problems of clinical research on children . . . [which] need to be present to, and understood by, a research ethics committee. The obvious way in which to so this is by having a paediatrician as a member of the committee.[76]

The argument made here is one of expertise. Those who have no professional involvement with children are not as qualified, presumably, to deal with both the scientific and ethical aspects of pediatric research. Where this line of reasoning is most compelling is in the domain of risk–benefit analysis. The same physiological differences between adults and children that make pediatric research necessary mean that children face different risks arising from research.

The BPA guidelines suggest that committees "considering a project involving children should be advised by people with a close, practical knowledge of babies and children."[77] This role need not be limited to pediatricians; the guidelines state that a children's ward nurse could be involved. Moreover, the nature of the involvement may vary with the circumstances, ranging from membership on the committee to serving as a member of a subcommittee specially constituted for the purpose. Guidelines issued by the RCP for the practice of research ethics committees[78] also recognize the special need for committees to have relevant expertise. Although the College disapproves of "the tendency of medical specialties to seek to set up their own committees," a possible exception can be made

in the case of "substantial specialist institutions e.g. paediatric hospitals." The U.S. regulations state that the committee membership should reflect the "research activities commonly conducted by the institution,"[79] thereby obliging research centers with a high pediatric workload to have suitably qualified members on the committee. A Canadian report recommended that committees include a "child representative," i.e., an individual with expertise in "children's growth, development, and care."[80]

Conclusions

This review has concentrated largely on materials issued by governments or organizations in the developed world, which limits the generality of any observations. With this limitation in mind, the following conclusions can be drawn.

1) There seems to be a general consensus that pediatric research is permissible but should only be conducted when research with adults cannot yield the same information.
2) Documents differ to a great extent in how they approach children's involvement in the decision to participate in research. Some adopt a highly protectionist stance, relying solely on parental consent, while others adopt the dual requirement of parental permission and children's consent.
3) Therapeutic procedures are subject to a favorable risk–benefit analysis, although some documents additionally look directly at the magnitude of the risk or benefit. Nontherapeutic research is permitted, subject to a limitation on the magnitude of the risk faced. Exceptions to this ceiling of "minimal" risk require a weighing of risks and benefits.
4) Codes give scant attention to the composition of research ethics committees that review proposals for pediatric research. Given that research with children raises unique issues, this is an area where further attention may be warranted.

Notes

1. See generally Grodin MA, Glantz L, eds. *Children as Research Subjects: Science, Ethics, and Law.* New York: Oxford University Press. 1994. Nicholson RH, ed. *Medical Research with Children: Ethics, Law, and Practice.* New York: Oxford University Press. 1986. Koren G, ed. *Textbook of Ethics in Pediatric Research.* Malabar, Florida: Kreiger Publishing. 1993.
2. This study is based on source materials available in the Health Legislation Unit, WHO. Although codes and laws from a variety of jurisdictions and national organizations and those promulgated by many international bodies have been examined, this paper does not purport to be a comprehensive review of all laws and codes governing medical experimentation with children.
3. Tunisia. *Decree No. 90-1401 of 3 September 1990 on Medical/Scientific Experimentation on Drugs for Human Use.* 1990:Section 2. Reprinted in *International Digest of Health Legislation* 1991;42:489.
4. British Paediatric Association. *Guidelines for the Ethical Conduct of Medical Research Involving Children.* 1992:3.
5. American Medical Association. *Current Opinions of the Council of Ethical and Judicial Affairs on Clinical Investigation.* 1992:5.
6. See, e.g., Medical Research Council of Canada. *Guidelines on Research Involving Human Subjects.* 1987:28. Medical Research Council (UK). *The Ethical Conduct of Research on Children.* 1991:13. Department of Health (UK). *Local Research Ethics Committees.* 1991:16. Royal College of Psychiatrists (UK). *Guidelines for Research Ethics Committees on Psychiatric Research Involving Human Subjects.* 1990:4.

Council for International Organizations of Medical Sciences [CIOMS]. *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* 1993:20. Australian Health and Medical Research Council. *Statement on Human Experimentation and Supplementary Notes.* 1987:7.

7. Hungary. *Ordinance No. 11 of 19 August 1987 of the Minister of Health on Biomedical Research.* 1987: Section 7(3). Reprinted in *International Digest of Health Legislation* 1988;39:97–8.
8. National Council on Bioethics in Human Research [NCBHR] (Canada). *Report on Research Involving Children.* 1992:7.
9. *U.S. v. Karl Brandt et al. Trials of War Criminals before the Nuremberg Military Tribunals Under Control Council Law No. 10.* Vol. I, Vol. II: 181–5, principle 2. 1949.
10. See note 4. British Paediatric Association. 1992:6. See note 6. CIOMS. 1993:20.
11. See note 5. American Medical Association. 1989:5.
12. Commission of the European Communities. *Good Clinical Practice for Trials on Medicinal Products in the European Community.* 1990:16.
13. European Parliament. *Resolution on a European Charter of Rights of the Child.* 1992:Paragraph 8.30. 1992. Reprinted in *International Digest of Health Legislation* 1993;44:139. See also note 7. Hungary. 1988;7(1). World Psychiatric Association. *Declaration of Hawaii* II. 1983:Art. 10.
14. See note 8. NCBHR (Canada). 1992:11.
15. United States. *45 Code of Federal Regulations* [CFR]. Part 46, sec. 408(a). 1991.
16. Council of Europe. *Preliminary Draft Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Bioethics Convention.* 1993: Article 6. 6 July 1993.
17. World Medical Association. *Declaration of Helsinki.* IV. 1989:principle 11. See note 6. CIOMS. 1993:20. See note 6. Australian Health and Medical Research Council. 1987:8. Council of Europe. *Recommendation No. R (90) 3 of the Committee of Ministers to Member States Concerning Medical Research on Human Beings.* 1990:Principle 4. Reprinted in *International Digest of Health Legislation* 1990;41:461, 463.
18. See note 8. NCBHR (Canada). 1992:3.
19. France. *Law No. 88-1138 of 20 December 1988 on the Protection of Persons Participating in Biomedical Research.* 1988:Article 209-10. Reprinted in *International Digest of Health Legislation* 1989;40:111–112.
20. See note 15. United States. 1991:sec. 408.
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22. See note 15. United States. 1991:sec. 408.
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