Assessment of risk in research on children

Proposed federal regulations regarding clinical research require that institutional review boards determine whether a research project involving children is justified and, if so, whether the child's assent and parent's permission should be required before the child becomes a research subject. A key factor in the IRB's decision is assessment of the risk to the child from participation in the research. Since data on frequency of risks associated with many pediatric procedures that may be employed in clinical research is lacking, a survey of pediatric department chairmen and pediatric clinical research center directors was conducted to ascertain their opinions of the risks of some procedures at various ages of childhood. Although most of these procedures were thought to be of minimal or less than minimal risk, a few (certain types of venipuncture, arterial puncture, and gastric and intestinal intubation) were thought to pose greater than minimal risk, especially in young children. Respondents were also asked to indicate the criteria used to decide whether a child is capable of giving assent to participate in an experimental procedure. In the majority of institutions (73%), it appears that this decision is left to the clinical judgment of the investigator or a member of the research group.

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"UNDER WHAT CONDITIONS is participation of children in research ethically acceptable, and under what conditions may such research be authorized by the subjects or their parents?"[1] The National Commission for the Protection of Human Subjects faced these questions when it was formed by the Department of Health, Education, and Welfare (now the Department of Health and Human Services) in 1974. The Commission requested papers from physicians, ethicists, jurists, and others, surveyed investigators whose work involved children, and conducted public hearings during which representatives of professional societies, public interest groups, federal agencies, and the general public expressed their views.[2] Recommendations with extensive critical comments were presented by the Commission to the Secretary of Health, Education, and Welfare in 1977.[3] After some modification, the recommendations were codified into proposed federal regulations.[4] When finally approved, the regulations will supplement federal regulation 45 CFR § 46, which in its original form provides guidelines for the protection of human subjects for research supported by DHHS but gives no special status to children as research subjects. The Food and Drug Administration has adopted almost identical regulations for projects which come under its jurisdiction and involve children.[5]

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Abbreviations used
IRB: institutional review board
DHEW: Department of Health, Education and Welfare
DHHS: Department of Health and Human Services

The proposed rules charge local institutional review boards with determining if a research project involving children is justified and, if so, whether the child's assent and parent's permission should be required. The proposed regulations abandon the dichotomy of therapeutic

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vs nontherapeutic research, terms that date back to the Declaration of Helsinki in 1964.[6] Instead the regulations require IRB members to first ask if a proposed project involves greater than minimal risk. Only if the IRB determines that a proposed project will in fact entail greater than minimal risk must its members additionally address other issues, such as whether there is the prospect of direct benefit to individual subjects or whether the child is mature enough to assent to the research; IRB members need not address these more complex questions if a project involves minimal risk or less. Thus decisions about risk must be made separately from and before any consideration of possible benefit is judged.

The proposed regulations do not, however, indicate how the IRB is to determine a child's maturity. The mechanism eventually selected will be one of the following: requiring that assent be acquired from all children above a certain age; recommending but not requiring that assent be acquired from children above a certain age; or leaving the decision entirely to the local IRB, with no age guidelines.[7]

It is important to assure that IRB members have access to appropriate information in order that they can intelligently carry out the task assigned to them. As risk assessment is the fundamental step in an IRB's approval of a project, the judgment of IRB members about degree of risk is critical to their role in judging the ethics of research. However, data on the risk inherent in many pediatric procedures are limited to listings of complications and case reports, neither of which provide the frequency of morbidity and mortality associated with the procedures. The literature on venipuncture, one of the most frequently performed pediatric procedures, is restricted to case reports of risk associated with septic arthritis of the hip (four cases),[8] gangrene of the lower extremity (two cases),[9] and arterial spasm (one case)[10] following femoral venipuncture in infants. A literature review published in 1966 states, "no statistical data are available for an analysis of the relative safety of the various methods of venipuncture [in children]. . . ."[11] The validity of that statement has not changed in the 14 years since publication of that review.

Reliable information on the frequency of both the physical and psychologic risks intrinsic to such research procedures as tympanocentesis, arterial puncture, skin biopsy, gastric or intestinal intubation, use of a metabolic bed, and bone scan are absent from the pediatric literature. One case report dealing with complications following intramuscular injection of the lateral thigh was found.[12] Handbooks of pediatric practice list hazards accompanying many procedures but give no indication of the rate of occurrence of these untoward effects.[13, 14] Psychologic risks associated with long-term hospitalization have been documented, with suggestions on how to minimize those risks.[15] Both Douglas[16] and Quinton and Rutter[17] showed that a single hospital stay of less than one week's duration for children 5 years of age or less had no adverse effects on emotional development in later childhood. Multiple, short hospital stays and stays longer than one week in early childhood were associated with an increased incidence of emotional problems in later years, according to the same researchers.

Therefore, in making judgments about the extent of risk, IRB members do not have prospective studies to provide them with data they need to make necessary judgments. In the absence of scientific evidence, the only alternative is the use of informed opinion. The following study attempts to assess such informed opinion and to ascertain common practice regarding the assent process.

METHODS

A questionnaire was sent to a 50% random sample of pediatric department chairmen identified on the membership list of the Association of Medical School Pediatric Department Chairmen, Inc.[18] In addition, all pediatric clinical research unit program directors listed in a directory of General Clinical Research Centers[19] were queried. Both types of individuals were thought to have experience with clinical procedures that would enable them to make informed judgments about the risks involved with each procedure in a research setting. Both groups were asked to have another member of their staff answer the questionnaire if they believed that the staff member was more familiar with the issues involved. As the two groups did not differ in their responses, the findings from both groups were combined for presentation.

Respondents were requested to use their "experience and clinical judgment" to assess each of various pediatric procedures as having no risk, minimal risk, minor increase over minimal risk, or greater than minor increase over minimal risk, assuming that a healthy child was the subject of the procedure. These are the same categories that IRB members must use to assess research according to the proposed federal regulations. The definition of minimal risk used in the proposed regulations ("the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy children"[20]) was provided to the respondents. Interpretation of minor increase over minimal risk was left to the judgment of the respondent, just as the proposed regulations leave the definition of that term to individual IRB members.

Common practice on assent was ascertained by asking

Table. Risk assessment: percentage of respondents indicating degree of risk*

	Newborn to 1 year			*1 to 4 yr*			*5 to 6 yr*			*7 to 11 yr*			*12 to 18 yr*		
	< *min*†	> *min*‡	>> *min*§	< *min*	> *min*	>> *min*	< *min*	> *min*	>> *min*	< *min*	> *min*	>> *min*	< *min*	> *min*	>> *min*
Venipuncture at:															
Antecubital fossa	78	19	3	88	12	0	98	2	0	98	2	0	97	1	2
Femoral vein	8	40	52	N/A‖	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Internal jugular vein	1	29	70	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
External jugular vein	28	62	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Arterial puncture	8	51	41	10	60	30	16	57	27	13	57	30	24	55	21
Tympanocentesis	14	46	40	34	31	35	25	55	20	33	47	20	35	45	20
Skin biopsy (punch)	55	41	4	57	38	5	65	31	4	65	32	3	68	29	3
Gastric/intestinal intubation	35	55	10	39	44	17	44	41	15	52	39	9	59	32	9
Metabolic bed (24 hr)	78	21	1	73	23	4	80	17	3	89	11	0	91	9	0
Bone scan	55	31	14	54	34	12	59	32	9	59	35	6	57	37	6
IM placebo injection	69	25	6	73	21	6	77	18	5	76	20	4	76	20	4
Questions to the child about sexual practice	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	57	39	4	67	27	6
Questions to the child about illicit drug use	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	62	32	6	71	23	6
Hospitalization for observation (24 hr)	75	24	1	65	32	3	77	22	1	81	19	0	86	14	0

*As all respondents did not reply to all questions, n varied between 64 and 73 with a mean of 70.
†Rated as no risk or minimal risk.
‡Rated as a minor increase over minimal risk.
§Rated as greater than a minor increase over minimal risk.
‖Not asked.

researchers to indicate the main criterion used by their units to decide whether a child is capable of giving assent to participation in an experimental procedure, and whether assent is obtained. If so, the frequency with which children's assent was recorded was also asked.

RESULTS

Individuals who failed to respond to the initial mailing were sent another. Of 28 clinical research centers surveyed, 19 eventually responded; 54 of 78 pediatric department chairmen replied, giving an overall response rate of 69%.

Risk assessment. Most respondents believed that the risk of antecubital venipuncture, skin biopsy (punch), confinement to a metabolic bed for 24 hours, bone scan, intramuscular placebo injection, and 24-hour hospitalization was minimal or less than minimal for infants and children regardless of age (see Table). A bare majority felt that the risk of gastric or intestinal intubation, of questioning a child about sexual practices, and of questioning a child about illicit drug use was less than minimal for children aged 7 to 18. If IRB members agree with this assessment, they may avoid issues such as benefit assessment and mandatory two-parent permission.

Risks of venipuncture of femoral, internal jugular, and external jugular veins for ages newborn to one year, and arterial puncture for ages newborn to 18 years, were rated by the majority as greater than minimal, and the risk of gastrointestinal intubation was rated as greater than minimal for ages newborn to 6 years (see Table). Here, consensus on risk suggests that projects involving these procedures require a more complex analysis by the IRB

and would have to meet more stringent requirements to avoid either disapproval or secretarial review.

Two procedures, femoral venipuncture and internal jugular venipuncture, done at age newborn to one year, were judged by the majority of respondents as greater than minor increase over minimal risk. These procedures would automatically require a secretarial review if done in a project not directly beneficial to the individual subject.

Assent by the child. Four of 73 respondents were unsure about assent procedures in their institutions. In two other institutions only infants served as research subjects, so that assent by the child was not an issue. Of the 67 remaining institutions, a child's assent is requested by 64 (96%) at least in some situations.

Respondents from these 64 institutions were asked to state "the main criterion used by their researchers to decide whether a child is capable of giving assent to participation in an experimental procedure." Forty-seven (73%) stated that the experimenter or a member of the research group uses clinical judgment regarding the maturity of the child to decide. Three respondents (5%) ask a third party not involved in the experimental procedure to judge whether the child is sufficiently mature to give assent. Of 13 respondents (20%) who indicated that the child's chronologic age was the sole criterion used to gauge maturity, four use 7 years, three use 12 years, two use 13 years, and one each uses 15, 10, 9, and 5 years as the minimum age when assent is first asked. Several of these respondents noted that an advocate may waive the assent requirement if the advocate judges the child incapable of understanding the procedure even if the child is of the required age. One research group attempts to obtain assent regardless of age and honors a child's firm objection to participate regardless of age.

Assent was never recorded when obtained in 61% of the institutions which require assent, was sometimes recorded in 32%, and was always recorded in 7% of those institutions.

DISCUSSION

Clinical research is an essential tool in the accumulation of knowledge in pediatrics and other branches of medicine. Without such research on children's behalf to ascertain the effectiveness of new drugs and procedures, they become the "therapeutic orphans"[21] of the medical community. Finely balanced against this great need is an equally important one: protection of research subjects from mental or physical harm, protection of their privacy, and respect for their autonomy. DHEW's proposed regulations fill a gap in the area of protection of children as research subjects. Putting a locally controlled IRB in charge of overseeing this task will assuage many scientists' fears of increasing federal government control over their lives.

In order to carry out their mandate, IRB members need to rely on whatever data are available to help them make their judgments. In the absence of frequency data about the extent of risk of most procedures, the opinions of experienced professionals associated with teaching hospitals and Clinical Research Units may help IRB members to assess risk when a research project incorporates one of the procedures addressed in this survey. For several reasons, such informed opinion should not continue to be the sole determinant of risk to children of procedures in research. (1) The respondents in this survey have a vested interest in the conduct of research and might tend to judge less risk than would other physicians, individuals without medical expertise, community representatives, and family members. The opinions of such individuals should certainly be sought in risk-benefit decisions. (2) The variability in assessment of risk, even among the academic pediatricians surveyed, suggests that these judgments are based on an inadequate body of knowledge.

We are aware of one other study of the experiences of researchers. In that study,[22] recipients of research grants were asked to provide information on the total number of individuals in their research and the number of "injuries" associated with the research in the course of the most recent three years. The report does not provide rates of injuries according to age of the subject or the particular research interventions, so that it is impossible to compare the results with those obtained in the present study. However, the long recall period makes it unlikely that the number of injuries (the numerator of the rate) and the total number of research subjects (the denominator of the rate) were recalled with accuracy, and the magnitude of the error in recall is unknown. Ideally, judgments about the degree of risk should be made on the basis of data collected prospectively and for the specific purpose of assessing risk.

Support of the collection of data from several research units employing the same techniques of observation, and recording of difficulties and complications of common procedures, would facilitate the difficult task of those who must make critical judgments about the risks encountered by children participating in research.

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