

NIH POLICY AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS
IN
RESEARCH INVOLVING HUMAN SUBJECTS

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P.T.

National Institutes of Health

SUMMARY: With this notice, the National Institutes of Health (NIH) establishes guidelines on the inclusion of children in research involving human subjects, including, but not limited to, clinical trials, supported or conducted by the NIH.

EFFECTIVE DATE: This policy applies to all initial (Type 1) applications/proposals and intramural projects submitted for receipt dates after October 1, 1998.

I. Introduction

This document sets forth the policy and guidelines on the inclusion of children in research involving human subjects that is supported or conducted by the National Institutes of Health (NIH). The goal of this policy is to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children. For the purposes of this NIH policy, studies involving human subjects include categories of research that would otherwise be exempted from the DHHS Policy for Protection of Human Research Subjects. These categories of research are exempted from the DHHS policy because they pose minimal risk to the participants, and not because the studies should not include children. Examples of such research include surveys, evaluation of educational interventions, and studies of existing data or specimens that should include children as participants. Nevertheless, the inclusion of children as participants in research must be in compliance with all applicable subparts of 45 CFR 46 as well as with other pertinent federal laws and regulations whether or not the research is otherwise exempted from 45 CFR 46.

II. Background

The policy was developed because medical treatments applied to children are often based upon testing done only in adults, and scientifically evaluated treatments are less available to children due to barriers to their inclusion in research studies. These concerns were specifically articulated in Congressional directives to the NIH as reflected in language from the FY 1996 House and Senate Appropriations Committee reports as follows:

HOUSE

The Committee is concerned that inadequate attention and resources are devoted to pediatric research conducted and supported by the National Institutes of Health. Most research on the cause, treatment and cure of diseases which affect children rely primarily on adults as subjects in clinical trials. Consequently, treatment options which may be effective for adults can have an adverse impact on the outcome of children as well as on their future growth and development. The Committee strongly encourages the NIH to strengthen its portfolio of basic, behavioral and clinical research conducted and supported by all of its relevant Institutes, to establish priorities for pediatric research, and to ensure the adequacy of translational research from the laboratory to the clinical setting. The Committee encourages the NIH to establish guidelines to include children in clinical research trials conducted and supported by NIH. The Committee expects NIH to develop performance indicators to measure specific progress on the above, demonstrated by the development of new programs or strengthening of existing programs and to report to the Committee prior to the 1997 appropriations hearings (H.R. Report No. 209, 104th Congress, 1st session, 80-81, 1995).

SENATE

Pediatric research---The Committee recognizes the substantial benefits that biomedical research offers to the health and well-being of our Nation's children. Savings from productive innovations in health care, derived from scientific investigations of the highest quality, can be significant in terms of dollars and

quality of life for children. The opportunities for advancements in the prevention and treatment of diseases which affect children or begin in childhood have never been greater. The Committee intends to work with the Office of the Director as it explores ways to take advantage of such opportunities and strengthen the NIH's capacity to support and encourage extramural pediatric research. Of particular interest is the establishment of guidelines to include children in clinical research trials conducted and supported by the NIH (S. Report No. 145, 104th Congress, 1st session, 112, 1995).

In June 1996, the National Institute of Child Health and Human Development (NICHD) and the American Academy of Pediatrics convened a workshop to address the inclusion of children as participants in research. After reviewing reports, background papers, and a study of a sample of NIH-sponsored clinical research abstracts that suggested that 10-20% inappropriately excluded children, the conveners concluded that there is a need to enhance the inclusion of children in clinical research. This conclusion is based upon scientific information, demonstrated human need, and considerations of justice for children in receiving adequately evaluated treatments. The need reaches across a broad spectrum of clinical research, including studies on pharmaceutical and therapeutic agents, behavioral, developmental and life cycle issues including childhood antecedents of adult disease, and prevention and health services research.

The American Academy of Pediatrics has reported that only a small fraction of all drugs and biological products marketed in the U.S. have had clinical trials performed in pediatric patients and a majority of marketed drugs are not labeled for use in pediatric patients. Many drugs used in the treatment of both common childhood illnesses and more serious conditions carry little information in the labels about use in pediatric patients. In order to address these inadequacies, the Food and Drug Administration (FDA) has published (<http://www.fda.gov/>) a proposed regulation calling for changes in the testing of prescription drugs to ensure that manufacturers specifically examine the drugs effects on children if the medications are to have clinically significant use in children.

In January 1997 the NIH announced (NIH Guide for Grants and Contracts, volume 26, Number 3, January 31, 1997) plans to develop a policy for the inclusion of children in NIH-supported human subject research. This publication fulfills the goal of the announced plan.

III. Policy

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all NIH conducted or supported research involving human subjects, including research that is otherwise "exempt" in accord with Sections 101(b) and 401(b) of 45 CFR 46 - Federal Policy for the Protection of Human Subjects. The inclusion of children as subjects in research must be in compliance with all applicable subparts of 45 CFR 46 as well as with other pertinent federal laws and regulations. Therefore, proposals for research involving human subjects must include a description of plans for including children. If children will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion.

In the research plan, the investigator should create a section titled "Participation of Children". This section should provide either a description of the plans to include children and a rationale for selecting or excluding a specific age range of child, or an explanation of the reason(s) for excluding children as participants in the research. When children are included, the plan must also include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. Scientific review groups at the NIH will assess each application as being "acceptable" or "unacceptable" in regard to the age-appropriate inclusion or exclusion of children in the research project, in

addition to evaluating the plans for conducting the research in accord with these provisions.

Justifications for Exclusions

It is expected that children will be included in all research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified:

1. The research topic to be studied is irrelevant to children.
2. There are laws or regulations barring the inclusion of children in the research. For example, the regulations for protection of human subjects allow consenting adults to accept a higher level of risk than are permitted for children.
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
 - a. The relative rarity of the condition in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition);
 - b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network, so that requiring inclusion of children in the proposed adult study would be both difficult and unnecessary (in that the topic was already being addressed in children by the network) as well as potentially counterproductive (in that fewer children could be available

for the network study if other studies were required to recruit and include them);

c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes).

While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested or the interventions to allow children to be included rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.

6. Study designs aimed at collecting additional data on pre-enrolled adult study participants (e.g., longitudinal follow-up studies that did not include data on children).

7. Other special cases justified by the investigator and found acceptable to the review group and the Institute Director.

IV. Implementation

A. Date of Implementation

This policy applies to all initial applications (Type 1)/proposals and intramural projects submitted for receipt dates after October 1, 1998.

B. Roles and Responsibilities

This policy applies to all NIH-conducted or -supported research involving human subjects. Certain individuals and groups have special roles and responsibilities with regard to the adoption and implementation of these guidelines.

1. Principal Investigators

Principal investigators should assess the scientific rationale for inclusion of children in the context of the topic of the study. Questions that should be considered in developing a study involving human subjects may include, but are not limited to, the following: When is the exclusion of children appropriate? Under what circumstances is it appropriate? At what ages is it appropriate? The principal investigator should address the policy in the application, providing the required information on participation of children in research projects, and required justifications for any exceptions allowed under the policy in the research plan under a section titled "Participation of Children".

2. Institutional Review Boards (IRBs)

The IRB addresses the appropriateness of the population studied in terms of the aims of the research and ethical standards. IRBs have the responsibility to examine ethical issues, including equitable selection of research participants in accordance with Federal Regulations (45 CFR 46). The participation of children in research, including children of both genders and children from minority groups, is important to assure that they receive a share of the benefits of research. IRBs have special review requirements (45 CFR 46, Subpart D, Sec. 401-409) to protect the well-being of children who participate in research. IRBs may approve research involving children only if the special provisions are met.

3. Scientific Review Groups

In conducting peer review of applications/proposals for scientific and technical merit, appropriately constituted scientific review groups, technical evaluation groups, and intramural review panels will evaluate the proposed plan for inclusion or exclusion of children as acceptable or unacceptable. Therefore, these groups must include appropriate expertise in research involving children to make the evaluation.

4. Institute/Center Obligations

Following scientific review and Council review, Institute/Center Directors and

their staff shall determine whether: (a) the research involves human subjects, and (b) the inclusion or exclusion of children meets the requirements of the policy. Program staff should assess exceptions to this policy in view of the IC research portfolio.

5. Educational Outreach by NIH to Inform the Professional Community

NIH staff will present these guidelines to investigators, IRB members, peer review groups, and Advisory Councils in a variety of public forums.

6. Applicability to Foreign Research Involving Human Subjects

The policy of inclusion of children in NIH-conducted or supported research activities in foreign countries (including collaborative activities) is the same as that for research conducted in the U.S.

V. Definitions

For the purpose of implementing these guidelines, the following definitions apply.

A. Child

For purposes of this policy, a child is an individual under the age of 21 years.

This policy and definition do not affect the human subject protection regulations for research on children (45 CFR 46) and their provisions for assent, permission, and consent, which remain unchanged.

It should be noted that the definition of child described above will pertain notwithstanding the FDA definition of a child as an individual from infancy to 16 years of age, and varying definitions employed by some states. Generally, State laws define what constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a research study. However, State laws vary, and many do not address when a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on State definitions of "child" for consent purposes. Consequently, the children

included in this policy (persons under the age of 21) may differ in the age at which their own consent is required and sufficient to participate in research under State law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Additionally, IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the State or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

B. Human Subjects

The definition of a human subject appears in Title 45 part 46 of the Department of Health and Human Services Regulations for the Protection of Human Subjects and is as follows: "Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) identifiable private information."

VI. Decision Tree for Participation of Children in Research

The inclusion of children in research is a complex and challenging issue. Nonetheless, it also presents the opportunity for researchers to address the concern that treatment modalities used to treat children for many diseases and disorders are based on research conducted with adults. The linked "[decision tree](#)" is intended to facilitate the determination of policy implementation by principal investigators and reviewers with regard to the inclusion of children in research involving human subjects.

VII. Additional Requirements for Research that Includes Children

The following chart summarizes the additional requirements under the DHHS Regulations 45 CFR 46, Subpart D based on the risks and benefits to children who participate in research:

Types of Research	Requirements
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No greater than minimal risk
permission

Greater than minimal risk AND
permission
prospect of direct benefit

justifies the

at least

Greater than minimal risk and
permission
no prospect of direct benefit

over

generalizable

child's

that is of

amelioration of

condition, AND

procedure

the child

commensurate

child's actual

dental,

or

Any other research
permission

Assent of child and
of at least one parent

Assent of child and
of at least one parent

Anticipated benefit
risk, AND

Anticipated benefit is
as favorable as that of
alternative approaches.

Assent of child and
of both parents

Only a minor increase
minimal risk

Likely to yield
knowledge about the
disorder or condition

vital importance for the
understanding or
the disorder or

The intervention or
presents experiences to
that are reasonably
with those in the
or expected medical,
psychological, social,
educational situations

Assent of child and
of both parents

research
opportunity
understanding,
alleviation of a
affecting the
children,

after
panel of
disciplines
medicine,
and
and public

IRB finds that the
presents a reasonable
to further the
prevention, or
serious problem
health or welfare of
AND
The Secretary approves,
consultation with a
experts in pertinent
(e.g., science,
education, ethics, law)
following publication
comment

VIII. NIH Contacts for More Information

The following senior extramural staff from the NIH Institutes and Centers may be contacted for further information about the policy and relevant Institute/Center programs:

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Dr. Marvin Kalt
National Cancer Institute Executive Plaza North, Room 600C, 6130 Executive Boulevard, Bethesda, Maryland 20892. Tel: (301) 496-5147. e-mail: mk74s@nih.gov

Dr. Jack McLaughlin, National Eye Institute, Executive Plaza South, Room 350, 6120 Executive Boulevard, Bethesda, Maryland 20892. Tel: (301) 496-9110. e-mail: jm82p@nih.gov

Dr. Ron Geller, National Health, Lung and Blood Institute, Rockledge Center 2,

Room 7100, 6701 Rockledge Drive, Bethesda, Maryland 20892. Tel: (301) 435-0260.
e-mail: rg33k@nih.gov

Dr. Mark Guyer, National Human Genome Research Institute, Building 38A, Room 604,
38 Library Drive, Bethesda, Maryland 20892. Tel: (301) 402-5407. e-mail:
mg25m@nih.gov

Dr. Miriam Kelty, National Institute on Aging, Gateway Building, Room 2C218F,
7201 Wisconsin Avenue, Bethesda, Maryland 20892. Tel: (301) 496-9322. e-mail:
mk46u@nih.gov

Dr. Kenneth Warren, National Institute on Alcohol Abuse and Alcoholism, Room 409,
MSC 7003, 6000 Executive Boulevard, Bethesda, Maryland 20892-7003. Tel: (301) 443-4375. e-mail: kw46m@nih.gov

Dr. John McGowan, National Institute of Allergy and Infectious Diseases, Solar Building, Room 3C20, 6003 Executive Boulevard, Bethesda, Maryland 20892. Tel: (301) 496-7291. e-mail: jm80c@nih.gov

Dr. Steven Hausman, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Building 31, Room 4C32, 31 Center Drive, Bethesda, Maryland 20892. Tel: (301) 402-1691. e-mail: sh41g@nih.gov

Dr. Yvonne Maddox, National Institute of Child Health and Human Development, Building 31, Room 2A03, 31 Center Drive, Bethesda, Maryland 20892. Tel: (301) 496-1848. e-mail: ym16x@nih.gov

Dr. Craig Jordan, National Institute of Deafness and Other Communication Disorders, Executive Plaza South, Room 400C, 6120 Executive Boulevard, Bethesda, Maryland 20892. Tel: (301) 496-8693. e-mail: cj34b@nih.gov

Dr. Lois Cohen, National Institute on Dental Research, Building 45, Room 4AN18E, 45 Center Drive, Bethesda, Maryland 20892. Tel: (301) 594-7710. e-mail: lc85n@nih.gov

Dr. Walter Stolz, National Institute of Diabetes and Digestive and Kidney Diseases, Building 45, Room 6AS25C, 45 Center Drive, MSC 6600, Bethesda, Maryland 20892-6600. Tel: (301) 594-8834. e-mail: ws23e@nih.gov

Dr. Teresa Levitin, National Institute on Drug Abuse, Parklawn Building,
Room 10-
42, 5600 Fishers Lane, Rockville, Maryland 20857. Tel (301) 443-2755. e-
mail:
tl25u@nih.gov

Dr. Anne Sassaman, National Institute of Environmental Health Sciences,
Building
3, Room 301, P.O. Box 12233, Research Triangle Park, North Carolina,
27709. Tel:
(919) 541-7723. e-mail: as56j@nih.gov

Dr. Sue Shafer, National Institute of General Medical Sciences, Building
45, Room
2AN32D, 45 Center Drive, MSC 6200, Bethesda, Maryland, 20892-6200. Tel:
(301)
594-4499. e-mail: ss78v@nih.gov

Dr. Richard Nakamura, National Institute of Mental Health, Parklawn
Building,
Room 17C-26, 5600 Fishers Lane, Rockville, Maryland 20857. Tel: (301)
443-4335.
e-mail: rn3p@nih.gov

Dr. Constance Atwell, National Institute of Neurological Disorders and
Stroke,
Federal Building, Room 1016, 7550 Wisconsin Avenue, Bethesda, Maryland
20892.
Tel: (301) 496-9248. e-mail: ca23c@nih.gov

Dr. Mary Leveck, National Institute of Nursing Research, Building 45,
Room 3AN12,
45 Center Drive, MSC 6300, Bethesda, Maryland, 20892-6300. Tel: (301)
594-5963.
e-mail: ml118t@nih.gov

Dr. Louise Ramm, National Center for Research Resources, Building 31,
Room 3B11,
31 Center Drive, Bethesda, Maryland 20892. Tel: (301) 496-6023. e-mail:
lr34m@nih.gov

Dr. Kenneth Bridbord, Fogarty International Center, Building 31, Room
B2C39, 31
Center Drive, Bethesda, Maryland 20892. Tel: (301) 496-2516. e-mail:
kbl6r@nih.gov

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Department of Health
and Human Services



National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892