

## **INCLUSION OF PERSONS UNDER THE AGE OF 21 IN RESEARCH**

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**SUMMARY:** This policy establishes guidelines on the inclusion of persons under the age of 21 years in research involving human subjects that is supported or conducted by CDC. This policy applies to all initial applications, proposals, and intramural projects submitted for receipt dates after the effective date of this policy.

### **I. PURPOSE**

The Centers for Disease Control and Prevention (CDC<sup>[1]</sup>) is committed to protecting the health of all people regardless of their age, sex, race, ethnicity, national origin, religion, sexual orientation, socioeconomic status, or other characteristics. To the extent that participation in research offers direct benefits to participants, under-representation of certain population subgroups, including persons under 21 years of age, denies them the opportunity to benefit. Moreover, for purposes of generalizing study results, investigators must include the widest possible range of population groups.

This document sets forth the policy and guidelines on the inclusion of persons under 21 years of age (including children as defined by Department of Health and Human Services (HHS) policy at [45 C.F.R. Part 46](#)) in research involving human subjects that is supported or conducted by CDC. The goal of this policy is to increase the participation of persons under 21 years of age in research, so that adequate data will be developed to support public health programs that benefit young persons as well as adults. For the purposes of this policy, research involving human subjects includes categories of research that would otherwise be exempted from the HHS Policy for Protection of Human Research Subjects. These categories of research are exempted from the HHS policy, because they pose minimal risk to the participants and not because the studies should not include children. Examples of such research include evaluation of educational interventions, observation of children's activities, and studies of existing data or

specimens that include children as participants. Nevertheless, the inclusion of children as participants in research must be in compliance with all applicable subparts of [45 C.F.R. Part 46](#) as well as with other pertinent laws and regulations, whether or not the research is otherwise exempted from [45 C.F.R. Part 46](#).

## II. BACKGROUND

This policy is created because public health practices applied to persons under the age of 21 may be based upon research performed only in adults, and scientifically evaluated treatments are less available to persons under the age of 21 because of barriers to their inclusion in research studies. Most research on the cause, prevention, treatment, and cure of diseases and conditions that affect persons under the age of 21 relies primarily on adults as subjects in research studies. Consequently, prevention and treatment options that may be effective for adults can have an adverse impact on the health outcomes of persons under the age of 21 as well as on their future growth and development.

## III. ACRONYMS AND DEFINITIONS

### A. For the purposes of this policy, the following acronyms will apply:

1. **CDC** – Centers for Disease Control and Prevention
2. **HHS** – Department of Health and Human Services
3. **IRB** – institutional review board
4. **NC** – national center<sup>[2]</sup>

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

1. **Human subject** – The definition of human subject is drawn from the U.S. Code of Federal Regulations, [45 C.F.R. Part 46.102\(f\)](#): “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.”
2. **Children** – The definition of children used in this policy is equivalent to the U.S. Code of Federal Regulations definition found at [45 C.F.R. Part 46.402\(a\)](#): “Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” The definition used by the Food and Drug Administration is substantially similar ([21 C.F.R. Section 50.3\(o\)](#)): “Children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.”

This policy and definitions do not affect the human subject protection regulations for research on children ([45 C.F.R. Part 46, Subpart D](#)) and their provisions for assent, permission, and consent, which remain unchanged.

3. **Persons under the age of 21** – This term is applied to all individuals less than 21 years of age. Depending on the applicable law of the jurisdiction in which the research will be conducted, some persons under the age of 21 will be considered children while others will be considered adults. For example, for a state that sets the age of majority at 18, individuals in that state who are 17 or younger would generally be considered children, while individuals who are 18 or older would be considered adults.

#### IV. POLICY

The policy of CDC is that persons under the age of 21 must be included in all human subjects research that is conducted or supported by CDC, unless there are scientific and ethical reasons not to include them. This policy applies to all CDC-conducted or CDC-supported research involving human subjects, including research that is otherwise exempt in accordance with Sections 101(b) and 401(b) of [45 C.F.R. Part 46, HHS Policy for the Protection of Human Subjects](#). Therefore, proposals for research involving human subjects must include a description of plans for including persons under the age of 21. If persons under the age of 21 will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion.

In an extramural research plan, the investigator should create a section titled "Participation of persons under the age of 21." This section should provide either a description of the plans to include persons under the age of 21 and a rationale for selecting or excluding a specific age range, or an explanation of the reason(s) for excluding persons under the age of 21 as participants in the research. When persons under the age of 21 are included, the plan must also include a description of the expertise of the investigative team for dealing with individuals at the ages included, the appropriateness of the available facilities to accommodate the included age groups, and the inclusion of a sufficient number of persons under the age of 21 to contribute to a meaningful analysis relative to the purpose of the study. Scientific review groups at CDC will assess each application as being acceptable or unacceptable in regard to the age-appropriate inclusion or exclusion of persons under the age of 21 in the research project, in addition to evaluating the plans for conducting the research in accordance with these provisions.

In an intramural research protocol, the investigator should provide either a description of the plans to include persons under the age of 21 and a rationale for selecting or excluding a specific age range, or an explanation of the reason(s) for excluding persons under the age of 21 as participants in the research. When persons under the age of 21 are included, the plan must also include a description of the expertise of the investigative team for dealing with individuals at the ages included, the appropriateness of the available facilities to accommodate the included age groups, and the inclusion of a sufficient number of persons under the age of 21 to contribute to a meaningful analysis relative to the purpose of the study. The reviewing IRB will assess each application as being acceptable or unacceptable in regard to the age-appropriate inclusion or exclusion of persons under the age of 21 in the research project, in addition to evaluating the plans for conducting the research in accordance with these provisions.

The inclusion of children (as defined by the applicable law of the jurisdiction in which the research will be conducted) as subjects in research must be in compliance with all

applicable subparts of [45 C.F.R. Part 46](#), as well as with other pertinent federal laws and regulations.

The policy of inclusion of persons under the age of 21 in CDC-conducted or CDC-supported research activities in foreign countries (including collaborative activities) is the same as that for research conducted in the United States.

## **V. EXCLUSIONS**

Persons under the age of 21 years are expected to be included in all research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified:

- A.** The research topic to be studied is irrelevant to persons under the age of 21.
- B.** There are laws or regulations barring the inclusion of children and other persons under the age of 21 in the research. For example, the regulations for protection of human subjects allow consenting adults to accept a higher level of risk than is permitted for children.
- C.** The knowledge being sought in the research is already available for persons under the age of 21 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. CDC program staff can be contacted for guidance on this issue if the information is not readily available.
- D.** A separate, age-specific study in persons under the age of 21 is warranted and preferable.

Examples include:

- 1.** The relative rarity of the condition in persons under the age of 21, as compared to persons 21 and older, such that extraordinary effort would be needed to include persons under the age of 21. 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 young population with the rare condition.
  - 2.** Issues of study design preclude direct applicability of hypotheses and/or interventions to both persons 21 and older and persons under the age of 21 (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding persons under the age of 21 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 persons under the age of 21 to be included rather than excluding them.
- E.** Insufficient data are available in adults to judge risk in persons under the age of 21 (in which case, one of the research objectives could be to obtain sufficient adult data to make this judgment). While persons under the age of 21 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 analysis of potential harms and benefits.

- F. 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 persons under the age of 21).
- G. Other special cases justified by the investigator and found acceptable to the review group and the Office of Public Health Research (for extramural awards) or to the IRB (for intramural research activities).

## **VI. ROLES AND RESPONSIBILITIES**

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

### **A. Responsibilities of principal investigators with regard to inclusion of persons under the age of 21 as participants in research involving human subjects**

Principal investigators should assess the scientific rationale for the inclusion of persons under the age of 21 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 inclusion of persons under the age of 21 appropriate?
- Under what circumstances is it not appropriate?
- At what ages is inclusion or exclusion appropriate?

In an extramural research application, the principal investigator should address the policy in the application, providing the required information on participation of persons under the age of 21 in research projects, and required justifications for any exceptions allowed under the policy in the research plan under a section entitled, "Participation of persons under the age of 21."

In an intramural research protocol, the principal investigator should address the policy in the protocol, providing the required information on participation of persons under the age of 21 in research projects, and required justifications for any exceptions allowed under the policy.

### **B. Responsibilities of institutional review boards with regard to inclusion of persons under the age of 21 as participants in research involving human subjects**

All IRBs have the responsibility to examine ethical issues, including equitable selection of research participants in accordance with federal regulations ([45 C.F.R. Part 46](#)). The participation of persons under the age of 21 in research, including those of both genders and representing different minority groups, is important to

ensure that each segment of the population receives a share of the benefits of research. IRBs have special review requirements ([45 C.F.R. Part 46, Subpart D](#)) to protect the well-being of children who participate in research that is conducted or supported by HHS. IRBs may approve research involving children only if the special provisions outlined in [45 C.F.R. Part 46, Subpart D](#) are satisfied.

The proper inclusion of persons under the age of 21 is an additional consideration for approval by a CDC IRB. CDC IRBs are expected to consider whether CDC investigators have adequately addressed the inclusion or exclusion of persons under the age of 21 in all research protocols that involve human subjects and require CDC IRB approval.

**C. Responsibilities of scientific review groups with regard to inclusion of persons under the age of 21 as participants in research involving human subjects**

In conducting peer review of applications and 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 persons under the age of 21 as acceptable or unacceptable. Therefore, these groups must include appropriate expertise in research involving persons under the age of 21 to make the evaluation.

**D. NC obligations for extramural research awards with regard to inclusion of persons under the age of 21 as participants in research involving human subjects**

Following scientific review, NC directors and their extramural research staff shall determine whether: (1) the research involves human subjects, and (2) the inclusion or exclusion of persons under the age of 21 meets the requirements of this and HHS policies. Note: IRB approval is not necessary prior to the selection of applications for funding; however, all funded applicants must submit documentation of IRB approval at the earliest possible date after receiving their Notice of Grant Award and before expenditure of funds for research involving human subjects.

**VII. REFERENCES**

- A. [HHS Policy for the Protection of Human Subjects, 45 C.F.R. Part 46, Subpart A, sect. 101\(b\); Subpart D](#), (2001). November 15, 2005.
- B. [NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects](#). NIH, March 6, 1998.
- C. [Office of Public Health Research Homepage](#) (<http://intranet.cdc.gov/od/ocso/ophr.htm>). February 2006.
- D. [Protection of Human Subjects](#), 21 C.F.R. 50, Subpart A, sect. 50.3 (2004). April 1, 2005.

## **Exhibit 1**

### **ADDITIONAL REQUIREMENTS FOR RESEARCH THAT INCLUDES CHILDREN**

The following summarizes the additional requirements under the HHS Regulations [45 C.F.R. Part 46, Subpart D](#), based on the risks and potential benefits to children who participate in research:

#### **No greater than minimal risk**

- Assent of child and permission of at least one parent.

#### **Greater than minimal risk and prospect of direct benefit**

- Assent of child and permission of at least one parent.
- Anticipated benefit justifies the risk.
- Anticipated benefit is at least as favorable as that of alternative approaches.

#### **Greater than minimal risk and no prospect of direct benefit**

- Assent of child and permission of both parents.
- Only no more than a minor increase over minimal risk.
- Likely to yield generalized knowledge about the child's disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition.
- The intervention or procedure presents experiences to the child that is reasonably commensurate with those in the child's actual or expected medical, dental, psychological, social, or educational situations.

#### **Any other research**

- Assent of child and permission of both parents.
- IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
- The Secretary of HHS approves after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, and law) and following publication and public comment.

## **Exhibit 2**

### **CDC CONTACTS FOR MORE INFORMATION**

The following senior staff from CDC's Office of the Chief Science Officer may be contacted for further information about the policy and relevant NC programs:

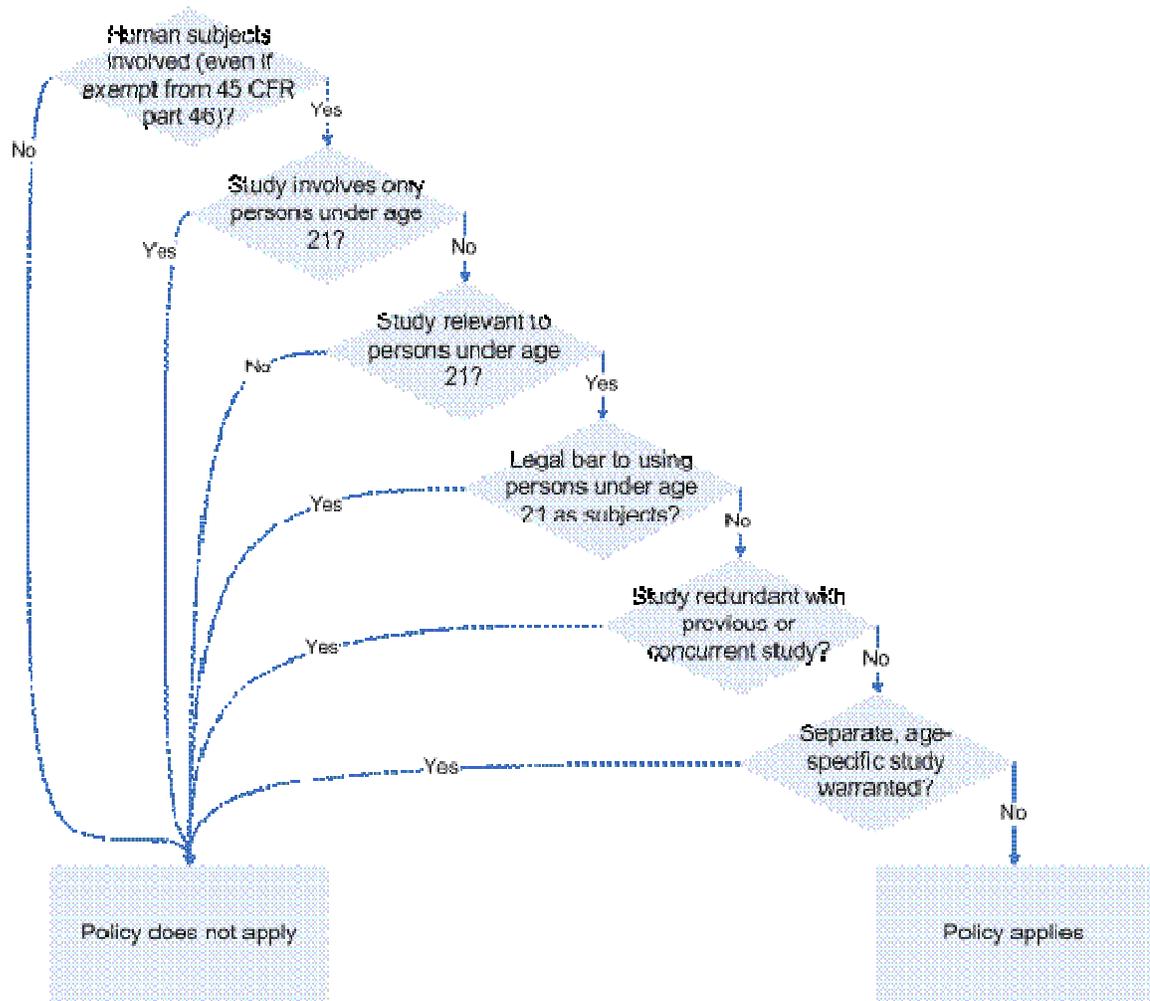
Director, Office of Public Health Research  
404-639-4621

Director, Office of Scientific Regulatory Services  
404-639-7226

## **Exhibit 3**

## DECISION TREE FOR PARTICIPATION OF PERSONS UNDER THE AGE OF 21 IN RESEARCH

The inclusion of persons under the age of 21 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 persons under the age of 21 for many diseases and disorders are based on research conducted with persons 21 and older. The decision tree shown below is intended to facilitate the determination of policy implementation by principal investigators and reviewers with regard to the inclusion of persons under the age of 21 in research involving human subjects.



<sup>[1]</sup> References to CDC also apply to the Agency for Toxic Substances and Disease Registry (ATSDR).

<sup>[2]</sup> For ease of reference within policy documents, “NC” will refer collectively to CDC’s national centers, institute, the National Immunization Program, the Office of Genomics and Disease Prevention, and the Agency for Toxic Substances and Disease Registry (an independent Health and Human Services Agency that is led by the CDC director and for which CDC provides administrative services).