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INCLUSION OF PERSONS UNDER THE AGE OF 21 IN RESEARCH

Sections

Exhibits

1. PURPOSE AND SCOPE

The Centers for Disease Control and Prevention (CDC)[2] 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. The under-representation of certain population subgroups, including persons under 21 years of age, has typically denied them opportunities to participate in and benefit from research. Moreover, for purposes of generalizing study results, investigators must include the widest possible range of population groups. This policy establishes guidelines on the inclusion of persons under the age of 21 years (including children as defined by Department of Health and Human Services (HHS) policy Title 45, Code of Federal Regulations [C.F.R.] Part 46.402 (a)) in research that involves human subjects and is supported or conducted by CDC. If there are statements in this policy that are unintentionally inconsistent with the regulations, this policy is superseded by regulations promulgated by the HHS Office for Human Research Protections (OHRP) and by the Food and Drug Administration (FDA). This policy applies to all initial applications, proposals, and intramural projects (hereafter referred to as "proposals") submitted after the effective date of this policy.

The goal of this policy is to promote and ensure the participation of persons under 21 years of age in research, so that adequate data will be collected 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

[1] Updated to conform to current policy format and organizational nomenclature.
[2] References to CDC also apply to the Agency for Toxic Substances and Disease Registry (ATSDR).

categories of research are exempted from the HHS policy, because they pose minimal risk to the participants even though the studies may 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.

2. BACKGROUND

Public health practices applied to persons under the age of 21 may be based upon research performed only in adult subjects. Due to barriers for their inclusion in research studies, scientifically evaluated treatments are less available to persons under the age of 21. 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 could potentially have adverse impacts on the health outcomes of persons under the age of 21.

3. 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/or 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 and CDC-SA-2010-01 (Human Research Protections).[3] 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 proposal must present an acceptable justification for the exclusion. (See Section 4. Exclusions)

In an extramural research plan, the investigator must create a section titled: "Inclusion of Children." This section must 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

[3] Research exempted from human subjects protection regulations as defined by 45 CFR 46.101(b), including Exemption 4, is not exempted from the CDC policy on inclusion of children and must be evaluated.

the age of 21 in the research proposal, as well as evaluating the plans for conducting the research in accordance with these provisions.

In an intramural research protocol, the investigator must 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 Institutional Review Board (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 proposal as well as 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.

4. 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 persons under the age of 21 in the research.

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 must be provided.

D. A separate, age-specific study in persons under the age of 21 is warranted and preferable.

Examples include:

- The relative rarity of the condition in persons under the age of 21, as compared to persons aged 21 and older

- Issues of study design preclude direct applicability of hypotheses and/or interventions to both persons under the age of 21 and those 21 and older (including different cognitive, developmental, or disease stages or different age-related metabolic processes)

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 typically would not be included in the initial group to be studied, in some instances, the nature and seriousness of the illness may warrant their participation 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 initially did not include data on persons under the age of 21).

G. Other special cases justified by the investigator and found acceptable to the Scientific Review Group and the Office of Science Quality, within the Office of the Associate Director for Science (for extramural awards) or to the IRB (for intramural research activities).

5. 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, as detailed below.

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 must 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 inclusion of persons under the age of 21 not appropriate?
- Under what circumstances is inclusion or exclusion of specific age ranges appropriate?

In an extramural research proposal, the principal investigator must provide the required information on participation of persons under the age of 21 in research and include required justifications for any exceptions allowed under the policy in the research plan under a section entitled, "Inclusion of Children."

In an intramural research protocol, the principal investigator must provide the required information on participation of persons under the age of 21 in research proposals, 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.

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.

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 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. Centers, Institute and Offices (CIO) 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, CIO 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 policy and HHS regulations. 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.

6. REFERENCES

A. HHS Policy for the Protection of Human Subjects, 45 C.F.R. Part 46, Subpart A, Sect. 101(b); Subpart D, (2009). July 14, 2009.

B. NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. NIH, March 6, 1998.

C. Office of the Associate Director for Science, Office of Science Quality. April 2011.

D. Protection of Human Subjects, 21 C.F.R. 50, Subpart A, sect. 50.3 (2004). April 1, 2011.

E. Human Research Protections, CDC-SA-2010-01.

7. ABBREVIATIONS AND ACRONYMS

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

CDC – Centers for Disease Control and Prevention
CFR – Code of Federal Regulations
CIO – Centers, Institute, Offices
HHS – Department of Health and Human Services
IRB – Institutional Review Board

8. DEFINITIONS

Human subject – The definition of human subject is drawn from 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."

Children – The definition of children used in this policy is equivalent to the definition found in 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."

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

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 whereas 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.

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 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 are reasonably commensurate with those in the child's actual or expected medical, dental, psychological, social, and/or educational situations

Any other research
- Assent of child and written 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 Associate Director for Science may be contacted for further information about the policy and relevant CIO programs:

Juliana Cyril, Ph.D., M.P.H.
Deputy Director, Office of Science Quality
404-639-4621

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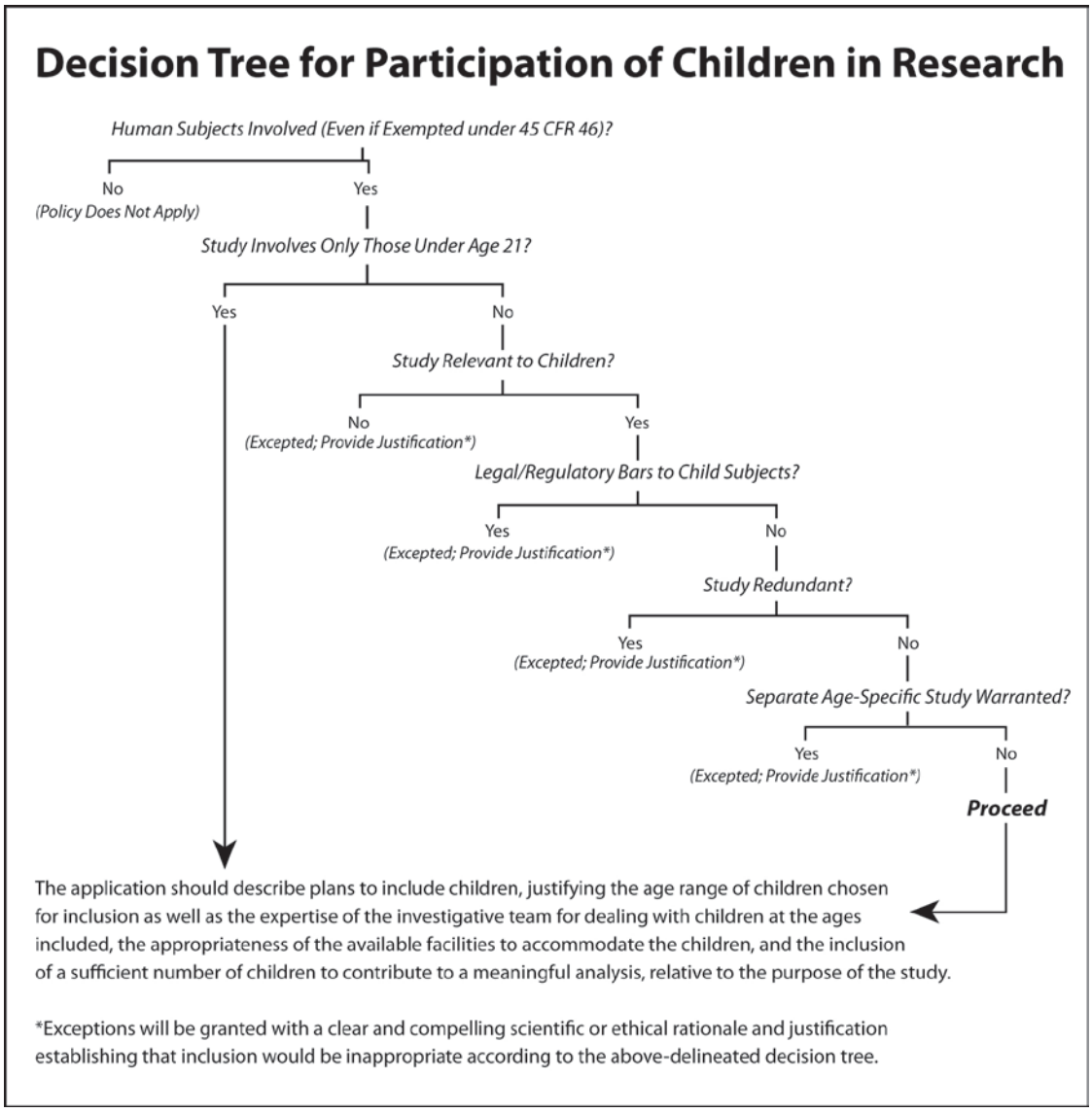
Director, Office of Scientific Integrity
404-639-7570

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.



ALTERNATE TEXT –
The graphic shows the ***Decision Tree for Participation of Children in Research***.

Question 1: ***Are human subjects involved (even if the research is Exempted under 45 CFR 46)?***
If the answer to Question 1 is NO, then the policy does not apply; and no other action is required.
If the answer to Question 1 is YES, then consider **Question 2:** ***Does the study involve only those under age 21?***
If the answer to Question 2 is YES, then the application should describe plans to include children, justifying the age range of children chosen for inclusion as well as the expertise of the investigative team for dealing with children at the ages included, 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.
If the answer to Question 2 is NO, then consider **Question 3:** ***Is the study relevant to children?***
If the answer to Question 3 is NO, then the study is Excepted and the application must provide sufficient justification that inclusion would be inappropriate [see footnote].
If the answer to Question 3 is YES, then consider **Question 4:** ***Are there legal/regulatory bars to child subjects?***
If the answer to Question 4 is YES, then the study is Excepted and the application must provide sufficient justification that inclusion would be inappropriate [see footnote].
If the answer to Question 4 is NO, then consider **Question 5:** ***Is the study redundant?***
If the answer to Question 5 is YES: then the study is Excepted and the application must provide sufficient justification that inclusion would be inappropriate [see footnote].
If the answer to Question 5 is NO, then consider **Question 6:** ***Is a separate age-specific study warranted?***
If the answer to Question 6 is YES, then the study is Excepted and the application must provide sufficient justification that inclusion would be inappropriate [see footnote].
If the answer to Question 6 is NO, then the application should describe plans to include children, justifying the age range of children chosen for inclusion as well as the expertise of the investigative team for dealing with children at the ages included, 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.
Footnote: Exceptions will be granted with a clear and compelling scientific or ethical rational and justification establishing that inclusion would be inappropriate according to the above-delineated decision tree.