

Guidelines for Reviewers: Protections for Human Subjects Review Criterion

Revision Notes — March 2019

- Revised definition for a Human Subject, in accordance with changes to the Common Rule 45 CFR 46.102(e)
- Revised human subjects research exemption descriptions, in accordance with changes to the Common Rule 45 CFR 46.104 (d)
- Added clinical trial definition and updated definition of NIH-defined phase III clinical trial

Requirements and Responsibilities

As required by federal regulations ([45 CFR 46](#)) and NIH policy, applications that propose to involve human subjects must address:

1. the risk to subjects
2. the adequacy of protections against risk
3. potential benefits of the research to subjects and others
4. the importance of the knowledge to be gained
5. for clinical trials, data and safety monitoring plan and a data and safety monitoring board for Phase III trials.

Applicant Responsibilities: Applications must designate if human subjects are involved, and if so, whether the proposed activities meet the criteria for exemption. Applications that involve human subjects must include a Protection of Human Subjects attachment that addresses the points noted above. Applications that are not proposing human subjects research but will use human data or biological specimens, must provide a justification for the claim of no involvement of human subjects.

Scientific Review Group (SRG) Responsibilities: NIH Peer Review regulations ([42 CFR 52h](#)) specify that reviewers will take into account the adequacy of the proposed protections for humans, to the extent that they may be adversely affected by the project proposed in the application, in determining overall impact that the research in the application could have on the research field involved. Therefore, the SRGs must factor their evaluation of the proposed plans to protect human subjects from research risks, into their overall evaluation of an application's scientific and technical merit and overall impact score.

Reviewer Responsibilities: Evaluate the application’s designation of human subjects involvement and the Protection of Human Subjects attachment and prepare written comments, including comments describing specific concerns, unless Not Applicable:

- I. *If the application designates that No Human Subjects are involved, does the research propose the use of human cells, specimens, or data from living individuals?*
 - i. If NO – Rate the Protection of Human Subjects as Not Applicable
 - ii. If YES – is there an adequate justification for the non-involvement of human subjects (the materials were collected for another purpose AND **none** of the investigators can readily link to subject identifiers)?
 - a) If Yes – Rate the Protection of Human Subjects as Not Applicable
 - b) If the justification is not provided or is inadequate– Rate the Protection of Human Subjects section as UNACCEPTABLE and EXPLAIN WHY

- II. *If the application designates one or more of the human subjects exemptions, is the claim for exemption adequately justified?*
 - i. If YES, Rate the Protection of Human Subjects as Acceptable
 - ii. If NO, Rate the Protection of Human Subjects as UNACCEPTABLE and EXPLAIN WHY

- III. *If the application designates Yes for Human Subjects without exemption, does the application adequately address the 4 points required in the Protection of Human Subjects attachment? If the application proposes a clinical trial, also consider if the application describes an appropriate Data and Safety Monitoring Plan, including a Board if applicable. Refer to Worksheet to Assist in Reviewing the Required Points of the Protection of Human Subjects Section (below) for more specific guidance.*
 - i. If YES, Rate the Protection of Human Subjects as Acceptable
 - ii. If NO, Rate the Protection of Human Subjects as UNACCEPTABLE and EXPLAIN WHY

Worksheet to Assist in Reviewing the Required Points of the Protection of Human Subjects

Point 4.1.1 Risks to Human Subjects *Does the application adequately describe Human Subjects Involvement, Characteristics, and Design, Sources of Materials, and Potential Risk, including:*

- description and justification for the proposed involvement of human subjects
- characteristics of subject population (number, age range, and health status)
- inclusion/exclusion criteria
- rationale for involvement of vulnerable populations (e.g. fetuses, pregnant women, children, prisoners, institutionalized individuals, or others)
- role of collaborating sites where research will be performed
- description and justification of research procedures (including dosage, frequency, etc of intervention)

- description of what research material, data, and information will be collected
- access to personally identifiable information collected and retained
- management and protection of materials and information
- all potential risks to subjects (physical, psychological, financial, legal, or other) including likelihood and seriousness
- any alternative treatments or procedures

Point 4.1.2 Adequacy of Protection Against Risks

Does the application adequately describe Recruitment and Informed Consent and Protections Against Risk, including:

- how subjects will be recruited
- description of informed consent, parental permission and assent
- waiver for any elements of consent
- how risks described previously, including privacy and confidentiality, will be minimized
- additional protections for vulnerable populations
- ensuring necessary medical/professional intervention for adverse events

Point 4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

Does the application adequately describe how potential risks to subjects appear reasonable in relation to anticipated benefits?

Point 4.1.4 Importance of the Knowledge to be Gained

Does the application adequately describe how potential risks to subjects appear reasonable in relation to the importance of the knowledge that may result from the study?

Point 4.1.5 Data and Safety Monitoring Plan/Board

If the proposed research includes a clinical trial, does the application describe an appropriate Data and Safety Monitoring Plan that includes:

- A description of a monitoring plan, who will be responsible for monitoring and the process by which Adverse Events (AEs) and Unanticipated Problems (UP) will be reported to all relevant regulatory bodies.
- A Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials

Background and References

Human Subjects Protection

Federal Regulations for Protection of Human Research Subjects (45 CFR 46):

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

More Information

[Research Involving Human Subjects](#)

Definition of Human Subject

A living individual about whom an investigator (whether professional or student) conducting research:

- i. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- ii. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
 - *Intervention* includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
 - *Interaction* includes communication or interpersonal contact between investigator and subject.
 - *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).
 - *Identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
 - *An identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Research Involving Coded Private Information or Biological Specimens

Research that involves only the use of human specimens or data is not considered human subjects research if:

- All subjects are deceased **OR**
- The data/specimens were not obtained specifically for the proposed research AND none of the investigators involved in the research can ascertain the identity of the subjects, either directly or indirectly.

See <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/biological-materials-and-data/index.html>

Human Subjects Research Exemptions (45 CFR 46.104)

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators

who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
 - i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

3. i. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
 - A. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - B. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - C. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
- ii. For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

- iii. If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.
4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
 - i. The identifiable private information or identifiable biospecimens are publicly available;
 - ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
 - iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
 - iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.*
5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.
 - i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or

- in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.
- ii. [Reserved]
6. Taste and food quality evaluation and consumer acceptance studies:
 - i. If wholesome foods without additives are consumed, or
 - ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.
 7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).
 8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:
 - i. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
 - ii. Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;
 - iii. An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

For more information on human subjects research exemptions see [the Exempt Human Subjects Research Infographic](#)

Data and Safety Monitoring Plan

For information, visit [Data and Safety Monitoring Plan](#).

NIH Definitions

Clinical Trial:

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

¹See Common Rule definition of *research* at 45 CFR 46.102(d).

²See Common Rule definition of *human subject* at 45 CFR 46.102(f).

³The term “*prospectively assigned*” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

⁴An *intervention* is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

⁵*Health-related biomedical or behavioral outcome* is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

NIH-defined Phase III clinical trial:

A broadly-based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.