Guidelines for Reviewers: Protections for Human Subjects Review Criterion

Requirements and Responsibilities

As required by federal regulations (45 C.F.R. 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 C.F.R. 52h) specify that reviewers will take into account the adequacy of the proposed protections for humans 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 fnd EXPLAIN WHY

II. *If the application designates one or more of the 6 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 obtains

1. Data through intervention or interaction with the individual, or
2. Identifiable private information.
    - *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment 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 which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

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 http://www.hhs.gov/ohrp/policy/cdebiol.html

Human Subjects Research Exemptions (45 CFR 46.101)

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
    i. research on regular and special education instructional strategies, or
    ii. research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
    i. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
    ii. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:
    i. the human subjects are elected or appointed public officials or candidates for public office; or
    ii. federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: public benefit or service programs; 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.
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.

Data and Safety Monitoring Plan

For information, visit Data and Safety Monitoring Plan.

NIH Definitions

Clinical research:

1. Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.
2. Epidemiologic and behavioral studies.
3. Outcomes research and health services research.

Phase III clinical trials research:

Phase III clinical trials research is defined as broadly based, prospective clinical investigations for the purpose of investigating the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.