IRB Tip Sheet: Considerations for Including Healthy Volunteers in Clinical Research

When conducting clinical research involving healthy volunteers, Institutional Review Boards (IRBs) must consider several ethical, legal, and scientific factors to ensure the protection of participants and the integrity of the research.

- There are no federal regulations that specifically address the participation of healthy, normal volunteers in research protocols.
- Research with healthy volunteers is fundamentally different from research with patient participants who may receive personal benefit from their participation.
- Since there is no personal benefit to the healthy volunteer, the risk-benefit analysis performed by the IRB should focus strongly on the importance of the knowledge to be gained and scrutinize the potential participants for non-obvious vulnerabilities.

Healthy Volunteers can be considered a **vulnerable population** in circumstances where:

  - They are at risk of undue influence by the offer of monetary compensation.
  - They are at risk of coercion when recruitment is performed by a person or group of persons in positions of authority.
  - They feel pressured if they are approached multiple times for participation in research to serve as members of a control group.

Assess the Risks of the Research for Healthy Volunteers

- Research involving normal healthy volunteers generally involves minimal risk, and foreseeable risks should be minimized. For greater than minimal risk (GTMR) studies, a robust justification should be provided for involving normal healthy volunteers in any GTMR procedures.
- Enrollment of healthy volunteers in Phase 1 drug trials or Controlled Human Infection studies (CHIs) have additional considerations that are not discussed in this tip sheet. There are references on this topic at the bottom of the page that may be of interest. [1,2,3]
- Screening Healthy Volunteers:
  - Screening should include the fewest and least risky tests/interventions necessary to determine study eligibility.
  - Screening procedures should minimize participant exposure to potential harm for those who fail screening.
- Study Participation:
  - The frequency and invasiveness of medical procedures as well as restrictions on participant activities (e.g. extended confinement to clinical facilities, restricted diet or physical activities) should be minimized and scientifically well justified.
  - IRB should carefully scrutinize procedures performed on healthy volunteers that are greater than minimal risk.

Assessing Compensation for a Healthy Volunteer's Contribution to Research

- Healthy volunteer compensation amounts, and payment schedules should adequately reflect the substantial time, inconvenience, and body-monitoring activities required of participants, as well as the management of expected adverse events.
- Compensation can be a concern for undue influence when there is a risk that the payment may undermine a valid informed consent process, that payment might induce participants to be untruthful about their themselves to ensure that they are eligible, and that payment might disproportionately attract participants of lower socioeconomic status.
- Note that such concerns may be addressed by putting safeguards in the selection and recruitment plan instead of making adjustment to what would otherwise be fair compensation for participation.
- See Gelinas L, et al. *A Framework for Ethical Payment to Research Participants.* N Engl J Med. 2018 Feb 22;378(8):766. https://doi.org/10.1056/nejmsb1710591

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[1] Walker, R., et al. *Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials, Ethics & Human . Research*. Ethics & Human Research. 2022 Sep;44(5):2-21. https://doi.org/10.1002/eahr.500139

[2] Kalbaugh CA, et al. *Healthy volunteers in US phase I clinical trials: Sociodemographic characteristics and participation over time*. PLoS One. 2021 Sept;16(9): e0256994. https://doi.org/10.1371/journal.pone.0256994

[3] Shah, S. & Rid, A. *Ethics of controlled human infection studies: Past, present and future.* Bioethics. 2020 Oct;34(8):745-748. https://doi.org/10.1111/bioe.12801

Subject Selection and Recruitment Process of Health Volunteers

- Healthy volunteers should be recruited and selected according to transparently communicated criteria and on the basis of wide outreach.
- The protocol should define who qualifies as a healthy volunteer and provide justification for the exclusion of any populations.
  - Inappropriate exclusions can limit the scientific generalizability and applicability of results and can disenfranchise communities from contributing to the common good.
  - Recruitment efforts for greater than minimal risk studies (GTMR) should also not disproportionately target members of healthy but disadvantaged or minority groups.
- The **recruitment plan** should be assessed to see where and how subjects are recruited and if they are at risk of coercion.
  - Review the recruitment plan to make sure that it avoids unfairly targeting any specific groups or excludes populations by design.
  - Disadvantaged minority group members and underserved communities should not be disproportionally targeted for enrollment.
  - Additional protections or safeguards may need to be in place for groups at risk of coercion, especially in places such as college campuses, places of employment, and places with a high concentration of disadvantaged persons.
- Any **recruitment material** should be assessed for the appearance of coercion and undue influence. There should be no undue emphasis on compensation and all materials must exclude exculpatory language that implies that volunteers could be made to waive any of their legal rights and release the researchers from liability for negligence.
- See the Guidelines for Recruitment Plan, Recruitment Materials and Screening Plan, for NIH Intramural Research Program Protocols (under Policy 302, Recruitment and Compensation).

Informed Consent Process for Healthy Volunteers

- The consent process must contain the elements of consent. Important sections to review specifically in the context of healthy volunteers would be the statement that participation is voluntary, language conveying the offered compensation, injury language and any known or unknown risks to the subjects.

Confidentiality and Data Protection for Healthy Volunteers

- Healthy volunteers are of special concern regarding confidentiality and security of their data since they would not have any of their data collected at an institution except for their willingness to contribute to research. Special consideration should be given to them with regard to collection of sensitive data.
- Collection of personal data should be first limited to the minimum necessary for screening or to determine study eligibility, and then limited to what would be required to address the proposed research.

Children as Healthy Volunteers

- Since healthy volunteers receive no personal benefit for their participation, the majority of studies that involve healthy children will involve minimal risk.
- SACHRP provides recommendations on **limited** circumstances where the IRB may determine that healthy children can be included in GTMR research under 46.406 *Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition*:
  - Healthy school children have a condition necessary to study the immunogenicity of a potential vaccine for a common childhood disease. Although the children are healthy, they have the condition of being a child at risk for the common disease under study.
  - Healthy children living in areas where the risk of a serious disease or adverse life events is high, may be determined by an IRB to have a condition necessary to be enrolled in a protocol designed to discover factors that may lead to an increased understanding or amelioration of the serious disease or adverse life situation/condition.
  - For interventions or procedures to be considered of “vital importance,” there must be clear and significant scientific evidence that their use is likely to yield generalizable knowledge that would contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration or treatment of a condition or disorder.