Human Research Protection Program
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Guidance for Human Subjects and Non-Subjects

Who are human subjects?

Per 45 CFR 46, which regulates the Protection of Human Subjects for research, in § 46.102(e) a human subject is defined as:

(1) ***Human subject*** means 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.

FDA defines a human subject in 21 CFR 50.3(g) as:

(g) ***Human subject*** means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Note that per 45 CFR 46, there are two conditions in which an individual is considered a human subject. This guidance document clarifies only the first condition (i) in which an individual is considered a human subject.

Who are non-subjects?

In research studies, **non-subjects** include any persons who may encounter the research who are not the subjects of the research. This includes **third-parties** that might be reported on during an interview or survey with a human subject. It could also include household or family members of the human subject who may be exposed to the risks of the research.

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Sometimes a third-party may become a subject of the research. This is determined on a case-by-case basis following guidance from OHRP (Office of Human Research Protections) under the Department of Health and Human Services (HHS). When a third-party becomes a subject, they are sometimes referred to as **secondary subjects**.

How do I know if a third-party is a subject?

Guidance from OHRP indicates that the *about whom* portion of the human subject's definition is key language for determining who is a subject of research. Who the research is about, who the research's objectives apply to, and who the questions posed in a survey are about, are important considerations.

For example, a medical history being done for research purposes where a participant is being asked questions about their family members' medical history does not necessarily transform that family member into a human subject. A participant may provide the relative's race, age, and medical diagnoses to the researcher, but the IRB may reasonably determine that this data is meant to pertain to the participant providing the information and not the family member.

Another example is if a researcher is asking questions to parents about their children. The researcher is asking for the parents' opinions on their relationship with their children. In this scenario, the parents and their opinions are *about whom* the researcher is studying. The IRB may reasonably determine that only the parents are subjects of the research.

In that same vein, if the researcher is asking the parents for factual information about their child rather than opinions, and the research objectives are related to the child, the IRB may reasonably determine that the children are human subjects of the research.

If the questions are both factual information about the parents and the children, and the research objectives pertain to both the parents and the children, then the IRB may reasonably determine that both the parents and children are subjects of the research.

These determinations are evaluated by the IRB on a case-by-case basis. It depends upon the data being collected and the objectives of the research.

Is it necessary to get third-parties' consent?

If the third-parties are considered human subjects, then yes, consent is generally required. However, a waiver of consent for third-parties is likely approvable by the IRB as permitted per the regulations.

To request IRB approval for a waiver of consent for third parties, this can be done within the protocol application. Within the consent process section select yes to, "During any part of your research, are you seeking a waiver of the consent process?" and justifying the request in the questions that follow, which the regulatory criteria for a waiver of consent.

Do you have additional resources?

OHRP provides some resources for the determination of human subjects and protections of non-subjects. We have included those below:

- What is human subjects research?
- The Protection of Non-Subjects from Research Harm