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Topic: Definition of Human Subjects Research

Overview of the Topic

The initial, and critical, decision of the IRB is whether a project meets the definition of human subject research and thus falls under the auspices of the IRB. If the answer is yes, the IRB either reviews it or makes an exempt determination, and if the answer is no, IRB involvement is no longer needed. There are two components of "human subject research," one, that it must involve a "human subject" and two, that it must be "research." A protocol must meet both of these components to be considered human subject research; if one is true but not the other the protocol does not constitute human subject research and does not warrant IRB review and oversight.

The DHHS regulations define **research** as *a systematic investigation including research development, testing, and evaluation designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities* (45CFR46.102(d)). This definition involves two main concepts, one is a **systematic investigation**, and the second is **generalizable knowledge**. However, while you are expected to use and adhere to this definition of research, the regulations do not define a systematic investigation nor generalizable knowledge. These concepts, and practical working definitions, need to be defined by your organization.

'Systematic' means using a careful system or method. In other words, systematic research is formal and planned, rather than haphazard and done randomly. Here are some suggestions what a systematic investigation may include:

- The activity attempts to answer research questions (in some research, this would be a hypothesis)
- The activity is methodologically driven, i.e. it collects data or information in an organized and consistent way
- Data or information collected is analyzed in some way, be it quantitative or qualitative data analysis
- Conclusions are drawn from the results

Here are two simple examples. A case study is not usually considered research because it is merely observing and reporting something that has happened under no control of the investigator. A case series may also not be research, but once an investigator starts to add data collection for research purposes, e.g. taking hourly blood pressure measures, it now becomes research because the process has been formalized and controlled by the investigator.

Generalizable knowledge is an even more contentious term to define. While some people equate generalizable knowledge with intent to publish (and indeed much of the research that IRBs reviews meets this criteria), many people will argue that publication itself does not mean the research is generalizable. Again, you must develop your own working definition of generalizable knowledge. Consider the following concepts for your definition:

- The information gained is intended to contribute to a theoretical framework of an established body of knowledge
- Results are expected to be generalized to a larger population beyond the site or population studied
- Results are intended to be replicated in other settings
- Most academic institutions consider a thesis or dissertation to be generalizable knowledge (of course this is only relevant if it includes human research).

Generalizable knowledge may be transmitted by journal articles, or abstracts and presentations at professional meetings. Web publications, which may or may not have been peer reviewed present a current challenge as to whether these materials constitute generalizable knowledge. Develop and refine your definitions of a systemic investigation and generalizable knowledge, make them known to your organization and apply them to your decisions.

Note that the FDA has its own specific definition of research: research, or a **clinical investigation**, is an experiment that involves a test article and one or more human subjects that is subject to the IND or IDE regulations or which collects data to be submitted to, or held for inspection by, the FDA (21CFR50.53(c)). This is straight forward and applies to most clinical trials conducted at organizations.

A **human subject** is defined as *a living individual about whom an investigator (whether professional or student) conducting research obtains (I) Data through intervention or interaction with the individual, or (2) Identifiable private*

Information (45CFR46.102(f)). Since the definition states living individuals, research involving cadavers is not included unless the research involves living relatives.

Intervention includes both physical procedures by which data are gathered (for example, 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 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. (45CFR46.102(f)) These are fairly straight forward definitions which usually do not create many problems.

For research covered by FDA regulations, 'human subject' means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. The FDA has another caveat: for research subject to FDA device regulations, subject means a human on whose specimen an investigational device is used or as a control (21CFR50.3(g)).

Currently, we consider research involving de-identified human specimens not to be human subjects research, because without the identity there is no subject to protect. However, this concept is changing with the increasing research and technology related to DNA and genetics and concerns about the privacy of this information. The OHRP Notice of Proposed Rulemaking (2015), basically considers secondary use of biospecimens, even without identifiers, to involve human subjects. The new rule would require consent for secondary use, although it could be done with 'broad' consent obtained at collection. This research could be considered exempt, but thus would still be considered human subjects research. So, be prepared for this change if the NPRM becomes regulation with this stipulation included.

Your organization should have a process to make determinations if an activity meets the definition of human subjects research. This process should include 1) Who is designated to make determinations, 2) A process for investigators to ask for determinations, and 3) A process to communicate determinations with investigators. As always, maintain the determinations in your IRB records. In summary, create and use detailed definitions for human subjects research so that your IRB can make fair, consistent and documentable decisions on whether a particular activity involves human subjects research. This will protect research participants when appropriate, and not involve IRB review when not needed. Investigators will appreciate clear definitions, consistent determinations and an efficient process.

Questions for the IRB to Consider

Questions your IRB may ask about whether a project constitutes human subjects research, using your definitions:

1. Is the study a systematic investigation?
2. Are the results of the study designed to contribute to generable knowledge?
3. Does the research involve human subjects?
4. If FDA regulated, does the research meet the FDA definitions of participant and clinical investigation?
5. **IRB Decision:** Does the activity involve human subjects research and requires oversight by the IRB?

Case Studies

Case 1. A surgery resident wants to conduct a wound healing research project but tells the IRB he has no intent to publish, that he is merely presenting his results at the annual surgery research day because he is required to. Does this research produce generalizable knowledge? What should the IRB do?

Case 2. A natural resources professor is studying paper use in copying machines from many companies. The data collected includes how many employees and how many reams of copy paper are purchased each month. Does this study meet the definition of human subjects research? Are there additional questions you would ask?

Case 3. A nursing student wants to do an anonymous survey of clinic patients to determine how often they use over-the-counter pain medications and which brands they use. Does this study meet the definition of human subjects research? Are there additional questions you would ask?

Prospective Thinking: Review your organization's definitions of systematic investigation and generalizable knowledge. Discuss if the definitions are working and cover all eventualities, or if improvements need to be made.