Current Issues for Investigators: Human Subjects Research

Valery M. Gordon, Ph.D., M.P.H.
Extramural Human Subjects Research Policy Officer
Office of Extramural Research, OD
National Institutes of Health
(301) 435-0945
vg10w@nih.gov

Outline

- Research Involving Human Data or Specimens
  (http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf)
- Definitions
- NIH implementation of requirements
  - Get ready for the SF 424 R&R!
- Case Studies
- Other issues

OHRP “Guidance on Research Involving Human Data or Specimens”

Directed toward IRBs, investigators, and funding agencies
- Provides clarification of terms in HHS regulations
  (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)
- Describes when research with coded data or specimens is or is not human subjects research
- Effective date: August 10, 2004
- Implemented by NIH: January 10, 2005
  (http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf)

Specific Information in Guidance

- Research with coded human data/specimens does not involve human subjects if:
  - Data/specimens not collected specifically for proposed study; and
  - Investigators cannot readily ascertain identities of donors because:
    - Key to code destroyed before research begins; or
    - Non-disclosure agreement between provider and investigator (no requirement for IRB approval); or
    - IRB policies prohibit release of key to code; or
    - “Other legal requirements” prohibit release of key to code

Recommendations in Guidance

- Institutions have policies designating the individual or entity authorized to determine whether research with coded data/specimens is human subjects research
- Investigators should not be given authority to make independent determination whether their proposed studies with coded data/specimens involve human subjects

Definition of Human Subject

- ... a living individual
- about whom an investigator... conducting research obtains
  1) Data through intervention or interaction with the individual,
  or
  2) Identifiable private information
  (http://www.hhs.gov/ohrp/humansubjects/guidance/45cr46.htm#46.102)
Definition of Obtain

- To receive or access individually identifiable human data or specimens
  - Includes an investigator’s use, study, or analysis of human data or specimens already in investigator’s possession


Case Study #1: Research with autopsy specimens

- An application describes the following proposed research activities:
  - An investigator receives autopsy specimens from a pathologist at the same institution.
  - The investigator will receive and record identifiable private information about the individuals from medical records

Case #1: Is the investigator conducting human subjects research?

- **No**: Research involving only specimens and data from deceased individuals is not human subjects research
  - Investigator is neither interacting nor intervening with living individuals for research;
  - Definition of “human subject” is not met

Case #1: What information should appear in Human Subjects section?

- “No human subjects research is proposed in the application”
  - Required for PHS 398 applications
  - Will not be required for SF 424 R&R

Definition of Investigator

- Includes anyone involved in conducting the research
  - For example:
    - Individuals who
      - Provide coded human data or specimens and collaborate on other activities related to conducting the research are involved in HS research
      - “Solely provide” previously-collected coded human data or specimens without a key to code are not involved in HS research

Case Study #2: Research using human blood

- An application describes the following proposed research activities:
  - An investigator will obtain blood from the Red Cross for basic research
  - Is the investigator conducting human subjects research?
    - **No**: Data/specimens not collected specifically for proposed study; and investigators cannot readily ascertain identities of donors because:
      - Red Cross is prohibited by law from disclosing identities of donors
Case #2: What information should appear in Human Subjects section?

- “No human subjects research is proposed in the application”

Definition of Coded

- Identifying information that enables the investigator to readily ascertain the identity of the individual has been replaced with a number, symbol, and/or letter; and
- A key to the code exists, enabling linkage of information to an individual

Definition of Research

- … a systematic investigation
  - research development
  - testing, and
  - evaluation
- designed to develop or contribute to generalizable knowledge

NIH Human Subjects section requirements

- Human Subjects
  - “Yes” or “No” must be checked
- Research Plan: Human Subjects Section
  - No proposed Human Subjects Research; or
  - Justification for Exemption; or
  - Protections for Human Subjects

- Human Subjects
  - “Yes” or “No” must be checked

Case Study #3: Discarded Surgical Specimens

- An application describes the following proposed research activities:
  - Investigators will obtain human specimens for basic research from a surgeon.
  - The surgeon will collect surgical specimens, at the request of the investigators, that would otherwise be discarded and provide them in a coded fashion.
  - The surgeon will have no other involvement in the proposed research.

Case #3: Is the surgeon involved in human subjects research?

- Yes: The surgeon is involved in human subjects research because he is interacting with living individuals and collecting specimens for the proposed research.
- The surgeon meets the definition of an investigator.
  - “OHRP considers the term investigator to include anyone involved in conducting the research.”
- The surgeon’s involvement may be limited to collecting, coding, and providing the specimens, however, this activity is conducted specifically for this study.
Case #3: Is the recipient investigator conducting human subjects research?

- **Yes:** The recipient investigator is conducting human subjects research, because
  - an investigator involved in the research (the surgeon) is collecting specimens from living individuals for the specific study, and
  - An investigator can readily link the specimens to the living individuals.

Case Study #4: Discarded Human Specimens

- An application describes the following proposed research activities:
  - Investigators will obtain human specimens for basic research from a surgeon.
  - The surgeon has IRB approval to collect specimens that would otherwise be discarded and provides them, in coded fashion, to any investigator upon request.
  - The surgeon requires that recipient investigators enter into a written agreement prohibiting the release of the key to the codes to the investigators under any circumstances.
  - The only involvement of the surgeon in the proposed research is to provide the specimens to the investigator.

Case #4: Is the surgeon involved in human subjects research?

- **Yes:** The surgeon is involved in human subjects research insofar as the surgeon is creating a research repository of human specimens.
  - Human Tissue Repositories “collect, store, and distribute human tissue materials for research purposes.”
  - Require IRB-approved written policies that prohibit release of key to codes.

Case #4: Is the surgeon involved in human subjects research with respect to the investigator’s study?

- **No:** The surgeon is not involved in the recipient’s research, however, because the surgeon is
  - “solely providing coded private information or specimens (for example, by a tissue repository)” and, therefore,
  - The surgeon is not an investigator in the recipient’s study.

Case #4: Is the recipient investigator conducting human subjects research?

- **No:** The investigator is not conducting human subjects research because:
  1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
  2) the investigator cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain because:
    - the investigator and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances.
    - The surgeon has promulgated policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances.

Case #4: What information should appear in Human Subjects section?

- “No human subjects research is proposed in the application”

http://www.hhs.gov/ohrp/policy/index.html#databases
Case Study #5: Retrospective Record Review

- An application describes the following proposed research activities:
  - An investigator obtains individually identifiable information on treatment outcomes of patients treated with two different FDA-approved drugs by accessing medical records.
  - The investigator records the treatment outcomes in a coded manner.

Case #5: Is the investigator conducting human subjects research?

- Yes: the investigator is conducting human subjects research because
  - the investigator obtains individually identifiable private information about living individuals; and
  - The investigator records the data in a coded manner allowing the subjects to be identified via the code.

Case #5: What information should appear in Human Subjects Section?

- Description of:
  - Risks
  - Protections against risks
  - Benefits to human subjects and others
  - Importance of knowledge to be gained
- Inclusion of women and minorities
- Inclusion of children or justification for exclusion; and
- Proposed/targeted enrollment tables

Case Study #6: Archived Human Specimens

- An application describes the following proposed research activities:
  - An investigator is using archived, individually identifiable specimens from an NIH-funded clinical trial.
  - The investigator removes identifiers from the specimens and does not maintain links to identifiers.
  - The investigator then conducts research on the anonymized specimens.

Case #6: Is the investigator conducting human subjects research?

- Yes: If the individuals from whom the specimens were obtained are living, then obtaining individually identifiable specimens is human subjects research.

Case #6: Does the study involve exempt human subjects research?

- Exemption 4:
  - Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens.
  - from publicly available sources or
  - if information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

- OHRP recommends that institutions adopt clear procedures under which the IRB (or some authority other than the investigator) determines whether proposed research is exempt from the human subjects regulations (45 CFR 46.101(b)).
Case #6: Does removing identifiers from existing specimens meet the criteria for Exemption 4?

- **Yes:** If all specimens are existing at the time the research is proposed to an institutional official or IRB for a determination of whether or not the research is exempt; and
- If the investigator collects the specimens and then removes links to identifiers from the specimens; then

  - This research activity meets the criteria for Exemption 4.
  
  [http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.101](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.101)

Case #6: Does the research with anonymized specimens involve human subjects?

- **No:** Conducting research using anonymized specimens is not human subjects research because the specimens cannot be linked to individually identifiable living individuals.

  - Criteria for “human subject” not met

Case #6: What information should appear in Human Subjects section?

- Description of:
  - Risks
  - Protections against risks
  - Benefits to human subjects and others
  - Importance of knowledge to be gained
- Inclusion of women and minorities
- Inclusion of children or justification for exclusion; and
- Proposed/targeted enrollment tables

Summary: Case study analyses

- In order to determine whether research with coded data/specimens is human subjects research, consider:
  - Role of data/specimen provider
    - Is the provider an investigator?
  - Role of recipient investigator
    - What is being obtained?
      - Data through interaction or intervention with living individuals?
      - Identifiable private information about living individuals?
      - Identifiable data or specimens for the proposed study?

Non-competing Progress Reports

- If institutions re-interpret ongoing research to conform to OHRP Guidance:
  - Involvement of human subjects has not changed
- Research classified as not involving human subjects will change to involve human subjects if investigators:
  - “Unexpectedly learn” identities of individuals; or
  - “For previously unforeseen reasons now believe that it is important to identify the individual(s).”

Other Issues or Questions?

NIH OER Human Subjects Website: