

Human Subject Issues for Experienced Investigators

Carlos E. Caban, Ph.D., M.P.H.
NIH Extramural Program Policy Officer
Office of Extramural Programs
Office of Extramural Research, OD, NIH, HHS
(301) 435-2690
cabanc@mail.nih.gov



NIH Regional Seminar, 2007

1

Outline

- Research Involving Human Data or Specimens
<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>
- Definitions
- NIH implementation of requirements
- Case Studies
- Other issues

2

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>

3

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

4

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

5

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/45cfr46.htm#46.102>

6

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

<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>

7

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

8

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

9

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

- "No human subjects research is proposed in the application"
 - Required for PHS 398 applications
 - Not required for SF 424 R&R

10

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

11

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

12

Case #2: What information should appear in Human Subjects section?

- "No human subjects research is proposed in the application"

13

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

14

Definition of Research

- ... a systematic investigation
 - research development
 - testing, and
 - evaluation
 - designed to develop or contribute to generalizable knowledge
- <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102>

15

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

16

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.

17

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.

18

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.

19

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.

20

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

<http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm>

21

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.

22

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....;
 - there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances,...

<http://www.hhs.gov/ohrp/policy/index.html#databases>

23

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

- "No human subjects research is proposed in the application"

24

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.

25

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.

26

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

27

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.

28

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.

29

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)].

30

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>

31

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

32

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

33

Summary: Definitions

- Human Subjects
 - Obtain
 - Investigator
 - Coded
 - Research
-

34

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?
-

35

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)."
-

36

**Other Issues or
Questions?**

NIH OER Human Subjects Website:
<http://grants.nih.gov/grants/policy/hs/index.htm>

37
