Best Practices for the Approval and Conduct of Secondary Research, including Repositories

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Outline

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II. When is New IRB Approval Required?
III. NIH Practices for IRB Approval and Conduct of Primary and Secondary Research
IV. Best Practices for Secondary Research
V. Best Practices for the Collection, Storage and/or Sharing of Biospecimens and Data for Future Research (Repositories)
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Concepts

Concepts, cont.

- **Human Subjects Research ("HSR"):** Activities in which an investigator conducting research:
  - Obtains information or biospecimens through intervention or interaction with an individual **or**
  - **Studies identifiable biospecimens or data**

  - **Human Subjects Research** includes research with coded biospecimens or data, when the investigator has access to the code key.

Concepts, cont.

- **Coded**:
  (1) Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and
  (2) A key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.[1]

[1] OHRP, *Coded Private Information or Specimens Use in Research, Guidance (16 October 2008)*

Concepts, cont.

- **“Not Human Subjects Research” (NHSR)*:** A research activity which does not involve human subjects, e.g. studying biospecimens or data which are not individually identifiable, i.e.
  - The identities are not known to and may not be readily ascertained by the investigator (or other members of the research team).
  - For example an investigator conducts analysis with coded biospecimens and data, with no access to a code key (or with fully anonymized biospecimens and data).
  - Research with identifiable biospecimens or data from deceased individuals also falls under the category of **Not Human Subjects Research**.

*This concept is not addressed in the regulations.

Concepts, cont.

- **Primary Research:** Research use of biospecimens and/or data for the original purpose(s) for which they were initially collected through interaction or intervention with living individuals (as identified in the original protocol and consent form)

- **Secondary Research:** Research use of existing biospecimens and/or data for a purpose other than the original purpose(s) for which they were initially collected through interaction or intervention with living individuals

Concepts, cont.

- **Repository:** An organized system to collect, maintain and store biospecimens and and/or data, most often for future research use. The materials may be prospectively collected for inclusion in a repository, or it may house existing materials collected for other purposes, including non-research purposes.
  - Repository activities involve three components:
    - (i) the **collectors** of human data or biospecimens;
    - (ii) the **repository** storage and data management center; and
    - (iii) the **recipient** investigators.[2]

- Repositories can also be referred to as registries, data banks, databases, or biobanks.

- [2]OHRP, Issues to Consider in the Research Use of Stored Data or Tissues (7 November 1997)

Concepts, cont.

- **Registry:** one form of a repository; the data may be collected specifically for research or may be collected for other purposes, e.g. clinical (e.g. to look at safety), quality improvement, or for more than one purpose.

  A common type of registry continuously collects clinical data from patients with a specific clinical condition, who are undergoing standard of care clinical treatment, over time. The data may be used to examine the natural history of a disease, treatment efficacy, adverse effects of standard treatment, a feature of illness or treatment, the efficacy of healthcare providers/sites/systems, etc.[3,4]

[3] SACHRP, *Attachment A: Human Subjects Research Implications of "Big Data" Studies (24 April 2015)*.

[4] SACHRP, *Attachment B: Recommendations Regarding Application of the Common Rule to Clinical Data Registries under the Medicare Access and CHIP Reauthorization Act of 2015 (12-13 September 2015)*.

When is New IRB Approval Required?

New Research Involving Subjects or Identifiable Materials

- An investigator, with an open IRB-approved protocol, needs **new IRB approval**, when he or she plans to:
  - Interact or intervene with living individuals to conduct **new research activities** (not explicitly described in the current IRB approved protocol); or
  - Obtain or use identifiable biospecimens or data to address **new aims or conduct new research analyses** (not explicitly described in the current IRB approved protocol)

Sharing of Biospecimens/Data Involving Return of Results

- Collaborations involving the receipt of identifiable results
  - For example, when an investigator shares coded and linked biospecimens or data with a collaborator for secondary research, and will receive coded results which he or she can be linked back to individual subjects, the investigator needs **new IRB review and approval for the research**.

  - In this case, the sharing investigator must:
    1) Submit a new protocol which addresses the new research to the NIH IRB, or
    2) Be added to the collaborator's research protocol as an AI (if the collaborator is external, a reliance agreement would need to be executed between NIH and the other institution)

  - The investigator will need to obtain consent for the new research, unless he or she is able to make a case for waiver of consent.

Sharing of Biospecimens/Data Involving Return of Results, cont.

- When a PI/AI shares coded and linked biospecimens or data with a collaborator for secondary research and will only receive summary level results (not results which can be linked back to individual subjects), the investigator **does not** need to seek IRB review and approval for the research.

  - However, the sharing investigator still must:
    1) Ensure that the original consent form addresses sharing for future research; and
    2) Ensure that the consent language is consistent with the planned research or allows for broad future research

  - If the original consent form does not contain language about sharing for future research ("is silent"), the investigator should reach out to the IRB Chair who will determine whether sharing is permissible or not.

Creation of Repositories or Use of Biospecimens or Data from Repositories

- The creation and maintenance of registries, repositories or databases **involving identifiable private information and/or identifiable biospecimens** for future research purposes is a considered human subjects research.
  - This requires IRB approval of a protocol and either new informed consent from subjects or IRB approval of waiver of consent[5,6].

  - **Any subsequent research** performed on stored identifiable biospecimens or data **requires IRB approval of a new protocol and new informed consent, specific to the planned research, or IRB approval of a waiver of consent**[5].

[5]SACHRP, *Appendix D: Application of the Privacy Rule to research databases and repositories needs further refining to align it with existing Common Rule requirements (27 April 2004)*.

[6]SACHRP, *Attachment C, Updated FAQs on Informed Consent for the Use of Biospecimens and Data (2018 March)*

NIH Practices for IRB Approval and Conduct of Primary and Secondary Research

Example #1

- The PI has a protocol under IRB oversight and the consent form includes language about use of the biospecimens and data for future research. Given the consent language, the investigator moves forward with conducting secondary research, i.e. new analyses not explicitly described in the protocol without seeking IRB approval of 1) an amendment; 2) a new protocol; 3) consent or 4) a waiver of informed consent for the new research.

Concern with Example #1

- Informed consent for future, unspecified research is not the same as IRB approval for new research with identifiable biospecimens and data.

- Prospective IRB approval of a protocol and consent form or waiver of informed consent is required before an investigator can conduct new research with identifiable materials.[6]

Example #2

- The PI amends an open IRB-approved protocol to add one or more sub-studies involving new aims and/or new research activities (secondary research) and seeks prospective IRB approval.

Example #3

- The PI closes a protocol with the IRB prior to the planned analyses (primary research) being complete or publications being accepted by journals.

- He or she then submits a new “data analysis” protocol to the IRB; or asks another PI to amend his or her “data analysis only” protocol to allow continued analysis from that protocol under the other one.
  - In some instances, various PIs’ protocols are subsumed under one protocol for data analysis only.

Concerns with Examples 2 & 3

- Not considered best practice because these approaches:
  - Weaken the scientific integrity of the primary protocol
    - Protocols should be single, self-contained units, not “multi-headed and multi-limbed” entities.

Concerns with Examples 2 & 3, cont.

- Present obstacles for the PI(s)/research team(s), monitors, auditors, DSMBs, and IRBs to ensure compliance:

  - Make it more difficult to track and report on deviations, AEs, SAEs, and Unanticipated Problems
  - Create challenges for those who are responsible for review and oversight of protocol activities
  - Are not compliant with FDA-required monitoring and reporting

Change in Practice

- Moving forward PIs will not be permitted to amend their open protocols to add sub-studies to conduct secondary research.
  - They will be required to write and submit a new protocol to the IRB.
- PIs will also not be permitted to close their protocols prior to primary data analysis being complete and then open a new protocol for ongoing data analysis.
  - The protocol should be kept open until all data analysis associated with the specific aims is complete (unless closed for another reason, e.g. the PI has left the institution, closure required by the IRB).
  - Best practice is that the primary protocol should not be closed until all publications have been accepted by journals, in order to allow validation or further analyses as requested by the journal.

Example #4

- The PI keeps a protocol open with the IRB even though all data analysis activities have ceased and any planned publications have been accepted.

Concern with Example #4

- Not considered best practice because it creates unnecessary work and confusion
  - PI must continue to submit continuing reviews (CR)*.
  - No regulatory or NIH policy requirement to keep a protocol open with the IRB when no research activities with human subjects or identifiable materials are taking place

*Please note: For protocols that went through IRB review and approval on January 21, 2019 or after, and went through expedited review or are in data analysis only, no CR will be required per the revised Common Rule.

Change in Practice

- If data analysis is complete and publications have been accepted:
  - Close the primary protocol with the IRB
  - Permanently anonymize and re-code biospecimens and/or data for future research, if identifiers will not be needed in the future; **or**
  - Retain the identifiable biospecimens and/or data (without an IRB approved protocol) as long as not being used for research
    - The PI must still ensure that the privacy and confidentiality of any identifiable biospecimens and/or data are maintained.
    - When the investigator wishes to conduct new research with identifiable materials, he or she could submit a protocol to the IRB.[5]

Best Practices for Secondary Research

Secondary Research with De-Identified Biospecimens and Data

- Goal: To conduct secondary research, when access to identifiers is not necessary
  - Fully de-identify/anonymize the biospecimens and data by removing all identifiers and re-coding or disposing of the code key
  - No one collaborating may have any way to re-identify the materials
  - Research would be considered “not human subjects research”
  - **No submission of a protocol or IRB review would be required**
  - If materials were collected with research consent, investigators must consider what subjects originally consented to with regard to future research[6]
    - If biospecimens or data were collected as part of a protocol subject to the revised Common Rule, the consent form language must specifically allow for future research

Secondary Research with Identifiable Biospecimens and Data

- Goal: To conduct secondary research with existing identifiable biospecimens and/or data

  - Submit a new protocol for review and approval to the IRB
    - Allowable even when materials were collected under a protocol which will remain open with the IRB
    - Must include specific hypotheses and planned analyses
    - Must explain the terms and conditions under which the biospecimens and data were originally collected[6]

Consent for Secondary Research with Identifiable Materials

- The language in the original consent form should be either consistent with the planned research use or consent or a waiver of consent would be required[5].
  - IRB may determine that the proposed use is within the scope of the approved research in the original protocol, and no additional consent is required.[6]
  - If the proposed use represents a new research, then IRB will require new consent or grant a waiver of consent.
  - If the consent addressed future research uses that are not consistent with the proposed project, the research may not be permissible.[6]
    - ❖ The PI has the option to create a consent form addressing the new use[3, 5] and obtain consent from the subjects.
  - If the consent stated there would be no future research or prohibited the proposed research activity, the research is not permissible.[6]

Consent for Secondary Research with Identifiable Materials, cont.

- If the original consent form was silent with regard to future research, or informed consent was not obtained at the time of the original collection (e.g. biospecimens were collected for clinical diagnostic purposes/pathological waste from surgery):
  - The PI could try to make the case for waiver of informed consent, e.g.
    - State new consent is impracticable
      - It is not possible to re-contact a sufficient number of subjects due to the large number and dispersion of the subjects.[3]
- In general, if the PI has an ongoing relationship with most of the subjects, approval of a waiver of consent in most cases would be unlikely.

Consent for Secondary Research with Identifiable Materials, cont.

- If the secondary research will involve genetic testing or sequencing or other types of genetic research, or use for drug development, subjects must have explicitly consented to this.

- If the repository will involve children, the protocol should include a plan to re-consent children once they reach the age of majority, or request a waiver of consent for the continued use.

- If the biospecimens or data may be used for commercial profit, the consent must address this as well as whether the subject will or will not share in the profit.[6]

Best Practices for the Collection, Storage and/or Sharing of Biospecimens and Data for Future Research

Storage and/or Sharing of Existing De-Identified Biospecimens and Data for Future Research

- Goal: To store and/or share existing biospecimens and data for **future unspecified** research, when access to identifiers is not necessary
  - Fully de-identify/anonymize the biospecimens and data by removing all identifiers or re-coding, and disposing of the code key
  - No one collaborating in any future research may have any way to re-identify the materials

Storage and/or Sharing of Existing De-Identified Biospecimens and Data for Future Research, cont.

- Any future research would be considered “not human subjects research”
- **No submission of a protocol or IRB review would be required**
- If materials were collected with research consent, investigators must still consider what subjects originally consented to with regard to future research or sharing
  - The Revised Common Rule requires a statement in the informed consent as to whether or not biospecimens or data will be de-identified and used for future use. This statement is binding.

Collection and Storage of Biospecimens and Data for Future Research

- Goal: To collect and store de-identified or identifiable biospecimens and data for **future unspecified** research, including sharing

  - Submit a **repository protocol** for review and approval by the IRB

    - Could involve the prospective collection of biospecimens or data (e.g. a registry) from subjects and/or the use of existing materials

Repository Protocol

- The protocol should:
  - Include policies and procedures for inclusion, management, stewardship, distribution, and withdrawal[6]
  - Address the nature and scope of any future research
    - ❖ Can be very broad
  - Not include specific research hypotheses and planned research analyses
  - Address plan to ensure privacy and confidentiality, if identifiers will be maintained

Repository Polices and Procedures

- Policies and procedures re: inclusion of materials, management and stewardship:
  - Source of biospecimens or data, e.g.:
    - Prospective collection from subjects as part of the repository protocol,
    - The PI's IRB-approved protocol(s),
    - Other PIs' IRB-approved protocol(s), or
    - Clinical biospecimens or data from other sites
    - If repository is to include biospecimens or data from other protocols, those protocols and consent forms must specifically allow for this.
  - Inclusion/exclusion criteria for biospecimens and/or data
  - Who will review the appropriateness of biospecimens and data being deposited?

Repository Polices and Procedures, cont.

- Consent
  - New consent for prospective collection of biospecimens and/or data from subjects
  - Previous consent for sharing and future use of existing biospecimens and data
    - Must be consistent with the planned sharing and future use
    - If the consent language varied over time, each version of the consent form would need to be reviewed.
    - If consent included a yes/no option for sharing, only those explicitly marking yes can be included.

Repository Polices and Procedures, cont.

- Protocol should include policies and procedures re: distribution and withdrawal from the repository:
  - Shared in an identifiable or de-identified (coded and linked or anonymized) manner or both[3]?
    - Use of an honest broker to distribute materials in a coded fashion where the repository staff can re-link to identifiers if necessary[6]
  - Open access/publicly available (minimal or no restriction, e.g. through a web site) or restricted/controlled access (e.g. after submission of a research plan, review by Specimen/Data Access Committee, etc.)[3,5,6,7]
  - Withdrawal by subjects

[7] SACHRP, *Attachment B: Considerations and Recommendations Concerning Internet Research and Human Subjects Research Regulations, with Revisions (12-13 March 2013)*

Analysis of Materials from Repositories = Need for New IRB Approval

- Repository protocols generally do not cover analysis of biospecimens or data.
- **Any research use of identifiable biospecimens and/or data from the repository would require that the investigator submit a new protocol to the IRB*.**
  - Specific aims must be within the scope of the repository protocol
- The plan for consent or request for waiver of informed consent should be consistent with the repository protocol.

*See slides 28 – 31 re: “Secondary Research with Identifiable Biospecimens and Data”

Accessing this Presentation

- This presentation is being videocast and will be available for future viewing here: https://videocast.nih.gov/PastEvents.asp.

- To request a pdf of this presentation (or ask questions about its content), please email Julie Eiserman at julie.eiserman@nih.gov.

Questions