Secondary Research; Fact, Fiction, Fears and Fantasies

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NIH Office of Intramural Research
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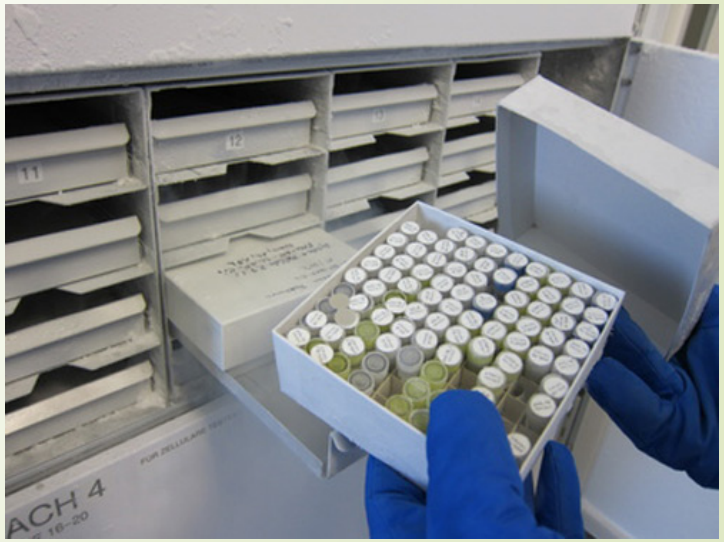
What is Secondary Research?

- Research conducted using information and/or specimens that were collected for purposes other than the current research.
  - May have been collected for clinical purposes
  - May have been collected under a different research protocol
- Secondary research is good!
  - Maximizes utility of data/specimens
  - Minimizes risk to subjects



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What is Not Secondary Research?

- Research with information and/or specimens collected under and used to meet the aims/objectives that are described in the IRB approved protocol
  - Primary/secondary objectives
  - Exploratory objectives

Primary Research

- Phase 1 protocol to determine the maximum tolerated dose of new checkpoint inhibitor drug XYZ123 for the treatment of metastatic lung cancer refractory to standard therapies.
  - Primary objective: Determine the safety profile, MTD and RP2D of XYZ123
  - Secondary objectives: Preliminary efficacy data, PK data
  - Exploratory objectives: Determine changes in immunologic profiles of subjects receiving the drug
- Investigator collects and stores specimens from before starting study drug and at each cycle.
- 2 years later when enrollment is complete, stored samples are analyzed for T cell subsets and cytokine protocols.

Secondary Research

- 5 years and several trials later, investigator has preliminary data from another study that suggests cigarette smoking leads to a specific epigenetic changes that increase susceptibility to certain infections. She realizes that she has pre-treatment samples from lots of cigarette smokers from prior lung cancer protocols that would be ideal to initially test this hypothesis.
- This is secondary research because samples and data were collected under another protocol for a different purpose.
  - This use of the samples/data is not described in the aims/objectives of the protocol under which the samples/data were collected.

Secondary research –yes or no?

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  - Primary objective: Determine the safety profile, MTD and RP2D of XYZ123
  - Secondary objectives: Preliminary efficacy data, PK data
  - Exploratory objectives: Determine changes in immunologic profiles of subjects receiving the drug
- After study is finished enrolling but is still open for analysis, investigator goes to a seminar and learns of an exciting new assay to determine cytotoxic T cell function. This assay was not specifically described in her protocol. She wants to use this on her stored specimens from this protocol.

Secondary research?

- NOT secondary research
  - Using a new assay to analyze samples in a way that is consistent with the aims described in the protocol is not new research.
  - A new experiment is not necessarily new research
- Don't get so granular in your protocol
  - Assays of immune cell function
  - Perform flow cytometry assessing CD4, CD8, CD69, PDL1. Proliferation in response to mitogen stimulation….

Secondary research?

- The following month, the investigator goes to another seminar and learns about a new assay to detect evidence of prior viral infections in patients. She thinks its really cool and might be useful in the future but wonders if her lab has the technical expertise to perform this assay. She wants to take a couple of old samples from the freezer and try out this assay.
- Is this secondary research?

Secondary research?

- NO
- Not research

How do I know if I am doing secondary research that requires IRB approval?

- Question 1: Am I doing research?
  - *Research* means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. (45 CFR 46.102(l))
  - "*Clinical investigation*" means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA...or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit (21CFR56.102(c))
- Question 2: Does it involve human subjects?
  - *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.
- Question 3: Am I using data/specimens that were collected for other purposes (either research or non-research)
- Question 4: Is the use of these data/specimens described in the aims/objectives of my IRB approved protocol?

Requirements to conduct any human subjects research

- A determination that the project is exempt; OR
- If non-exempt
  - Consent of the subject or a waiver of consent; AND
  - IRB approval of the project

Why is IRB review required?

- Subjects gave you their samples and data with an understanding they would be used for a specific purpose. IRB review assures that the new use is not counter to that intent nor likely to introduce new risks not previously disclosed to the participant or considered by the IRB.
- Ensures appropriate privacy and confidentiality protections.

IRB review of secondary research

- Use our template (irbo.nih.gov)
  - Identify the source of the samples/data you will use (original protocol #)
- Minimal risk, typically eligible for expedited review
- If initially collected for research, what did the initial consent say?
  - Must honor those terms.
  - If initial consent said no future use or otherwise prohibited the proposed use, then the data/samples cannot be used for secondary research without re-consent.
  - If consistent with the terms of the initial consent, then IRB can waive consent for the secondary research.
  - If consent was silent, then IRB will consider whether the proposed use is acceptable with a waiver or if reconsent is required
    - Does the secondary research use impose new or significantly greater risks (including privacy risks) not described in the initial consent form?
    - Are there known concerns of the study population(s) about the proposed secondary use?

Secondary research aims-take the goldilocks approach

- The aims should describe what it is that you want to do.
  - Determine if expression of marker xyz is elevated in patients with lung cancer as compared to controls.
- What if my secondary research is more exploratory?
  - Characterize everything I can ever think of in cells from any patient with any sort of cancer – too broad
  - Measure how many pg/ml of IL-6 using ELISA in the serum of patients aged 11 years old that received CAR T cell therapy – too narrow
  - Study the immunophenotype of patients that have received CAR T cell therapy – just right?

Ways to avoid IRB review of secondary research

- Use deidentified data/samples
  - Major risk of secondary research is a privacy risk, the unauthorized disclosure of private information about a subject. Deidentification eliminates this risk.
  - Research with data/samples that are not identifiable is not human subjects research and does not require IRB review and approval
- Deidentified means that the investigator has no way to link back to the identify of the subject
  - Coded is identifiable if you are a member of the study team that has access to the code key.
  - Must be stripped of all identifiers (18 HIPAA identifiers, PII elements under Privacy act)

The future use language is not consent

Future Use Language is not consent

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding [disease/condition], or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.
I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes_____ No
Initials Initials

Future use language is neither consent nor IRB approval

- Consent to participate in research requires disclosure of 9 specific elements, some of which are not contained in the future use language (notably the purpose of the research).
- The IRB approval pertains only to the primary study, not to as yet to be determined unspecified research.
- The future use language an be thought of as a statement of intent by the subject, that allows the IRB to waive consent for the future use of the specimen for research that is compatible with the information stated in the future use language.

Does agreement to future use have to be optional?

- If the primary research protocol has therapeutic intent or a prospect of direct benefit to the participant, then agreement to unspecified future use should be optional.
  - Why?
- If the primary research protocol does not have any prospect of direct benefit, then agreement to future use does not have to be optional
  - Healthy volunteer studies
  - Repositories
  - Natural history studies that do not involve any therapies as part of the research.

Do I have to keep my protocol open if I am storing samples?

- NO
- Identifiable samples can be stored even after primary protocol is closed
- Protocol only has to be open if you are using the samples for research purposes
  - Original protocol if research is described in that protocol
  - Secondary research protocol if a new project

Sharing data/samples and secondary research

- Sharing is good too!
- When can you share data/specimens from your protocol?
  - When your consent allows for it.
  - Subject agreed to participate in *your* study not someone else's. Should have been made aware that their data/specimens might be shared.

Do I need IRB approval to share data/ specimens?

- The sharing of the specimen does not require IRB approval, it is the downstream use that may require IRB approval. BUT:
  - The consent under which the data/specimen was collected must allow for sharing, or at least not prohibit it.
  - The proposed research use of the shared specimens should be consistent with the terms of the consent under which it was collected.
- If the consent says the samples will never be shared, that must be respected.
  - You must honor the terms of the consent.
  - Cannot share even if anonymized.
  - You could reconsent if you want to share.

Do I need IRB approval to share data/ specimens?

- I am sharing specimens with a non-NIH investigator and getting identifiable results back from the non-NIH investigator. Does this matter?
  - YES
  - Because you are receiving identifiable data in return, this is now human subjects research.
  - The IRB approval is not about the sharing of the specimen, it is about the use of the data that the investigator is receiving.
    - If not described in your approved protocol, you need IRB approval to use these data for research purposes.
    - New protocol or amendment, depending on the specific situation.

New protocol or amendment-it depends

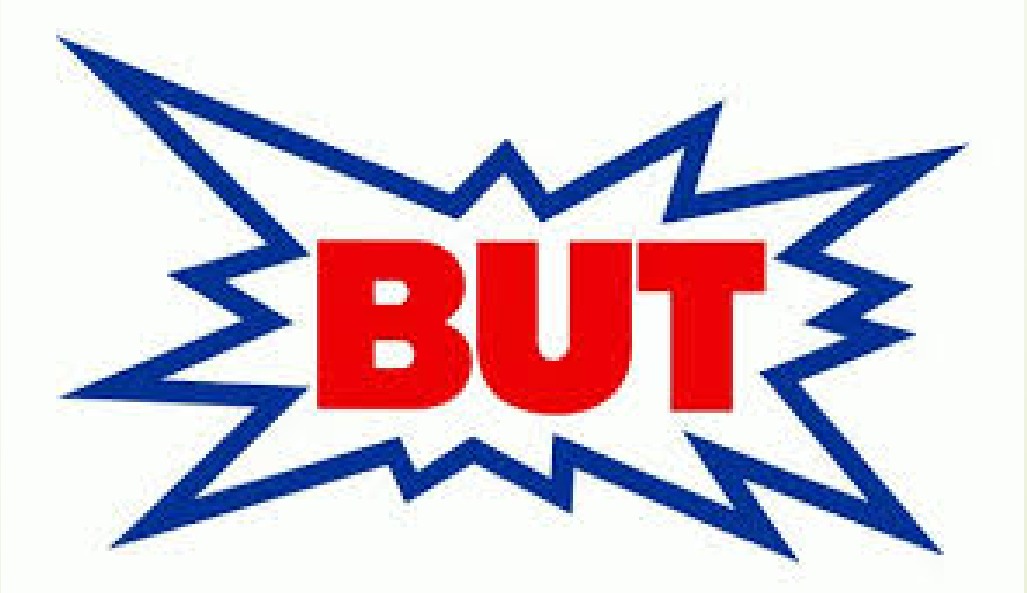
- New ideas need new protocols
- Is the proposed research captured under the original aims/objectives?
  - NO –new protocol
  - Yes- amend
    - For example, approved protocol is for prospective collection and analysis of biospecimens. Now you want to do the same analysis but add an already collected data and sample set

Why can't I amend?

- Protocols should be cohesive, with a unified theme
- Disconnected collections of ideas or random lists of experiments are not approvable as research

Broad Consent

- 2018 Common Rule contains a provision for "broad consent"
- Secondary research conducted with data and specimens collected under the new broad consent are exempt.



Broad Consent

- When agreeing to provide samples for unspecified future use, "Regulatory" Broad consent requires individual to have signed an informed consent document containing 12 specific elements.
- If a subject declines broad consent, the IRB can not grant a waiver for any future use of those data and samples.
  - Requires reliable segregation and tracking
- Future use of those samples/data requires prospective submission and approval of an exempt protocol by the researcher and limited IRB review.
  - IRB to determine privacy and confidentiality protections are adequate
  - Proposed use is consistent with the terms of the broad consent.

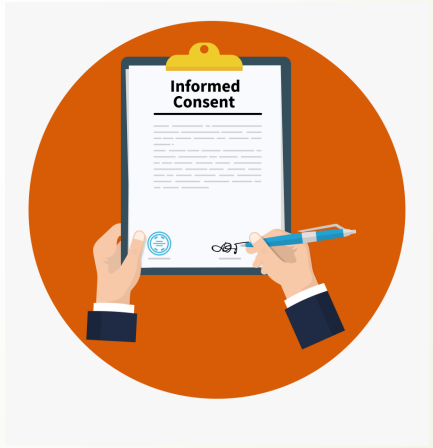
Special Considerations

- Research using specimens collected from Native American or Alaskan Native populations
  - Distinct culture, beliefs and values
  - Concern for potential community harms
  - Specimen ownership
  - Independent oversight system based on tribal sovereignty and self government.
- Past abuses
  - Havasupai
- Secondary research may require additional ethical review by IHS or Tribal IRB and permission from tribal government.

Repositories

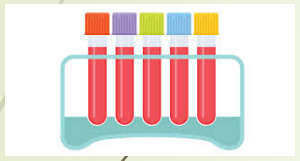
- A repository is a mechanism to store and maintain identifiable samples and/or data for future research purposes
- Repositories that house identifiable data/samples for research purposes require IRB approval and oversight.
- The repository protocol itself generally does not describe the secondary research.
- The repository can provide the data/samples to investigators for secondary research.
  - De-identified through an honest broker
    - no IRB approval needed for secondary use
  - Identifiable
    - IRB approval needed for secondary use.


Informed
consent


Informed
Consent

Primary research

Repository



Protocol 1
Deidentified, no IRB

Protocol 2
Deidentified, no IRB

Protocol 3
Identifiable
IRB needed

Why use a repository?

- Allows for collection, maintenance and storage under a uniform set of terms and conditions
- Data can be continually updated in the repository
- Provides ability for an honest broker to deidentify and therefore downstream secondary research is NHSR

Quiz time

- Dr Samples is conducting a Phase 1 protocol to determine the maximum tolerated dose of new tyrosine kinase inhibitor drug XYZ123 for the treatment of idiopathic pulmonary fibrosis. Blood samples are collected at each monthly study visit and stored.
  - Primary objective: Determine the safety profile and MTD of XYZ123
  - Secondary objectives: Preliminary efficacy data, PK data
  - Exploratory objectives: Determine changes in immunologic profiles of subjects receiving the drug

Quiz time

- Enrollment is complete and Dr Samples is busy analyzing his samples in the lab. His colleague and friend, Dr Data with a lab down the hall is studying how certain proteins are expressed on normal lungs and various forms of lung disease and approaches Dr Samples about a collaboration. Dr Samples thinks this is a great idea. What should Dr Samples do?
  - A. Submit an amendment to his protocol to study the expression of proteins in interstitial lung disease.
  - B. Give Dr Data the samples and say "go for it" and lets talk again when you have the data
  - C. Start examining the expression of the proteins in the samples himself and write up the paper.
  - D. Submit a new secondary research protocol to the IRB in collaboration with Dr Data.

  A, A and C, B and D, ABC, D only or All of the above

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Quiz time

- Before Dr Samples writes up the secondary research protocol, what factors should he consider?
  - What the consent under which the samples were collected said about future use and sample sharing.
  - Was future use or sharing optional? If so, can he identify who opted in or out?
  - Is it necessary to use identifiable samples, or could he anonymize them?
  - Nothing….his consent had the IRB template future use language, so he is covered.

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Quiz time

- Dr Samples is done with the research described in his protocol, but he wants to be able to do additional research in the future with the samples collected under this protocol. What should he do?
  - A. Close the protocol and strip the samples of identifiers and keep them
  - B. Keep the protocol open forever so he can use them for anything anytime
  - C. Close the protocol and keep the samples in the freezer, but not use them until he gets IRB approval for my new research project.
  - D. Destroy them
  - E. Transfer the samples to another protocol that is still ongoing so he can keep using them.

Quiz time

- Dr Samples becomes the head of a group of highly talented lung disease researchers, each of whom has several distinct protocols. What is the best way he can facilitate the ethical and compliant collaboration and sharing of specimens and data between them?
  - A. He shouldn't do that, because research is survival of the fittest and he wants to see who lives and who dies
  - B. Tell them to remember that the most important lessons of life were learned in kindergarten.
  - C Set up and manage a repository protocol and encourage them to offer co-enrollment to all of their participants in the repository protocol.

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Resources

- SACHRP FAQs

https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-faqs-recommendations-and-glossary-informed-consent-and-research-use-of-biospecimens-and-associated-data/index.html