Secondary Research Ethical Review

Belinda Smith, MS, RD, CCRC

1

Objectives

1. Secondary Research
2. IRB Review Options
3. Ethical Considerations
4. Informed Consent Waiver Criteria

2

What is NOT Secondary Research?

Collecting Data/Biospecimens directly from individuals for the Research …not "Secondary Use"

"Secondary Use" applies to data collected for other purposes

[OHRP Director Jerry Menikoff]

Ada Sue Selwitz

3

What is Secondary Research?

Research use of information or bio-specimens for other than the original purpose(s) for which the information or bio-specimens were initially collected through interaction or intervention with living individuals, including

- A primary or separate research activity (e.g., research dataset, registry/repository), or
- A non-research activity (e.g., clinical care, academics, business)

Primary Research

Registries & Repositories

Non-Research Sources

Office for Human Research Protections

4

Retaining Research Material from a Primary Study for Future Secondary Use & Sharing

5

Creating Data or Specimen Repositories Specifically for Secondary Use & Sharing

6

UK Guidance

UK Research Bio-specimen Bank Guidance
www.research.uky.edu/uploads/ori-d1290000-uk-research-biospecimen-bank-guidance-pdf
UK ORI Research Registry Guidance
www.research.uky.edu/uploads/ori-d1300000-uk-research-registry-guidance-pdf

- Infrastructure needed
- Role honest broker (https://oig.hhs.gov/compliance/safe-harbor-regulations/)
- Avoid self-imposed restrictions
- Future research must comply with informed consent
- If use tiered options in consent, manage use = subject wishes

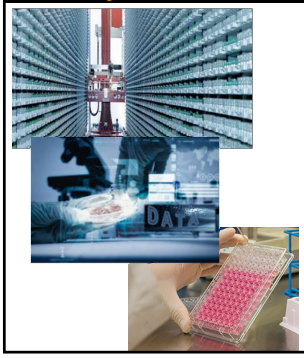
7

To develop repository that supports unspecified future use and data sharing:

- Expedited/Full Convened IRB Review
- Justify for why not using established repository
- Informed Consent for broad unspecified use and sharing - Sample Repository/Registry/Bank Consent [WORD] & key info example [PDF]

8

If you've seen 1 bank or registry… you've seen 1 bank!



- Material Specific (personal information, blood, data, tissue)
- Product Specific (medical device registry)
- Disease Specific
- Leftover
- Extra
- Genetic
- Genomic
- Share internal
- Share external
- Share de-identified
- Share de-identified with scrubbed medical data
- Share identifiable

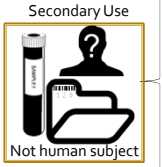
9

Bank provides recipient research with De-ID Biospecimens – IRB may provide NHR Determination

Honest Broker

Bank Provides *De-Identified* data/specimen or *Coded* data/ specimen w no access to key

Recipient Researcher Secondary Use



Not human subject

IRB Not Human Research (NHR) Determination

REDCapNHR FORM

Note: not applicable for genomic data sharing of samples collected post 2015

10

Bank provides recipient research with Identifiable Information/Biospecimens – Recipient Researcher must obtain IRB review for their secondary research protocol

- Recipient Researcher is provided with identifiable information

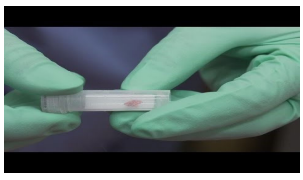
Is Human Subject

Submit Protocol in E-IRB

IRB Reviews secondary researcher's protocol

IRB determines if Secondary use is consistent with terms described in bank consent & if researcher agreed to same security measures since they now have custody

11



12

Other primary activity (clinical care, academics, etc.)

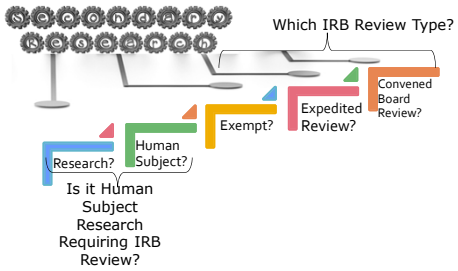
- Outcomes research conducted as retrospective or prospective record reviews or observational studies.

- Conducted with consent/authorization or waiver

13

14

IRB Regulatory Framework Stepwise Process



15

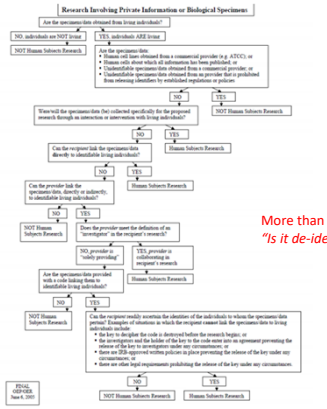
Circumstances in which coded private information or biological specimens may not meet the definitions of "human research" requiring IRB review

- the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens

OHRP 2008 Coded Data Specimen Guide
www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html
& NIH Decision Chart
https://grants.nih.gov/grants/policy/hs/private-information-biospecimens-flowchart.pdf

16

National Institutes of Health Office of Extramural Research Decision Chart



More than just determining *"Is it de-identified? "*

17

Is it "human research" requiring IRB review?

- Investigator obtains de-identified human data from a colleague with a data use agreement in place that states identifiers will never be released to the investigator and the investigator cannot readily ascertain identity of humans provided data and agree not to attempt re-identification.
- Colleague will not be involved in the interpretation, analysis, and authorship of the results

Is Not Human Subject Research

18

Is it "human research" requiring IRB review?

- Investigator creates a large specimen repository – procurement, management, storage, sharing. Investigator is also a scientist and wishes to conduct a basic science experiment with select specimens stored in their bank.

Is Human Subject Research

19

Common Rule Exempt Category Four

20

Secondary Research that qualifies for Exempt Review?

- Exempt Category 4 includes options for accessing material collected for a different original purpose (e.g., separate research, clinical care).
- However, the options have limitations that may not support the establishment of research repositories that need identifiers, share data, re-identify or re-contact subjects.

21

Category 4 I- Secondary Research for Which Consent is Not Required: Use of Identifiable Information or Identifiable Biospecimen that have been or will be collected for some other 'primary' or 'initial' activity, if ONE of following criteria met:

I. Biospecimens or Information is Publicly Available (not private)

Examples:
Public Dataset
Salary database
Purchased Biospecimens with at least one identifier

iSPECIMEN

If no identifier, may also qualify as "Not Human Subject" Determination

22

Category 4 II- Secondary Research for Which Consent is Not Required: Use of Identifiable Information or Identifiable Biospecimen that have been or will be collected for some other 'primary' or 'initial' activity, if ONE of following criteria met:

II. Information recorded so subject cannot readily be identified (directly or indirectly/linked); Investigator does not contact subjects and will not re-identify the subjects

No different from former Exempt Category in that:
- NO IDENTIFIERS RECORDED (Can Not Re-Identify)

Different from former Exempt Category in that:
- Record review may be both Retrospective and Prospective (continue to collect new secondary data after IRB Approval)

23

Category 4ii

- Can you see and use identifiers to find desired subjects?
- Can you record direct identifiers?
- Can you record codes to identifiers?

24

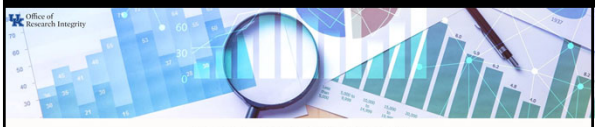
Category 4 III- Secondary
Required: Use of Identifiable Information or Identifiable Biospecimen that have been or will be collected for some other 'primary' or 'initial' activity, if ONE of following criteria met:

III. Collection and Analysis involving Investigators Use* of Identifiable Health Information when use is regulated by:
- HIPAA Health Care Operations [privacy notice]; or
- HIPAA Research [research HIPAA authorization/waiver]; or
- HIPAA Public Health Surveillance [disclosure]

* "*Collection and Analysis involving Investigators Use*" potentially restricts sharing

25

https://rwebmedia.ad.uky.edu/ORI/Secondary_Research_Tool/story.html



SECONDARY RESEARCH TOOL

Secondary research involves re-using material collected for some other 'primary' or 'initial' activity, for research. Several factors are involved in determining whether secondary research requires IRB review, and if so, the appropriate review type.

This tool uses the regulatory framework to provide you with a preliminary determination on whether to request a Not Human Subject (NHR) determination or submit an Exempt or Expedited IRB application.

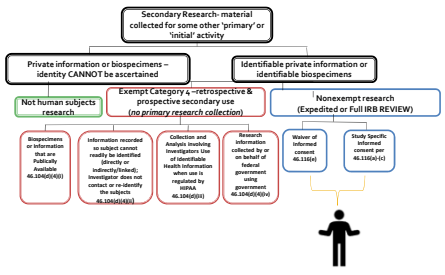
The tool is a guide, not a guarantee. The outcome may differ based on ethical variables and risk interpretation by the IRB. You are always welcome to contact ORI staff for consultation regarding your specific secondary research plans.

Click review type charts and answer questions for guidance on need for IRB review of Secondary Research

1. NOT HUMAN RESEARCH
2. EXEMPT
3. EXPEDITED

26

Revised Common Rule
UK Secondary Research Options

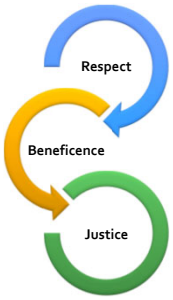


27

Adapted from OHRP/Ivor Prichard

27

Ethics - Tension between principles



28

Leftover Biospecimens
Beneficence vs. Respect

29

Regulations or laws that may limit or prohibit waiver:

- Family Educational Rights and Privacy Act (FERPA) generally requires prior written permission to access to student records
- Protection of Pupil Rights Amendment (PPRA) parental permission requirements related to select survey research
- NIH Genomic Data Sharing – consent required for specimens obtained after 1/2015; prior collections – consent must not prohibit sharing
- NIH Human Fetal Tissue – 7/2019 consent required for donations obtained from elective abortions
- Children's Online Privacy Protection Act (COPPA) - uses age of 13 years as a cut-off for when parental permission isn't needed

30

Waiver Criteria – check all that apply

- Minimal Risk to subjects
- Retrospective collection
- Waiver will not adversely affect subject rights & welfare
- Obtaining consent isn't practicable
- Research isn't practicable without requested waiver
- Research isn't practicable without using identifiable information/specimens
- If appropriate, pertinent information will be provided after study participation

31

Consider all 5 criteria

WAIVER
OR ALTERATION

32

Provided the IRB finds and documents that:

1. the research involves no more than minimal risk to the subjects;
2. the research could not practicably be carried out without the waiver or alteration;
3. if the research involves using identifiable private information or identifiable biospecimens and the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. the waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. whenever appropriate, the subjects will be provided with additional pertinent information after participation.

45 CFR 46.116

33

Rights & Welfare Considerations

- Methods and procedures to secure information and protect confidentiality
- Whether the subject population, in general, would:
  - object if they knew of the waiver and its intent in facilitating research
  - consider that the waiver has the potential to cause adverse consequences for their welfare or general well being
  - consider the value of the research and potential discovery to be worth relinquishing control of private information or specimens

34

Participant's Views on Data Sharing

- 93% were very or somewhat likely to allow their own data to be shared with university scientists
- greatest concerns
  - data sharing might make others less willing to enroll in clinical trials (37%),
  - that data would be used for marketing purposes (34%),
  - or that data could be stolen (30%)
- greatest benefits
  - ensuring that people's participation leads to scientific benefit (18%) and
  - helping to get answers to scientific questions faster (17%).

Source: New England Journal of Medicine, Mello, et. al., June 2018

35

PRACTICABILITY

Commonly accepted definitions are:

(a) feasible;
(b) capable of being effected, done or put into practice; and
(c) may be practiced, performed, done or accomplished with available means or resources*,

**cost or convenience should never be a sole criteria for a waiver*

36

PRACTICABILITY

For approval of a waiver of informed consent requirements, the IRB determines whether _____ could not practicably be carried out without the waiver.

A) **informed consent**
B) **documentation of informed consent**
C) **the research**
D) **the recruitment**

37

Justifications for why informed consent might not be practicable

- **Ethical concerns** such as:
  - a risk of creating additional threats to **privacy** by having to link otherwise de-identified data with nominal identifiers in order to contact individuals to seek consent.
  - a risk of inflicting **psychological, social or other harm** by contacting individuals or families.
  - scientifically and ethically justifiable rationale why the research could not be conducted with **a population** from whom consent can be obtained.

39

Justifications for why informed consent might not be practicable

- Researcher does not have **access** to study population: no clinical relationship (pathologist, radiologist); timing (ED 24 hour coverage); intensive clinical treatment prohibits research.
- **sample size required is so large** (e.g., population-based studies, epidemiology trials) including only those samples/records/data for which consent can be obtained would prohibit conclusions to be drawn or bias the sample such that conclusions would be skewed.
- subjects are no longer followed and may be **lost to follow-up**. For example the proportion of individuals likely to have relocated or died may be a significant percentage of the subject population and there would be a loss of statistical power.
- disclosure of the **study purpose** as part of the consent process would bias the research subjects so that the results will not be meaningful (**deception**)
- **Informed Consent bias** sufficient to jeopardize the overall validity or render the population as non-representative

40

Informed Consent Bias

Subjects who aren't offered or who refuse to consent, differ systematically from those who do consent.

- Canadian Stroke Registry – investigators closed registry when they identified differences in prognostic characteristics between participants (P) and non-participants (NP).
- Observational studies also have documented higher proportions of minority populations, uninsured, and/or Medicaid patients among NP while those consenting have higher education and more comorbidities than NP.
- Loss of potential subjects with rare conditions may impact study power.

Bias renders data ungeneralizable

41

Is Informed Consent Bias Justification for Waiver?

If bias exists, the investigator would need to provide the IRB with a DATA-DRIVEN ARGUMENT – literature and data collected on participants and non-participants to determine if consent bias is impacting scientific validity
Impact would need to matter given context of the study!

42

Tension between Principles

MATERIAL FROM
underrepresented populations not available

43

Example of Justification Univ of Utah IRB determined to be Valid

- Rare disease, cervical spine injury (CSI), occurs in less than 2% of children who sustain blunt trauma. We determined the feasibility of the proposed project's sample size of 22,222 by using the enrollment rates and incidence of CSI in the pilot study and applying it to information regarding this study's participating sites obtained from Pediatric Emergency Care Applied Research Network (PECARN) core data project.
- Prior similar work in children with head injury and abdominal trauma has demonstrated that we are able to achieve enrollment rates of 80% with waiver of consent. If written informed consent had been required for these prospective cohort participants, enrollment would have decreased by 45% due to lack of an available parent or legal guardian during the emergency visit.
- Further, we have concerns that the established cohort would not be representative of the spectrum of children at risk for CSI and thus would result in ascertainment bias. Our prior work has demonstrated that those patients at highest risk for severe injury will be more difficult to consent (e.g., absent guardian, time critical injuries, etc.) while lower risk patients will be easier to consent (e.g., arrive with guardian, stable injuries, etc.).

https://irb.utah.edu/search/index.php?q=waiver+prospective+data+collection&gcse_action=site

44

Questions

1. Secondary Research
2. IRB Review Options
3. Ethical Considerations
4. Informed Consent Waiver Criteria

45