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Final Rule Material:
Secondary Research with Identifiable Information and Biospecimens

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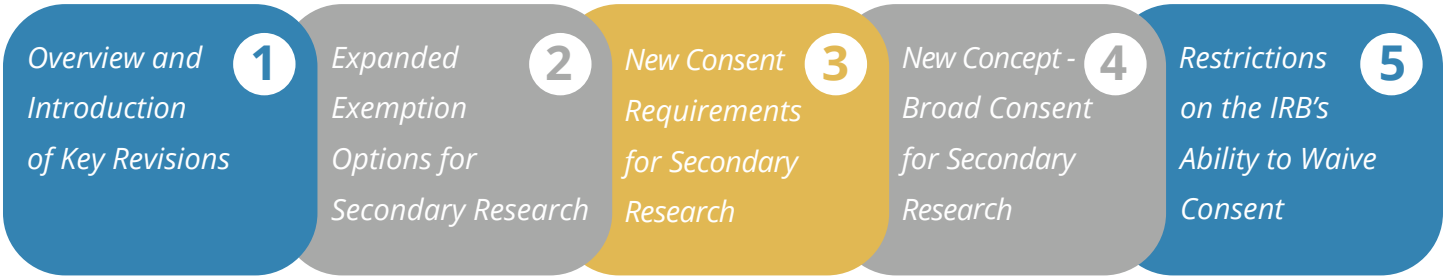
Introduction

Secondary research is a general term typically describing research projects using information or biospecimens for some other purpose after the primary research or clinical intervention used to collect them. Initial collection may come through a separate research study or non-research activity (for example, clinical care). The Final Rule includes several changes regarding how secondary research involving identifiable private information or identifiable biospecimens may be conducted. Changes include new informed consent requirements, expansion of when such secondary research is exempt from the Common Rule, and new restrictions on when Institutional Review Boards (IRBs) can waive consent for such use. This material on secondary research is divided into five parts.



This material will refer to the pre-2018 rule (the current Common Rule) and the Final Rule (the revised Common Rule), and for consistency and clarity it uses citations to the U.S. Department of Health and Human Services (HHS) regulations at 45 CFR 46, Subpart A version of the Final Rule as published in the *Federal Register* on 19 January 2017.

Part 1: Overview and Introduction of Key Revisions

Introduction

On 19 January 2017, HHS issued a Final Rule in the *Federal Register* to update the current regulations at 45 CFR 46, Subpart A - "Federal Policy for the Protection of Human Subjects" (the Common Rule). The Final Rule makes significant revisions intended to "modernize, strengthen, and make more effective" the current system of oversight, which was virtually unchanged since 1991.

The precursor to the Final Rule was the Notice of Proposed Rulemaking (NPRM) that included a change to consider any biospecimen as identifiable; however, this change was not adopted in the Final Rule. The Final Rule retains the current scope that only applies to research using identifiable private information or identifiable biospecimens. If information or biospecimens are sufficiently de-identified then secondary research use of the information or biospecimens is likely exempt or does not meet the definition of human subjects research (to determine if information or biospecimens are considered de-identified see the Office for Human Research Protection's [OHRP] guidance entitled "Coded Private Information or Specimens in Research").

Identifiable Private Information or Biospecimens → **Regulated by Final Rule**

De-Identified Information or Biospecimens → **Exempt / Not Human Subjects Research**

This resource will primarily cover the new requirements and provisions for secondary use of identifiable information or biospecimens in the Final Rule.

Same Concept, but New Language - "Data" and "Information or Biospecimens"

The pre-2018 rule referred to "data," but the Final Rule refers to "information or biospecimens." This language change was necessary to present contemporary language reflecting current practice (Final Rule Preamble). The new language has a similar effect as the previous language. Review the updates (at 46.102) below ***(revisions in bold).***

Pre-2018 Rule

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:

- Data through intervention or interaction with the individual; or
- Identifiable private information.

(46.102[f])

Final Rule

Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

- **Obtains information or biospecimens** through intervention or interaction with the individual, **and uses, studies, or analyzes the information or biospecimens;** or
- **Obtains uses, studies, analyzes, or generates** identifiable private information **or identifiable biospecimens.**

(46.102[e])

Implementation Date

The changes applicable to secondary use of information or biospecimens are effective for all research approved by an IRB on or after 21 January 2019 (HHS 2018). Research institutions, IRBs, and investigators will have to revise forms, documents, and practices for compliance with the revisions.

How can secondary research with identifiable private information or identifiable biospecimens be conducted under the Final Rule?

Action	Explanation
Make the Information or Biospecimens Non-Identifiable	No substantive change from pre-2018 rule; secondary use of non-identifiable information or biospecimens is still exempt.
Obtain IRB Approval for Research with an IRB Waiver of Consent	Same practice as currently exists under pre-2018 rule with waiver; however, there are some new limits on when IRBs can waive consent.
Obtain IRB Approval for Research with Prospective Consent from Subjects	Only change from pre-2018 rule is that the Final Rule requires informed consent forms to include new required language about secondary use of information or biospecimens.
NEW Use the Broad Consent Option	New option for secondary research use of identifiable information or biospecimens.
UPDATED Make Use of Expanded Exemption 4 Criteria	Updated options to use exempt category 4. For instance, secondary research projects where the identifiable information is protected under Health Insurance Portability and Accountability Act (HIPAA) requirements now may qualify as exempt from the Final Rule.

Transition Provisions

Research studies approved (or determined to be exempt) before the Final Rule's effective date are "grandfathered," meaning they will not be required to comply with the changes in the Final Rule. Such research may continue to completion or closure without change.

Institutions and IRBs can voluntarily choose to apply the Final Rule on a study-by-study basis for previously approved studies, or by formally adding a requirement to their policies. If the Final Rule is applied to the grandfathered research, then all Final Rule requirements must be applied (no picking and choosing what to apply from pre-2018 and Final Rule regulations – it is all or none).

The intent of the transition phase is to minimize burdens associated with ongoing research that is conducted over an extended period of time and avoid a requirement that such research be subject to two sets of rules during the life of the research.

U.S. Food and Drug Administration (FDA) Harmonization

Utilization of identifiable biospecimens and data for research is not currently a key focus of FDA regulations under 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards). The FDA regulations are primarily designed for clinical investigations involving FDA-regulated products. Some limited research activities involving identifiable information or biospecimens are subject to the FDA regulations if the resulting data from the research will be used as part of a marketing application to the FDA or in situations where human specimens are needed for testing of *in vitro* diagnostic devices.

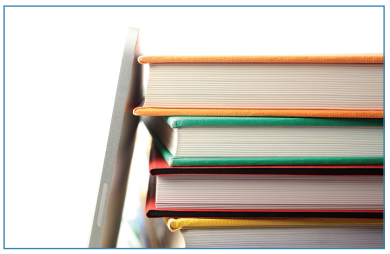
The FDA has stated over the past six years (since the HHS' Advance Notice of Proposed Rulemaking [ANPRM] published in 2011) that it plans to update its regulatory language in concert with the government-wide effort to modernize rules governing the use of human subjects in research. However, the FDA's regulatory jurisdiction only extends to research involving an FDA-regulated product. It is uncertain if FDA regulations will be updated to adopt all the new Final Rule provisions regarding secondary use of identifiable information or biospecimens.

Final Rule Key Concepts and Requirements for Secondary Research

Concept/Requirement	Explanation
"Data" is now referred to as "Information or Biospecimens"	No substantive change from pre-2018 rule, but emphasizes that research involving identifiable biospecimens is covered under the Final Rule
Expansion of Exemption Criteria	Allows for broader use of exemption category 4, and new exemptions 7 and 8 for research where information or specimens were originally obtained using broad consent
NEW Consent Requirements	Notifies subjects of potential secondary use of information or biospecimens
NEW Broad Consent Requirements	Provides option for consent for secondary research use of identifiable private information or biospecimens
Changes in the IRB Waiver Criteria	Limits when IRBs can waive consent for research involving identifiable information or biospecimens

Part 2: Expanded Exemption Options for Secondary Research

The Final Rule expanded exemptions for secondary research involving use of de-identified information and biospecimens. Importantly, the Final Rule did not adopt the idea that all biospecimens are inherently identifiable. The Final Rule also significantly expanded the types of secondary use research projects considered exempt.



Expanded Exempt Category 4

Key expansions for exempt category 4 are:

1. *Information or biospecimens no longer must be "existing" at the time of the exemption determination.*
2. *Certain research use of identifiable information may be considered exempt from the Final Rule if such data are subject to HIPAA protections.*

> *Preamble Comment on 46.104(b)(4)*
>
> "By 'secondary research,' this exemption is referring to re-using identifiable information and identifiable biospecimens that are collected for some other 'primary' or 'initial' activity...It is important to recognize that this exemption does not cover any primary collections of either information or biospecimens."

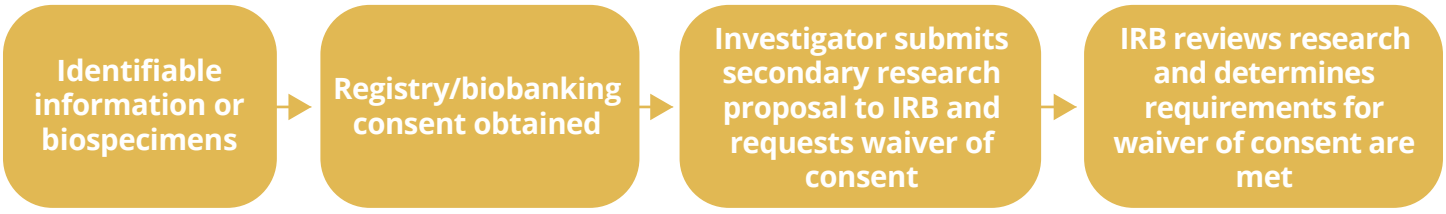
Expansion of the category 4 exemption criteria may allow organizations to determine that more research projects involving secondary use of information or biospecimens are exempt from the Final Rule requirements than had been possible in the past (pre-2018 rule).

New Exempt Categories 7 and 8

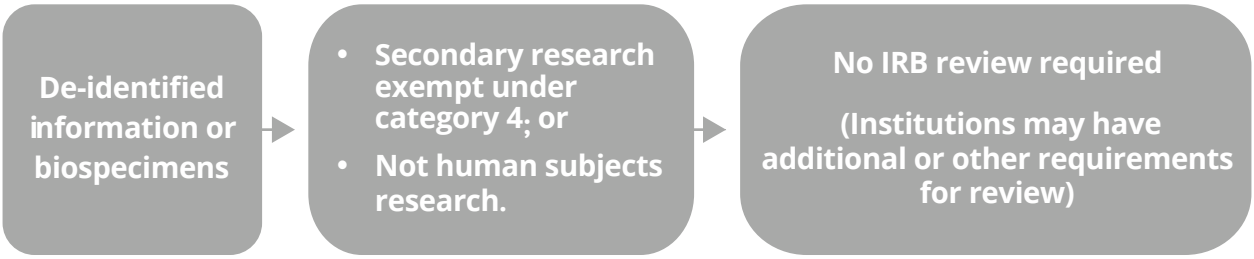
The Final Rule includes new exemptions for secondary use of identifiable information or biospecimens when broad consent is obtained using the new broad consent provisions. The Final Rule exemption categories at 46.104(d)(7) and (8) remove most of the IRB review responsibilities required if broad consent was used to collect the information or biospecimens. The IRB does have some limited responsibility to provide input and determinations during the exemption determination process. Because subjects will originally be providing an option for broad consent to secondary use, such secondary use research does not require a full and separate IRB review -- even for research using identifiable information or biospecimens (Final Rule Preamble).

Identifiable Information or Biospecimens → **Broad Consent Obtained** → **Limited IRB Review** → **Research Exempt Under Category 7 or 8**

If information or biospecimens are collected using a study-specific or registry/biobanking consent (for example, a consent process not meeting all the new broad consent requirements under 46.116), secondary research involving the information or biospecimens can still occur. The investigator would submit a research proposal involving information or biospecimens collected for another purpose to the IRB (likely with a waiver of consent request). The IRB would then review the proposed research project just as it does now under the pre-2018 rule. There would be no option to make an exemption determination under the new categories (7 or 8), and the IRB would need to apply the expanded waiver of consent criteria. For instance, investigators can continue to develop retrospective chart/specimen review studies looking at existing biospecimens and their associated identifiable medical records, and submit those studies for IRB review as minimal risk expedited with an associated request for waiver of informed consent under 46.116(f).



Investigators can avoid the requirements for IRB review by conducting research on de-identified information or biospecimens as such research would almost never be considered human subjects research, or qualify for exemption 4 under the expanded category 4 requirements. However, institutions may have additional requirements and expectations beyond the Final Rule requirements. Investigators must check with their institutions to determine local requirements (such as, state law or institutional policy).



Part 3: New Consent Requirements for Secondary Research

As stated in the Final Rule's preamble, the goal of updated 45 CFR 46.116 consent requirements is to facilitate a prospective subject's (or legally authorized representative's) understanding of how the subject's information or biospecimens will be used in secondary research and provide "key information" a prospective subject might need to determine whether to participate in secondary research. There are numerous new requirements related to consent in the Final Rule. This resource focuses specifically on secondary research provisions.

New Required Consent Statement for Secondary Research

Subsection 46.116(b)(9) is a new required element of informed consent that specifically applies to any research involving the collection of identifiable information or biospecimens. Research not involving the collection of information or biospecimens would not require this statement. It will be up to the IRB to determine when the language might not apply. It is also anticipated that OHRP will issue guidance on the types of statements it would consider adequate to satisfy this new required element of consent.

Preamble Comment on 46.116(b)(9)

"If a specific technology or technique determined to be capable of generating identifiable private information or identifiable biospecimens through [consultation with appropriate experts] described in section 46.102(e)(7)(ii) will be used, that information should be included in the description of the research as required by 46.116(b)(1)."

NEW Required Consent Statement per 46.116(b)(9)	Example Consent Language
A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility (46.116[b][9][i]).	*Any personal information that could identify you will be removed from your sample. Your sample may be used for future research studies without the investigator asking for your additional permission.*
A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies (46.116[b][9][ii]).	*Any personal information that could identify you will be removed from your sample. Your sample will not be used for any future research studies.*

New Additional Elements of Consent

Three new optional elements of informed consent were added at 46.116(c)(7), (8), and (9) to cover disclosure to the subjects regarding issues that may relate to secondary use of their information or biospecimens. Unlike the new required element at 46.116(b)(9), the new optional elements do not specifically apply only to secondary use. Although not required by the pre-2018 rule, the types of disclosures covered in the new optional elements of the Final Rule commonly appear in contemporary consent forms. The Final Rule formalizes these disclosures as information that the subject may need in order to make an informed decision about participating in the research. The new optional elements of consent may or may not be included in the consent at the IRB's discretion.

NEW Additional Elements of Informed Consent per 46.116(c)	Example Consent Language
A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit, and whether the subject will or will not share in this commercial profit (46.116[c][7]).	*Your sample may be used to develop new drugs or other products for commercial purposes. If these products make money there are no plans to share the money with you.*
A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions (46.116[c][8]).	*Example 1 - Results of research testing on your sample will be returned to you.* *Example 2 – Results of research testing on your sample may be given to you or your doctor. This will be done only if the results may be necessary for your care.*
For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (in other words, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen) (46.116[c][9]).	*Research testing on your sample will include whole genome sequencing. This means we will map your entire genetic code. If you have questions about this ask the study staff.*

Summary of New Requirements for Informed Consent Form Language

NEW Requirement at 46.116(b)(9) is to include one of two statements about the collection of private information or identifiable biospecimens for future research:

- **Identifiers might be removed and the de-identified information or biospecimens used for future research without additional informed consent from the subject.**
- **The subject's information or biospecimens will not be used or distributed for future research studies even if identifiers are removed.**

NEW Added at 46.116(c)(7), (8), and (9) are new additional elements of consent relating to use of information and biospecimens. These optional elements are included at the IRB's discretion (some institutions may also require these additional elements as a matter of institutional policy).

Note: New elements for informed consent in the Final Rule do not appear in corresponding FDA regulation at 21 CFR 50.25. FDA is expected to harmonize guidance in the future.

Part 4: New Concept - Broad Consent for Secondary Research

Broad consent is a new option from the Final Rule allowing for subjects to agree to a wide range of future secondary research studies using their identifiable information or biospecimens. Broad consent may be used for secondary research studies meeting the full range of requirements under the Final Rule, or to qualify certain secondary research activities for an exemption.

The new broad consent options are outlined in 45 CFR 46.116(d). It is important to note the new provisions for broad consent are "an alternative to the informed consent requirements." This is not a waiver, but an alternative process of obtaining consent.

Use of the broad consent concept and process is optional. Obtaining consent by traditional methods is still allowed in the Final Rule as long as those methods comply with the updated elements of informed consent outlined in 46.116 (a) through (c).

The Final Rule allows broad consent for either a specific type of specified future research (for example, prostate cancer research) or a broader scope of research.

The Final Rule did not contain any templates for broad consent forms. Institutions and investigators may develop their own to satisfy the required conditions.

Are investigators required to use broad consent?

Investigators are never required to obtain informed consent through a broad consent process; it is an available alternative procedure.

Instead of obtaining broad consent, an investigator may:

1) Conduct the research on non-identifiable information or non-identifiable biospecimens, and request that the IRB waive the requirement for additional prospective informed consent.

2) Obtain consent for a specific study. Even if the investigator wanted to use the biospecimens with identifiers attached, the option still exists of asking an IRB to waive the requirement to obtain additional prospective informed consent instead of using broad consent.

Broad Consent Requirements	
46.116(d)(1)	Requires some basic elements of consent: • Risks • Benefits • Confidentiality • Voluntary statement • Commercial Profit (when appropriate) • Whole genome sequencing (when appropriate)
46.116(d)(2)	Requires a general description of the types of research that may be conducted. The IRB must assess whether the description of the research included in the broad consent form is adequate to permit a reasonable person to provide consent for the currently proposed secondary research study.
46.116(d)(3)	Requires a description of the information or biospecimens that might be used in future research; whether sharing might occur; and the types of institutions or investigators that might conduct research.
46.116(d)(4)	Requires a description of the length of time that the information or biospecimens may be stored, maintained, and used.
46.116(d)(5)	Requires a statement on whether subjects will or will not be informed of the details of any subsequent research.
46.116(d)(6)	Requires a statement that clinically relevant research results either will or will not be disclosed to subjects.
46.116(d)(7)	Requires that contact information be provided in the broad consent.

Investigators conducting secondary research with information or biospecimens will continue to have the option of conducting secondary research with non-identifiable information or biospecimens outside the Final Rule's scope. They may also conduct secondary research with information or biospecimens where the information is recorded in such a manner that identity cannot be readily ascertained (for example, coded information where the code is held by a trusted third party or honest broker. Using an honest broker system allows for the collection of additional information by the broker about the subjects over time through the coding mechanism).

In both instances, no additional consent would be required because the research would not involve human subjects as defined by the Final Rule or would qualify for the expanded exemption 4 criteria. Even if the investigator wanted to use information or biospecimens with identifiers attached, the option still exists of asking an IRB to waive the requirement to obtain informed consent. That is, if the IRB approves the research project and finds the new expanded waiver criteria are met.

Preamble Comment on 46.116(d)(1) and (b)(8)

"When appropriate, this element of broad consent will inform subjects that information that has been stripped of identifiers might not be traceable, and thus it might not be feasible to withdraw consent for future use or distribution in this case.

However, if an investigator commits to permitting a subject to discontinue use of the subject's identifiable private information or identifiable biospecimens, it is expected that the investigator will honor this commitment by not removing identifiers."

Part 5: Restrictions to the IRB's Ability to Waive Consent

IRBs may continue to waive the requirements for informed consent under the Final Rule. The four waiver or alteration criteria found in the pre-2018 rule at 45 CFR 46.116(d) appear unchanged, but in a new location at 46.116(f)(3). A new "fifth" waiver criteria relating to use of identifiable information or biospecimens appears in the Final Rule at 46.116(f)(3)(iii). In addition to the pre-2018 rule's waiver or alteration criteria, under the Final Rule IRBs must also determine if research research involving identifiable information or biospecimens could not practicably be carried out using non-identifiable information or biospecimens. In addition to the current justification about whether a research project could not practicably be carried out without waiving consent, investigators must now justify why they cannot practicably do the secondary research project using non-identifiable information or biospecimens.

Avoiding Additional Justification

Investigators can avoid the additional waiver of consent justifications necessary under 46.116 (f)(3)(iii) by:

- Using information or biospecimens obtained under the new broad consent provisions
- Using non-identified information or biospecimens for the secondary research to qualify for exemption 4, or being considered not human subjects research and therefore not subject to the Final Rule

For subjects who are offered a broad consent for future use of their identifiable information or biospecimens, and actively decline to provide consent for secondary future use, there is a restriction under 46.116(f)(1) that the IRB may not waive consent for secondary research using identifiable information or biospecimens. This restriction is intended to uphold the *Belmont Report* principle of respect for persons, by preserving an individual's express refusal in the broad consent process from being overridden. Institutions will need to develop tracking mechanisms to honor requests by potential subjects who refuse additional broad consent for secondary research.

References

- Institutional Review Boards, 21 CFR § 56 (2015).
- Office for Human Research Protections (OHRP). 2008. "Coded Private Information of Specimens Use in Research, Guidance (2008)." Accessed June 26, 2017. https://www.hhs.gov/ohrp/regulations-and-poli-cy/guidance/research-involving-coded-private-information/.
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