



Secondary Research with Biospecimens and Data Under the Revised Common Rule

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Objectives

By the end of the session, you will be able to:

1. Articulate the **autonomy, beneficence, and justice arguments** around different approaches to secondary research with specimens and data
2. Explain the **regulatory trajectory** toward the revised Common Rule's approach to secondary research with specimens and data
3. Identify outstanding concerns about the new option for **broad consent**



Overview

- The old rules
 - The ethical controversy
- The proposed rules
 - The ethical controversy
- The new rules
 - Open questions



Where do data and specimens come from?

- **Research**
 - Data/specimens collected for a particular hypothesis-driven protocol
 - Used for that study
 - “Leftovers” for future use
 - Or might be contributed specifically to a research repository
- **Clinical care**
 - Patient records
 - Specimens collected for diagnosis or during treatment
- **“Real life”** – data trail



The Common Rule

- Regulatory requirements applicable to most human subjects research conducted or funded by the federal government
 - In “common” across many agencies, e.g., HHS, DoD, VA, EPA, etc.
- “Research” with “human subjects” – operative definitions
- If not “research” or no “human subjects,” CR does not apply
- If “research” with “human subjects,” CR applies...
 - Could be **exempt** – do not need (traditional) IRB approval or informed consent
 - Could be **non-exempt** – need (traditional) IRB approval and informed consent/waiver of consent

The Old Rule

- Research: “**systematic investigation** . . . designed to develop or contribute to **generalizable knowledge**”
- Human subject: “**living** individual **about whom** an investigator . . . conducting research obtains”
 - “Data through **intervention or interaction** with the individual” **OR**
 - “**Identifiable private information**”
 - Identifiable = “the identity of the subject is or may readily be ascertained by the investigator or associated with the information”

The Old Rule

How does this apply to research with biospecimens and data?

- **Primary research**: collected specifically for that study → requires interaction with individual source → if living, then “human subjects”
- **Secondary research**:
 - Collected in another context, e.g., separate research or clinical care → no interaction or intervention for present research purposes
 - ONLY counts as research with “human subjects” IF the specimens or data are individually **identifiable** (and contain private information)

The Old Rule

If secondary research and **identifiers are retained** . . .

- Could be **exempt** from CR
 - Collection or study of existing data or specimens if sources are publicly available or information recorded without identifiers
- Could be **non-exempt** from CR = IRB review +
 - **Waive consent** IF:
 - Research is minimal risk
 - Waiver will not adversely affect the rights and welfare of subjects
 - Research could not “practicably” be carried out w/o waiver of consent
 - Debriefing after participation, when appropriate
 - If conditions for waiver not satisfied, then consent required
 - But could be general consent at the time data/specimens were collected

The Old Rule

If secondary research and
identifiers are removed . . .

- **Not human subjects research**
- No IRB review or consent required



The Old Rule

- Bottom line: Old rule allowed **LOTS of ways** to carry out secondary research with biospecimens and data **without IRB review and/or informed consent**
 - Remove identifiers – no IRB review/consent
 - Don't record identifiers – no IRB review/consent
 - Retain identifiers w/ consent waiver – IRB review only
- Research infrastructure built on these premises
 - Change should be supported by compelling need



The Old Rule



Arguments in **favor** of this approach

- Promotes **scientific advancement**
 - Few hurdles for researchers to carry out their work
 - Could be difficult/impossible to track down specimen/data sources to ask for consent later
 - Could be difficult to track consent if sought at time of collection, especially if complex options
 - If some opt-out, science could be harmed (biased results)
- Very **low risk** to specimen/data sources
 - Low privacy/confidentiality risks when identifiers removed or not recorded
 - Alternative ways to protect source rights if identifiers retained but consent waived (IRB oversight)
- **Social obligation** to participate in low risk/low burden activities that benefit society
 - Autonomy should not necessarily trump beneficence/justice
 - Avoid free-riding (if all benefit, some shouldn't get to opt-out)
- U.S. legal precedent to date suggests source retains **no property interest** in specimen

The Old Rule



Concerns about this approach

- It may **surprise** people who would expect to be asked before materials/information derived from them are used for research
 - Could lead to **mistrust** in the research enterprise – reduce public support
- Some believe they should control materials/information derived from them, even if not identifiable and even if low risk (**autonomy**)
- It may be viewed as **disrespectful**
- Even when identifiers are removed:
 - Increasingly possible to **reidentify** data/specimens – privacy/confidentiality risks
 - A **group** may be identifiable and subject to harm
 - Individuals have **other interests** in protecting their fundamental values even if not worried about reidentification

Challenging the Status Quo

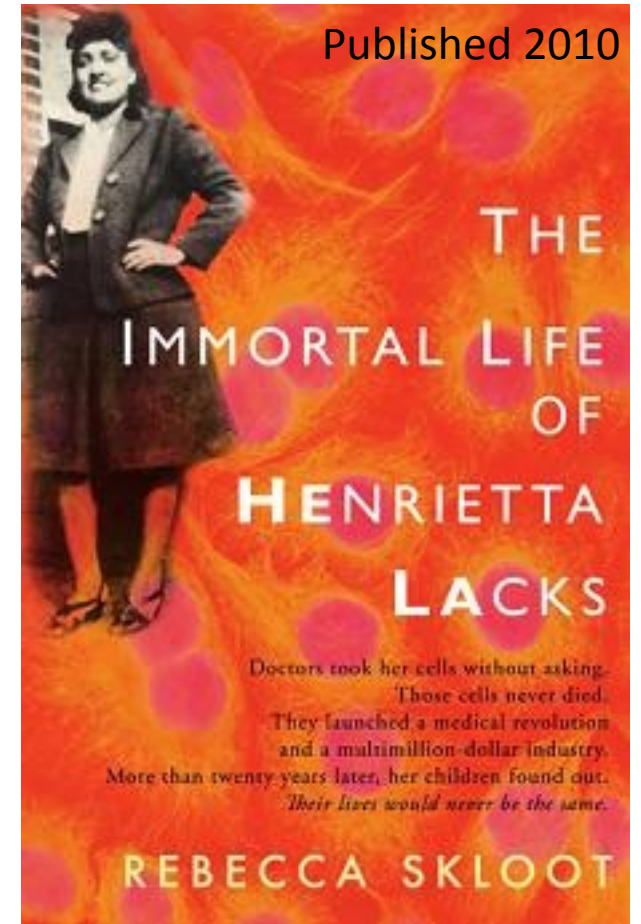
Increasing questions about the approach of allowing secondary research without consent

- High profile cases/examples bringing the issue to **public attention**
- Heightened **privacy concerns**
- More empirical data about **public expectations** and preferences



Henrietta Lacks

- Young African American woman received treatment for cervical cancer at Hopkins in the 1950s
- Cells collected from biopsy of her tumor cultured w/o her knowledge/permission (typical of the time)
- Additional cells may have been taken for research
- Generated a self-perpetuating cell line: HeLa
- Most valuable cell line in history, major breakthroughs in cancer research and therapy
 - She and her family received no \$\$\$/recognition
- Public controversy following bestselling book/movie
- [Hypothetically] how would the “old” rule apply?



Newborn Blood Spots

- Mandatory newborn screening for genetic disease
- Leftover blood spots used for research w/o consent [deidentified]
- State litigation by parents claiming illegal search and seizure, privacy considerations
- Settlements included destruction of existing samples following testing, addition of opt-out rights
- Newborn Screening Saves Lives Act



Havasupai Tribe

- 1990 diabetes study – researchers collected blood samples from tribe members
- Talks with tribe leaders focused on diabetes
- Consent forms described research generally on causes of behavioral and medical disorders
- Researchers used specimens in studies unrelated to diabetes and shared them with other researchers
 - Schizophrenia, In-breeding, Ancestry/origin
 - Group identification of tribe
- Lawsuit – unconsented research (ASU settled for \$\$\$ and returned specimens)



Reidentification risks

It is increasingly possible to **reidentify deidentified information** using publicly available resources

- Since biospecimens contain genetic information, it may not be possible to completely deidentify
- Deidentified data (including data derived from specimens) can be combined with other publicly available data (even non-genome data) to reidentify individuals
- Might also be able to use summary statistics about group data to detect an individual's presence in the group

Should solution be to restrict research or punish reidentification?

Reidentification risks

So far, reidentification of research data/specimens has only been for **demonstration purposes**, i.e., by experts with resources to show it is possible, not for nefarious use

- Reidentification possibility doesn't equate to **likelihood** – especially if research data and specimens are protected/controlled
- Reidentification doesn't necessarily equate to **harm** – that would require misuse

What do people want?

- Empirical studies involving more than 100K people around the world have examined views on future research use of stored specimens
- Overall, people “want to decide whether or not their biospecimens are used for research”
- But most people don’t care about specific details of future research, e.g., disease being studied, tech used, study target, or product
- After initial consent, most are willing to have samples used for research without further consent, except:
 - Research involving human cloning
 - Research involving indigenous peoples
 - Possibly commercial or for-profit research

Suggests ethical support for broad consent to future research, with exceptions

What do people want?

- But there's not universal agreement about this
- Other literature reviews suggest a desire for more control
 - “[D]onors want control over their own specimens and results, while being ensured privacy and confidentiality They either want to dictate up-front the specific types of research that can use their specimens, or they expect to be contacted and re-consented every time another study or researcher wants to use their samples.”

Rivera SM & Aungst H. What specimen donors want (and considerations that may sometimes matter more). In *Specimen Science: Ethics and Policy Implications*. MIT Press; 2017.

Suggests broad consent may not suffice to meet expectations – but given tradeoffs, autonomy interests are not necessarily determinative

What do people want?



- Data on public opinion is not always clear
 - **Specifics matter**, e.g.:
 - Is it ok to use your specimens for whatever purpose we want without asking you?
 - Is it ok to use your specimens without asking you if we promise to protect your privacy?
 - Would you still want to control how your specimens were used even if:
 - The risks to you were low?
 - An IRB will review specific uses?
 - Obtaining your consent would hinder scientific/medical progress?
- Caution that many members of the public have a poor understanding of medical research
- Public opinion matters, but it's **not the only thing that matters**

Notice of Proposed Rule Making

- Issued in 2015, after 2011 ANPRM – response to some of these concerns
 - More frequent research using data and specimen repositories
 - Research risks shifting from physical to informational
 - “[P]eople want to be asked for their permission”
- Aims:
 - Better protect subjects
 - Facilitate valuable research
 - Reduce burden, delay, ambiguity



NPRM – Human Subjects Definition

- NPRM: “Continuing to allow secondary research with biospecimens collected without consent for research places the publicly-funded research enterprise in an increasingly untenable position because it is **not consistent with the majority of the public’s wishes**, which reflect legitimate autonomy interests.”
- **Proposed revised definition of “human subject” to include all biospecimens**, even if not identifiable
- Opposition:
 - Lack of evidence of harm from status quo
 - Concerned about hindering important research
- Response: Regardless of risk, people want some control over how materials derived from them are used

NPRM – Human Subjects Definition

If biospecimens are all “human subjects,” then **all research with biospecimens would be subject to CR**

- Require IRB review + consent or consent waiver
- Propose to also eliminate exemption for specimen research recorded w/o identifiers



NPRM – Consent Waiver

- NPRM would **restrict consent waiver** by adding more conditions
 - Research could not practicably be conducted w/o identifiers (specimens + data)
 - For specimens, consent waiver only if:
 - **Compelling scientific reasons** for research use (not specified further)
 - Could that ever justify exploratory research?
 - Research could not be conducted with other biospecimens for which **consent was or could be obtained**
 - Impossibly high standard to be aware of all possible specimens
- Consent waiver intended to be **rare** for biospecimens

NPRM – Broad Consent

- Without consent waiver, could seek **specific consent** to each secondary research use of biospecimens (but hard/resource intensive)
- Or NPRM offered new exemptions: **broad consent + limited IRB review** for secondary research with biospecimens and identifiable data
 - Storage or maintenance of biospecimens/identifiable data for secondary research use if broad consent
 - Secondary research use of biospecimens/identifiable data stored with broad consent
 - Plus limited IRB review of consent process only + privacy safeguards (not typical exemption)
 - If individual results will be returned, cannot use exemption
- **Intended to make consent required for secondary research**, but not necessarily specific consent (**compromise**)

NPRM – Broad Consent

- What is **broad consent**?
 - Would be **offered when specimens/data collected** (e.g., in primary research or clinical care)
 - Would include some but not all elements of typical research consent
 - Would provide general information about possible future uses
 - Would describe the specimens/identifiable data covered
- Different from opt-out
 - Specimen/data sources would have to make an affirmative decision to allow future research
 - Consent waiver would not be permitted if individuals were asked and refused to provide broad consent

NPRM – Limited IRB Review

- **Limited IRB review**
 - IRB not applying usual approval standards (e.g., risk/benefits, etc.)
 - Look only at whether process for obtaining broad consent was appropriate
 - Make sure privacy standards are met (could be one time/institution-wide)
- Uniform privacy protection standards for all research with biospecimens and identifiable data
 - Would apply even to exempt research

NPRM – Data

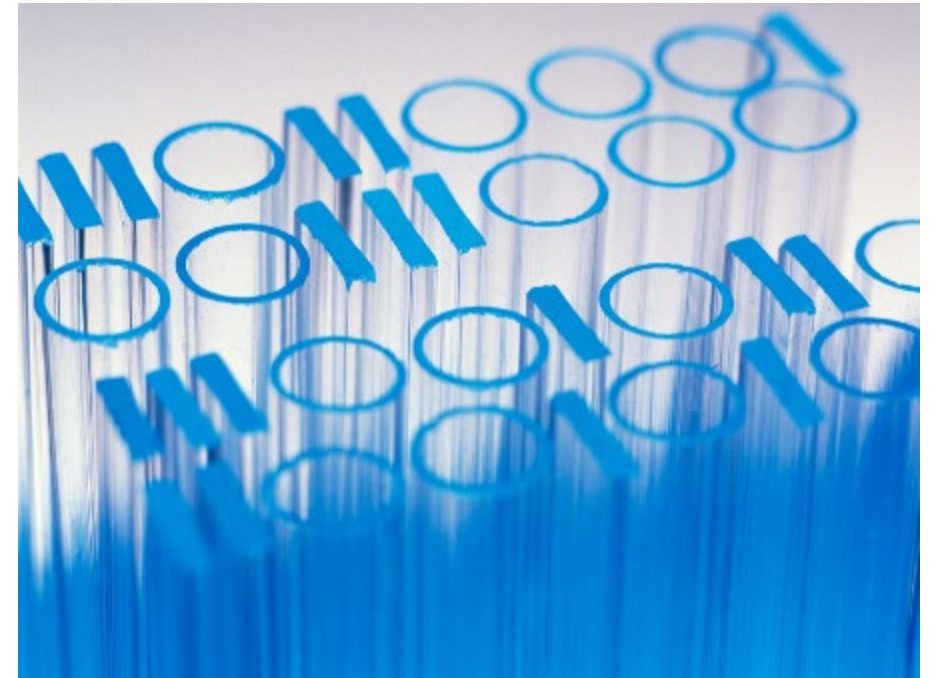
- **Would continue to treat deidentified data as not “human subject”**
- Would allow identifiable data to be excluded from CR if recorded w/o identifiers
- Would allow identifiable data from surveys and interviews to be exempt even if recorded with identifiers
- Would allow secondary research with identifiable data to be exempt (with conditions for notice and privacy protections)
- Would still be able to routinely get consent waiver



NPRM – Data

Why **biospecimen exceptionalism** when same issues arise for data?

- Risks associated with biospecimen research are from associated data
- Why treat full genome sequence differently from the biospecimen it was derived from?
- Privacy/confidentiality and autonomy issues all similar



NPRM – Upshot

- Research with biospecimens would be harder
 - Only effective option realistically would be broad consent (but concerns)
 - Deidentification wouldn't work
 - Specific consent likely too difficult
 - Consent waiver narrowed so much as to become unusable
- Research with data would be facilitated



NPRM – Concerns About Broad Consent

- Would require **foresight**
 - Seek broad consent when specimens/data are collected in clinical care or research to make sure to preserve capacity to be used in future research
- Would require **resources and infrastructure**
 - For securing consent and then tracking consent, refusals, and limitations
 - Extensive and seamless IT systems capacity for institutions/health systems
- Practically speaking, could only work in systems with fully interoperable med records systems

NPRM – Concerns About Broad Consent

- Likely to result in **fewer specimens available for research**
 - Not because of source objection but because of logistical difficulties
 - High priority for AMCs
 - Lower priority for doctor's offices, nursing homes, clinics, community hospitals that carry out less research and have fewer resources
 - Will broad consent be adopted abroad?
 - Result: skewed sets of samples
 - Might be less likely to cover international populations and poor/minority populations served by community hospitals
 - Could miss out on advancements

NPRM – Concerns About Broad Consent

- Can these potential downsides be justified simply because people might “want to be asked first”?
 - How should we balance autonomy and beneficence/justice?
 - Even if there are autonomy concerns, are they great enough to trump public interest? Free-riding concerns?
- And is this really what people want?



NPRM – Concerns About Broad Consent

Status quo may be preferable for protecting source interests

- IRB review + consent waiver permits IRBs to review every specific secondary use and assess source rights/welfare
- **Limited IRB review + broad consent – no one reviewing each specific use**
 - Might have given broad consent, but specific future study would contravene interests
 - Ex. Havasupai concerns would not be prevented by NPRM approach
- If broad consent allows lots of options, even harder to track
- Better to have IRBs review proposed project to determine if it would be **objectionable to or against the interests of study population**
 - Dignitary/group harms are legitimate concerns

NPRM – Concerns About Broad Consent

- Concern that broad consent will be **routinized/meaningless** (e.g., HIPAA forms at dr offices)
- Better to encourage other types of public education about the value of secondary research, low risk, etc.
 - Serve goal of avoiding surprise and promoting public trust



“Sign here to indicate you have no idea what you’ve signed.”

NPRM comments

- 2,186 received (not necessarily representative)
- Most comments received re: biospecimen provisions + broad consent
 - **Patients and research community opposed:** Concern about reducing availability of specimens for research, slowing medical advances, adversely affecting health – prohibitive logistics and cost
 - PCSBI opposed: deidentified specimen research poses no risk to subjects and is unlikely to impact their autonomy interests
 - SACHRP opposed: proposal won't improve autonomy
 - General public (not identifying as “patient”) divided: some in favor of autonomy/control, some wanted the proposal to go even further, others worried about medical advancement

Final Rule

- Published Jan. 19, 2017
- Effective Jan. 19, 2019 (with some exceptions)
- **Major changes from NPRM** based on public comments

Final Rule

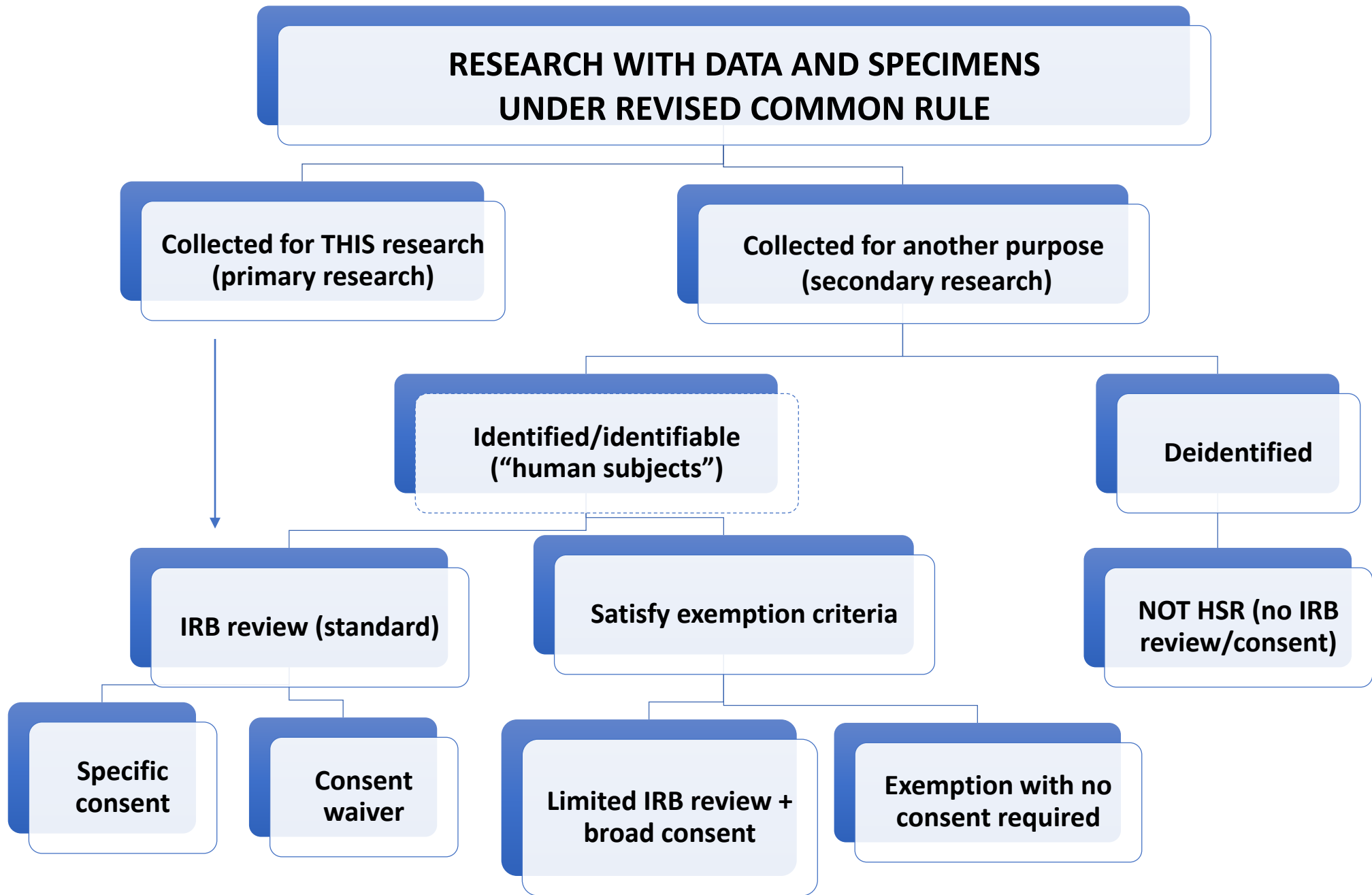
- “As explained in the NPRM, one of the core reasons for proposing that the rule be broadened to cover all biospecimens, regardless of identifiability, was based on the premise that continuing to allow secondary research with biospecimens collected without consent for research places the publicly funded research enterprise in an increasingly untenable position because it is not consistent with the majority of the public’s wishes, which reflect legitimate autonomy interests. **However, the public comments on this proposal raise sufficient questions about this premise such that we have determined that the proposal should not be adopted in this final rule.”**

Final Rule – Overview

- **Dropped proposal to make all biospecimens count as human subjects**
 - Retain status quo of identifiability as threshold for application of Common Rule to secondary research with data and specimens
 - **If deidentified, not human subjects research** – no IRB/consent
 - But now provide more information about secondary research uses of deidentified data and specimens as part of research consent
- Revert to treating biospecimens and data consistently
- Drop most restrictive new consent waiver criteria, so waiver remains a realistic possibility
- Adopt **new option of broad consent** + limited IRB review, but now truly optional in practice

Final Rule – Identifiability?

- Definition of identifiable continues to matter – BUT UNSTABLE
 - Regulation requires reexamination of meaning of “identifiable biospecimen” and “identifiable private information” w/i 1 year and every 4 years after to account for technological developments
 - May alter definition of identifiability via guidance
 - Similar process to assess whether there are new technologies/techniques that should be considered to generate identifiable data/specimens when applied to otherwise deidentified data/specimens (via notice and comment)
- More activities could be deemed identifiable later – closer to NPRM
 - Should we care about identifiability per se OR risk OR harm?



RESEARCH WITH DATA AND SPECIMENS UNDER REVISED COMMON RULE

“Old Broad Consent”

- Used for many years
- Informal/no regulatory recognition
- Seek consent when data/specimens collected
- Full IRB review at time of specific use – determine whether it constitutes adequate consent

consent

waiver

Limited IRB review +
broad consent

Exemption with no
consent required

- Broad consent obtained when data/specimens collected
- IRB reviews for privacy/confidentiality protection, checks that broad consent obtained and research is within scope
- Study plan does not include individual results return

Deidentified

NOT HSR (no IRB
review/consent)

RESEARCH WITH DATA AND SPECIMENS UNDER REVISED COMMON RULE

- Maintain all existing requirements
- Dropped criteria that would have made waiver “rare” for secondary research with specimens
- 2 new criteria for research with identifiable data and identifiable specimens:
 - Research cannot practicably be carried out w/o using identifiers
 - If asked for broad consent and refused, consent cannot be waived (technically could still deidentify or use for non-research purpose)

another purpose
(secondary research)

Deidentified

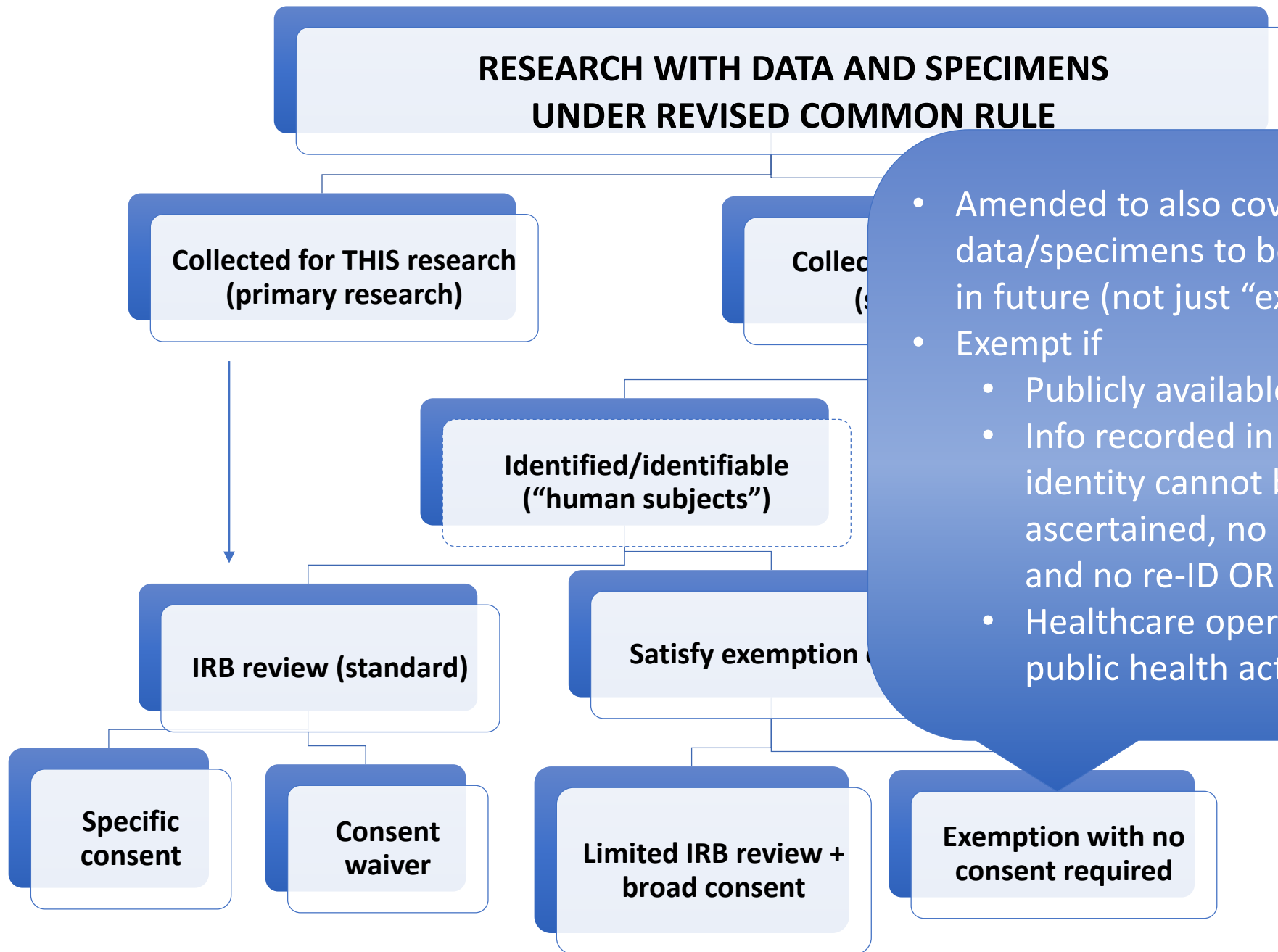
NOT HSR (no IRB
review/consent)

Specific
consent

Consent
waiver

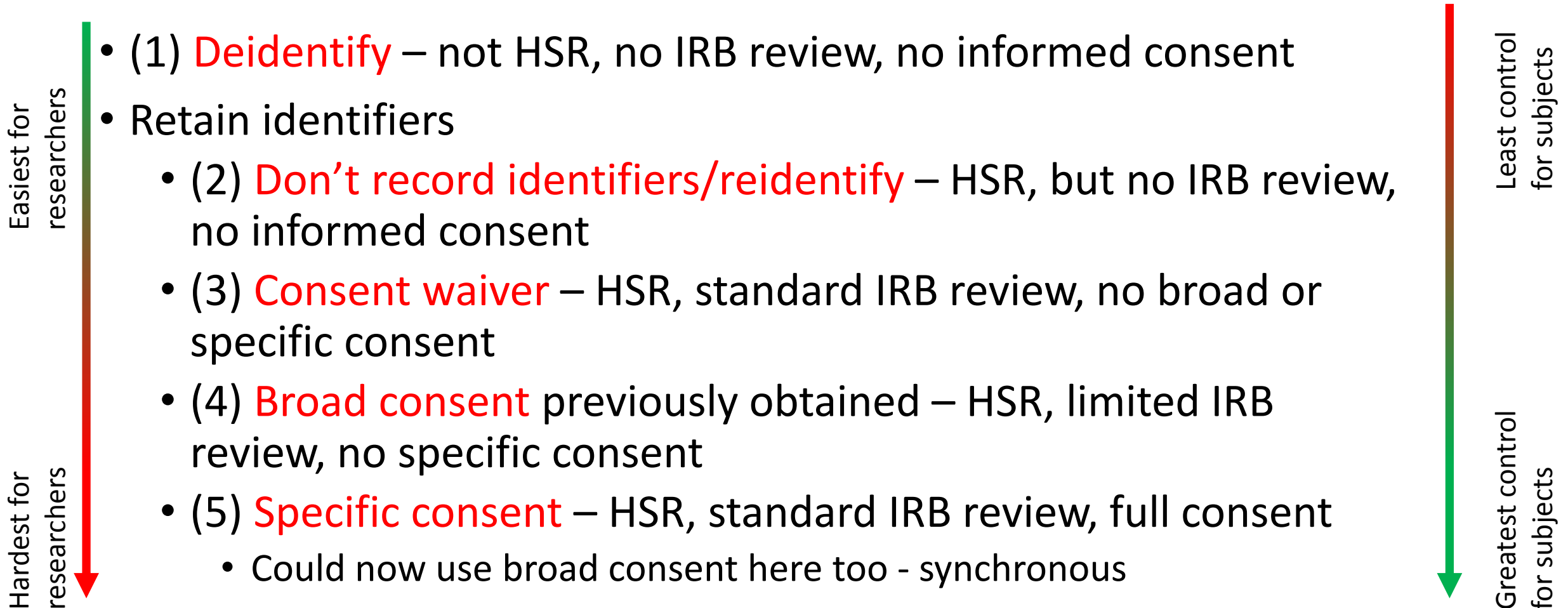
Limited IRB review +
broad consent

Exemption with no
consent required



- Amended to also cover data/specimens to be collected in future (not just “existing”)
- Exempt if
 - Publicly available OR
 - Info recorded in a way that identity cannot be ascertained, no recontact, and no re-ID OR
 - Healthcare operations or public health activity

Final Rule – Options for Secondary Research



Final Rule – Fate of Broad Consent?

Will **broad consent** exemption be utilized?

- Likely to be difficult in practice (all the same concerns as under NPRM)
- **Reasonable when included as an option** rather than de facto requirement
- If consent waiver and deidentification remain available under new rule, why would anyone use broad consent?
 - Respectful of autonomy
 - But big risk – if broad consent is offered and declined, lose opportunity to waive consent
 - Might scare people off if they didn't understand status quo
 - Cannot plan to return results (despite ethical obligations) – perhaps on ad hoc basis
- May be right back where we started...deidentified or consent waiver
- Most useful when need identifiers but ineligible for consent waiver

Final Rule – Fate of Broad Consent?

- Most useful for identified biorepository or databank study with purpose of collecting specimens/data for future research
 - Could obtain broad consent in study consent
 - Researchers can use exemptions later
- Could be useful for research studies in which researchers seek to integrate broad consent to facilitate future use
- **Very difficult to implement for specimens/data derived in clinical care**

Final Rule – Broad Consent Content

- Some standard elements (risks, benefits, confidentiality, voluntariness)
- Statement that biospecimens might be shared for **profit**, and if \$ will be shared
- Whether biospecimen research will or might include **WGS**
- General description of **types of research** that may be conducted
- General description of **types of identifiable data/specimens** that might be used
- Whether **sharing** of identifiable data/specimens might occur
- Types of **institutions or researchers**
- Period of **time** for storage/use (could be indefinite)
- Subject will **not be provided details** about specific future uses, and could include some things they would have chosen not to consent to
- **Results** will not be returned (unless they will be in all circumstances)
- Who to contact with **questions** or if harmed

Final Rule – Broad Consent, SACHRP Guidance

- Need to clarify **what counts as refusal** (given impact on eligibility for waiver)
 - Express refusal is easy
 - But what about silence/nonresponse?
 - Should NOT be treated as refusal (especially given how frequent it will be)
 - Should not be treated as broad consent
 - Should still allow waiver if conditions met
 - Need to explain consequences of saying yes, no, and nonresponse
- Need to clarify **who is bound by refusal**
 - Just those investigators, just that institution - or everyone?
 - Broad consent itself should specify intent of who is covered
- Need to clarify **if refusal precludes asking again**
 - People may change their mind
 - Should allow re-ask w/o harassing, even by same researchers/institutions

Final Rule – Broad Consent, SACHRP Guidance

- Need to clarify **consequences of withdrawal** of broad consent
 - Preamble: if broad consent is withdrawn, may continue future use if deidentified; but if broad consent promised withdrawal w/o further research, honor that promise
 - Broad consent should carefully specify consequences of withdrawal
 - Should clarify that withdrawal does not apply to data/specimens already used

Final Rule – Broad Consent, SACHRP Guidance

- Need to clarify **how to make description of future uses appropriate**
 - Could be very broad or somewhat narrow w/o being specific
 - Should make sure to include any potentially controversial areas of research or types of research for which specific consent is required by state laws
 - E.g., genetic research, HIV/STDs, mental health
- Not technically required by regs, but IRB should make sure research is **not inconsistent with prevailing community attitudes/shocking**
- Need to clarify **combination consent forms**
 - Broad consent for research should be separate from clinical consent to emphasize difference between research and clinical care
 - Broad consent should typically be separate from research consent to allow independent decision about each, unless future research essential to current research

Final Rule – Additional Changes

- People were surprised to learn what was happening with their specimens/data, so revisions to standard research consent
- **New research consent elements** – part of standard consent
 - **Identifiers might be removed** and info/specimens used/shared for future studies without new consent (OR research info/specimens will not be used/shared for future research, with or w/o identifiers)
 - Specimens may be used for **commercial profit** (and if subject will share profit)
 - Whether clinically relevant research results will be returned, and under what conditions
 - Whether research will or might include whole genome sequencing

Final Rule – Additional Changes

- **Doesn't cover ALL surprises re: use of clinical specimens/data:**
 - Would not have had research consent – so no notice of deidentified use
 - May not have had broad consent
 - Could still be deidentified and used (not HSR)
 - Could be used with identifiers under waiver of consent or exemption
- **Does improve info for people whose specimens/data are used:**
 - After being collected in research
 - After being collected with broad consent

Summary

- Some concern about status quo
- But worry about autonomy trumping public interest
- **Final Rule: compromise approach**
 - **New option (not de facto requirement) for broad consent**
 - **New disclosures**
- Still lots of ways to do research with specimens and data – but now subjects will be better informed, even if they lack total control
- Still many open questions
 - Will broad consent be useful/feasible?
 - Will subjects find Final Rule approach adequate?
 - How will identifiability be defined?

Discussion Questions

- How should secondary research consent be handled?
- How should we balance the relevant interests?
- Is broad consent truly protective of autonomy?