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Finding Flexibility in the  
Regulations – It's There if  
You Look

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**Areas for consideration within the regulations**

- Use of exemptions
- Use of expedited procedure
- Waiver of documentation of the consent process
- Waiver of parental permission
- Waiver of assent of children
- Consent disclosures
- Anonymous tissue specimens for *in-vitro* devices

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**Areas of consideration – assurance of compliance**

- Documentation of the consent process
- Reporting to regulatory agencies
- Research presenting no more than minimal risk and involving pregnant women
- Incidental incarceration after enrollment
- At least annual continuing review
- Categories of research eligible for review by the expedited procedure
- The 407 category

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## Rigidity

- Under utilization or unnecessary restrictions of exemptions
- Under utilization of the expedited procedure
- Not waiving documentation of the consent process
- Not waiving parental permission
- Not waiving assent of children
- Unnecessary consent disclosures
- Not limiting designation of anonymous tissue specimens for *in-vitro* devices as human subjects to circumstances when data will be submitted to the FDA

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## Under utilization or unnecessary restrictions on exemptions

- Some organizations do not grant exemptions
- Some organization add restrictions to the criteria
  - Involvement of vulnerable populations
  - Applicability of HIPAA
  - Recording of identifiers
  - Collection of identifiable data
  - Use of deception techniques
  - Video/audio taping

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## Sample ethical considerations for exempt research (Element I.3.E)

- Presents no more than minimal risk
- Equitable selection
- Consent process and disclosures
  - *May omit if no participant contact, or interferes with research and unreasonable*
- Documentation of consent process
  - *May omit unless a legal requirement*
- Privacy interests of participants protected
  - *May omit if no participant contact*
- Confidentiality of data maintained
  - *May omit if data are anonymous*
- Protections for vulnerable populations
  - *May omit if no vulnerable populations*
- Consent process
  - Sufficient opportunity to decide
  - No coercion or undue influence
  - Understandable language
  - No exculpatory language
- Consent disclosures
  - The study involves research
  - The purposes of the research
  - The expected duration
  - Procedures to be followed
  - Extent to which confidentiality will be maintained
  - Whom to contact to ask questions
  - Participation is voluntary

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### Under utilization of the expedited procedure

- Some organizations do not use the expedited procedures

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### Not waiving written documentation of the consent process

- An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all participants if it finds:
  - That the research presents no more than minimal risk of harm to participants; and
  - Involves no procedures for which written consent is normally required outside of the research context.

[45 CFR 46.117(c)(2), 21 CFR 56.109]

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### Waiver of written documentation of the consent process

- Research reviewed using the expedited procedure:
  - No more than minimal risk of harm and
  - Includes procedures in categories (1)-(7).
- Waiver of documentation criteria
  - No more than minimal risk of harm and
  - In almost all cases, written consent is normally not required when procedures in categories (1)-(7) are performed outside of the research context
- Therefore, consent documentation may be waived for almost all research approved using the expedited procedure.

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### Not waiving parental permission or assent of children

- May waive parental permission under the provisions for waiver contained in 45 CFR 46.116
- If the IRB determines that a protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (e.g., neglected or abused children), it may waive permission:
  - An appropriate mechanism for protecting the children who will participate as participants in the research is substituted
    - Depends on the nature and purpose of the research activities, the risk, potential benefit to research participants, their age, maturity, status, and condition.
  - The waive is not inconsistent with federal, state, or local law

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### Not waiving assent of children

- The IRB shall determine that adequate provision are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.
  - IRB shall take into account the ages, maturity, and psychological state of the children involved.
  - This judgment may be made for all the children involved in the protocol or for each child, as the IRB deems appropriate.
- IRB may determine that assent is not a necessary condition for proceeding with the research when:
  - The IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted
  - The IRB determines that the intervention procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.
- The IRB may waive the requirement for assent under provisions for waiver of consent contained in 45 CFR 46.

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### Unnecessary consent disclosures – those that are irrelevant to some types of research

- Any experimental procedures.
- Any reasonably foreseeable risks or discomforts.
- Any reasonably expected benefits to participants or others.
- A disclosure of appropriate alternatives, if any.
- The extent, if any, to which confidentiality will be maintained.
- For research involving more than minimal risk, ...
  - No requirement to disclose what is not part of the research, not a consequence of the research, or not related to the research.
  - If disclosure element includes "any" and there is nothing that falls into the disclosure category, may consider this element not to apply.

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### Not limiting designation of anonymous tissue specimens for *in-vitro* devices as human subjects to circumstances when data will be submitted to the FDA

- Only applies when data are submitted to the FDA.
- FDA defines a human subject to include individuals on whose specimens a device is used.
- FDA does not allow waiver of the consent process or DHHS Category #4 exemptions.
- Option
  - Follow “Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable.”  
<http://crpac.od.nih.gov/FinalFDAGuidanceonICforIVDDDeviceStudieswithLeftoverSpecimensthatAreNotIndividuallyIdentifiable.pdf>

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### Medical device research on anonymous tissue specimens

- The study involves an *in-vitro* diagnostic device investigation.
- The testing is noninvasive.
- The testing does not require an invasive sampling procedure that presents significant risk.
- The testing does not by design or reaction introduce energy into a participant.
- The device is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- One of the following is true:
  - For a product in the laboratory research phase of development, and not represented as an effective *in-vitro* diagnostic product, all labeling bears the statement, prominently placed: “For Research Use Only. Not for use in diagnostic procedures.”
  - For a product being shipped or delivered for product testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed: “For Investigational Use Only. The performance characteristics of this product have not been established.”
- The study uses one of more of the following leftover specimens:
  - Specimens collected for routine clinical care or analysis that would have been discarded
  - Specimens obtained from specimen repositories
  - Leftover specimens that were previously collected for other research purposes.
- The specimens are not individually identifiable as both of the following are true:
  - The identity of the participant is not known to the investigator or any other individuals associated with the investigation, including the sponsor
  - Neither the investigator nor any other individuals associated with the investigation, including the sponsor can readily ascertain the identity of the participant.
- One of the following is true:
  - The identity of the participant is not known to and may not readily be ascertained by the investigator or any other individuals associated with the investigation, including the sponsor.
  - If the specimen is coded, neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the participant from whom the specimen was collected, either directly or indirectly through coding systems.
- Either of the following are true:
  - The specimens are not accompanied by clinical information
  - Clinical information that accompanies the specimens does not make the specimen source identifiable to the investigator or any other individual associated with the investigation, including the sponsor.
- The individuals caring for the patients are different from those conducting the investigation and do not share information about the patient with those conducting the investigation.

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### Flexibility within the assurance of compliance process

- **Federal Policy for the Protection of Human Subjects** (Subpart A regulations of DHHS, Ed. DOE, DOD, NSF, or other agency that has adopted the federal policy (“Common Rule”), depending on the agency, this may include other subparts and regulations)
  - Meet the federal agency’s definition of “research.” (45 CFR 46.102(d) or equivalent)
  - Involve “human subjects” as defined by the federal agency. (45 CFR 46.102(f) or equivalent)
  - Are conducted, supported, or otherwise subject to regulation by a federal agency that has taken appropriate administrative action to make the policy applicable to such research. (“Common Rule Agency”) (45 CFR 46.101(a) or equivalent)
  - Not exempt. (45 CFR 46.101(b) or equivalent)
- If your organization engages in research that is conducted, supported, or otherwise subject to regulation by a federal agency that has adopted the federal policy, your organization must have a federalwide assurance.
- In your assurance you may decide whether to commit to:
  - Follow the regulations, including the subparts, for all research
  - Follow Subpart A for all research
  - Follow the regulations, including the subparts, for some research
  - Follow Subpart A for some research
- Note: FDA regulations might apply

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## Flexibility in assurance commitments

- If your organization engages in research that is conducted, supported, or otherwise subject to regulation by a federal agency that has adopted the federal policy, your organization must follow the applicable federal regulations.
- For other research:
  - If you commit in your assurance to follow the DHHS regulations for some or all research, then you have to follow the regulations to the extent of your commitment (Subparts A, B, C, or D);
  - If you do not commit to follow the DHHS regulations for some or all research, what are the options?
    - To follow the DHHS regulations and subparts without a formal commitment
    - OR
    - Apply equivalent protections
  - Next series of recommendations do not apply:
    - To research subject to DHHS regulations (or regulations of another federal agency)
    - To research subject to FDA regulations
    - If your assurance commits you to follow the DHHS regulations for all research involving human participants without qualification
  - There is a great deal of flexibility in how you may word the optional part 4(b) of your assurance.

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## Documentation of consent process

- Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the participant or the participant's legally authorized representative. A copy shall be given to the person signing the form. [45 CFR 46.117]
- Options when the research is not subject to the federal regulations and the organization has not elected to apply DHHS regulations to all research:
  - Video or audio taping
  - Documentation by a witness
  - Clicking "I agree" on a Web site
  - Providing a copy of the audio or video tape

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## Reporting to regulatory authorities

- Each organization [*shall have*] written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of any: [45 CFR 46.103(b)]
  - Unanticipated problems involving risks to participants or others
  - Serious or continuing noncompliance with [*the regulations*] or the requirements or determinations of the IRB.
  - Suspensions or terminations of IRB approval.
- Option when the research is not subject to the federal regulations and the organization has not elected to report the above items to regulatory authorities:
  - Report to:
    - IRB
    - Appropriate organizational officials

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## Research involving pregnant women

- [Unless exempt], this subpart [B] applies to all research involving pregnant women ... conducted or supported by DHHS. [45 CFR 46.201(a)]
- ...or if there is no such prospect of benefit, ... the purpose of the research is the development of important biomedical knowledge ... [45 CFR 46.204(b)]
- Options when the research is not subject to the federal regulations and the organization has not elected to apply DHHS Subpart B regulations to all research:
  - Follow Subpart B, but omit "biomedical."
  - Have no specific protections when the research does not target pregnant women and involves no more than minimal risk to pregnant women.

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## Incidental incarceration after enrollment

- The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects. [45 CFR 46.204(b)]
- Problem: A participant becomes incarcerated after enrollment and the research does not focus on prisoners or individuals at increased risk of incarceration.
- Options when the research is not subject to the federal regulations and the organization has not elected to apply DHHS Subpart C regulations to all research:
  - Follow Subpart C, but omit requirement for a prisoner representative.
  - Review administratively to determine whether participant is at unexpected increased risk of harm, and if so have convened IRB review as unanticipated problem involving risk to participants or others.
- Note: Watch for state law

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## At least annual continuing review

- An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year. [45 CFR 46.109(e)]
- Options when the research is not subject to the federal regulations and the organization has not elected to apply DHHS regulations to all research:
  - Allow the IRB to determine that continuing review can be conducted at intervals greater than annually.
  - Allow the IRB to determine that continuing review is not required unless a specific event occurs, such as until a certain enrollment has been reached, statistical significance has been met, or a phase has completed.
  - Allow the IRB to determine that continuing review is not required.

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### Categories of research eligible for review using the expedited procedure

- An IRB may use the expedited review procedure to review either or both of the following some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, [45 CFR 46.110(b)(1)]
- Options when the research is not subject to the federal regulations and the organization has not elected to apply DHHS regulations to all research:
  - Allow the use of the expedited procedure for all research involving no more than minimal risk, regardless of category and omit use of other applicability criteria.
  - Allow qualified IRB staff who are not IRB members to conduct review.

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### The 407 category

- DHHS will conduct or fund research that the IRB does not believe meets the requirements of 46.404, 46.405, or 46.406 only if ... the Secretary, after consultation with a panel of experts ... and following opportunity for public review and comment, has determined ... [45 CFR 46.407]
- Options when the research is not subject to the federal regulations and the organization has not elected to apply DHHS Subpart D regulations to all research:
  - Form your own expert panel to review the research.
  - Obtain consultation from an external IRB.
  - Develop additional criteria.

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