IRB 101

INTRODUCTION TO RESEARCH ETHICS, REGULATORY COMPLIANCE, AND NAVIGATING THE IRB

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2023 RSNA Clinical Trials Methodology Workshop

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FINANCIAL DISCLOSURES

NO DISCLOSURES

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LEARNING OBJECTIVES

- **Evaluate** the **human subjects research (HSR) regulations in** their **historical context**
- **Identify** applicable research **regulatory requirements**
- **Describe best practices** for **navigating** the IRB

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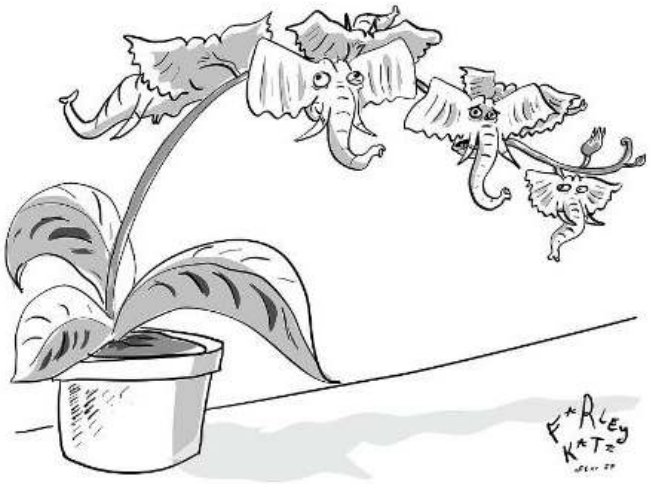
AGENDA

- Brief History of Research Ethics
- HSR Regulations and Key Definitions
- Understanding the IRB is Essential to Navigating the IRB
- Four Keys to IRB Success

I'M HERE TO HELP, GUILLERMO.

A BRIEF HISTORY OF RESEARCH ETHICS



"The scientists never stopped to ask if they should—only if they could."

HISTORY OF ABUSE IN RESEARCH

PRE 1930	1930 -1939	1940-1949	1950 - 1959	1960 - 1969
Marion Sims Gynecological Surgeries on Slave Women without Anesthesia 1840s	Tuskegee Study Begins 1932 Nazi Experiments 1933-1939	Radiation Experiments Begin 1944 Tuskegee Study Continues	Thalidomide Introduced Willowbrook State School Experiments begin 1956 Radiation Experiments Continue Tuskegee Study Continues	Jewish Chronic Disease Hospital Experiments Milgram Study 1963 Beecher NEJM 1966 Thalidomide use, Radiation Experiments, and Tuskegee Study Continue

EVOLUTION OF HUMAN SUBJECTS RESEARCH ETHICS AND REGULATIONS

1940 - 1959	1960 - 1969	1970 - 1979	1980 - 1999	2000 -
Nuremberg War Crimes Trials 1946	Declaration of Helsinki 1964	National Research Act 1974	HHS and FDA Revised Regulations 1981	21st Century Cures Act 2016
Nuremberg Report 1948	US PHS Requirements for IRBs and Informed Consent 1966	Belmont Report 1979	Common Rule Codified by 16 Federal Agencies as of 1991	Revised Common Rule 2018
				FDA Proposed Revisions re: Informed Consent, Continuing Review, sIRB 2022

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OBSERVATIONS ON HSR HISTORY

- Birth and evolution of HSR ethics, oversight, and regulation did not come about solely in response to Nazi War Crimes – research abuses span time and geography
- Modern HS research ethics and regulatory frameworks were made possibly by a unique moment in American political history
- HSR ethical and regulatory frameworks have evolved along opposite trajectories – as ethical frameworks simplified and condensed, regulatory requirements have grown in number and complexity

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HSR REGULATIONS AND KEY DEFINITIONS

HIERARCHY OF HSR POLICIES AND REGULATIONS

- Federal Law*
- State Law
- Grants and Contracts
- Institutional Policies and Procedures

FEDERAL LAW

COMMON RULE & FDA REGULATIONS

Common Rule

45 CFR 46

FDA Regulations

21 CFR 50

21 CFR 56

21 CFR 312

21 CFR 812

"Well, I was bitten by a radioactive lawyer and ended up with the power of attorney."

FEDERAL LAW

45 CFR 46

Subpart A – Research and IRB Requirements (the Common Rule)

Subpart B – Protections for Pregnant Women and Fetuses

Subpart C – Protections for Prisoners

Subpart D – Protections for Children

FEDERAL LAW

WHAT IS THE COMMON RULE?

The **Common Rule** is the Federal Policy for the Protection of Human Subjects, a 1981 statute and rule of ethics for biomedical and behavioral research in human subjects in the U.S. It is found at 45 CFR 46 (Subparts A, B, C, D). **16 agencies and departments** signed onto the original Federal Policy for the Protection of Human Subjects, including DHHS, DoD, DoE, EPA, which is why it is called the "Common Rule." A total of 20 agencies have or will sign the Revised Common Rule. The Common Rule applies to research funded by a federal Common Rule agency or department.

The Department of Health and Human Services (DHHS) issued revisions to the Common Rule which become effective January 21, 2019.

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FEDERAL LAW

HOW AND WHY WAS THE COMMON RULE REVISED?

Revisions to the Common Rule took effect in January 2019 and 2020. The revisions effective January 2019 were intended to **strengthen protections for human subjects**, to **modernize the rule, reduce burden on investigators and the IRB**, and to **make the rule more effective**. These revisions included changes to informed consent, the requirement for continuing review, and the types of studies eligible for an exemption. The single IRB mandate codified in the Revised Rule took effect in January 2020.

Research approved prior to the January 21, 2019 effective date is governed by the (old) Common Rule. Research approved on or after that date is governed by the Revised Common Rule. Institutions may choose to transition studies from the old rule to the Revised rule.

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WHAT DOES THE COMMON RULE ESTABLISH?

- What **research is subject to regulation under the Rule,** and what types of research are exempt from regulation by the Rule
- **Requirements regarding the make up and operation of the IRB,** required **IRB policies,** requirements for **IRB documentation**
- **General requirements for informed consent,** documentation of consent
- Cooperative Research – **requirements for sIRB**

WHAT AGENCIES OR DEPARTMENTS HAVE ADOPTED THE RCR?

Department of **Homeland Security**	**Housing and Urban Development**	Department of **Health and Human Services**
Department of **Agriculture**	Department of **Justice***	**National Science Foundation**
Department of **Energy**	Department of **Labor**	Department of **Transportation**
NASA	**Defense** Department	Office of the **Director of National Intelligence****
Commerce Department	Department of **Education**	**Central Intelligence** Agency**
Social Security Administration	**Veterans Affairs** Administration	**Consumer Product Safety** Commission
Agency for **International Development**	**Environmental Protection** Agency	

* DOJ intends to adopt the RCR
** Required to follow RCR by Executive Order

FEDERAL LAW

KEY DEFINITIONS

- **Research**: a **systematic investigation,** including research development, testing, and evaluation, **designed to develop or contribute to generalizable knowledge** (45 CFR 46.102(l)).
  - **Scholarly activities, public health surveillance** activities, **information** or **biospecimens collected for use by a criminal justice agency,** and "**authorized operational activities… in support of intelligence, homeland security, defense, or other national security missions**" are excluded from the definition of research in the Revised Common Rule.

KEY DEFINITIONS

WHAT IS A CLINICAL TRIAL OR INVESTIGATION?

NIH & COMMON RULE

A research study in **which one or more human subjects** are **prospectively assigned to one or more interventions** (which may include placebo or other control) **to evaluate the effects of those interventions** on health-related biomedical or behavioral outcomes.

FDA

An experiment that **involves a test article and one or more human subjects** and that either is subject to requirements for prior submission to the Food and Drug Administration under [applicable portions of the FFDCA], **or is not** subject to requirements for prior submission to the FDA under [these sections] of the act, **but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.**

KEY DEFINITIONS

WHO IS A HUMAN SUBJECT IN RESEARCH?

COMMON RULE

A **living individual about whom an investigator** conducting research (45 CFR 46.102(e)(1)):

- (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.**

FDA

- An **individual who is or becomes a participant** in research**, either as a recipient of the test article or as a control.** A subject may be either a healthy human or a patient (21 CFR 50.3(g)).
- A human who participates in an investigation, either as an **individual on whom or on whose specimen an investigational device is used or as a control.** (21 CF 812.3(p)).

FEDERAL LAW

KEY DEFINITIONS

- **Minimal Risk**: the **probability and magnitude of harm or discomfort anticipated** in the research **are not greater** in and of themselves **than those ordinarily encountered in daily life or during** the performance of **routine physical or psychological examinations** or tests (45 CFR 46.102(j)).

FEDERAL LAW

KEY DEFINITIONS: MORE ON MINIMAL RISK

MINIMAL RISK PROCEDURES	GREATER THAN MINIMAL RISK
Collection of data through non-invasive means (NOT requiring general anesthesia or sedation) routinely employed in clinical practice, including MRI (3 Tesla or under), ECG, or ultrasound	MRI requiring sedation or contrast X-Rays DEXA scans
Research using biospecimens previously collected or that will be collected for purposes of standard of care	Extra biopsies when other biopsies are already being taken for standard diagnostics; Punch biopsies
Collection of blood by venipuncture from healthy adults and children (subject to additional requirements)	Collection of blood from an indwelling catheter, regardless of the reason for the placement of the catheter*
Collection of data from voice, video, digital, or images made for research purposes	Research in which the identification of subjects or their responses would reasonably place subjects at risk of civil, criminal, or reputational harm

FEDERAL LAW

HOW DO I KNOW WHAT REGULATIONS APPLY TO MY RESEARCH?

- **Common Rule (Pre-2018 Rule):** Governs studies approved before **1/21/19** that are subject to the Common Rule (generally federally funded) and have not been transitioned to the revised Common Rule.
- **Revised Common Rule (2018 Rule):** Governs studies approved on or after **1/21/19** that are subject to the Common Rule; Department of Justice has not signed on.
- **FDA:** Governs clinical investigations of products subject to regulation by FDA; FDA has yet not aligned with the revised Common Rule, however as of September 2022, FDA has proposed two rule changes to further and enhance harmonization
- **Federally Funded Research that is also FDA-regulated:** Must comply with the consent requirements under the Revised Common Rule but cannot otherwise apply the Revised Common Rule (e.g., continuing review is required even if eligible for no continuing review under the Revised Common Rule). FDA in guidance has stated that they new consent requirements under the revised Common Rule do not conflict with FDA regulations.

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FEDERAL LAW

ADDITIONAL SOURCES OF FEDERAL LAW IN HSR

- **HIPAA:** Depending on your role and the status of your institution, HIPAA may apply to your use of protected health information (PHI) in research.
  - NOTE: **Per exempt category 4(iii), [when] research involves only information collection and analysis involving the investigator's use of identifiable health information** when that use is **regulated under 45 CFR parts 160 and 164**, subparts A and E, **for** the **purposes of** "health care operations" or "**research**" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b), **that research is secondary research for which consent is not required**. These are your medical chart review studies.
- **21st Century Cures Act:** Signed into law on December 13, 2016, Cures is **intended to "accelerate medical product development… and enhance [FDA's] ability to modernize clinical trial designs** (including the use of real-world evidence)." Cures also **requires FDA, to the extent possible, to harmonize its regulations with the provisions of the Revised Common Rule**. On September 28, 2022, FDA made available for comment two proposed revisions to the FDA regulations governing HSR. The proposed revisions include adopting the informed consent, continuing review, and sIRB requirements adopted in the Revised Rule.

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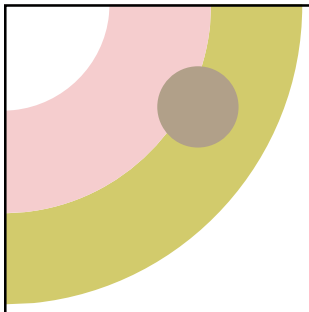

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UNDERSTANDING THE IRB IS KEY TO NAVIGATING THE IRB

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WHAT IS THE NATURE OF THE I.R.BEAST?

- IRBeast acts as a surrogate for federal regulators
- HSR regulations cannot be easily separated from the legacy of abuse from which they emerged. In promulgating the HSR regulations, Congress chose to view risks and responsibilities through a wider lens than it has historically used to assess their clinical counterparts.
  - Our obligation to mitigate risks to another individual depends on the nature and scope of our obligation to that individual
  - Modern HSR regulations establish a broader scope of obligation in research than in the care setting
- Particularly in the context of FDA regulations – but also to some extent with the Common Rule – HSR protections were retrofitted into a regulatory framework designed for consumer protections
  - Both the Common Rule/Revised Common Rule and FDA were promulgated pursuant to the Commerce Clause
  - Common Rule applies only when the research is funded by a Common Rule agency. FDA regulations apply to all clinical investigations of FDA-regulated products, regardless of the source of funding.
- The IRBeast operates in a highly regulated environment, subject to inconsistent definitions, outdated regulations with varying applicability, and conflicting legal/ethical imperatives

WHAT WORK DOES THE IRB REVIEW?

Federal-Wide Assurance required for federally funded research

In general, academic medical center IRBs will review:

- research conducted by their faculty/senior staff
- research conducted on medical center premises
- research conducted with federal grant money

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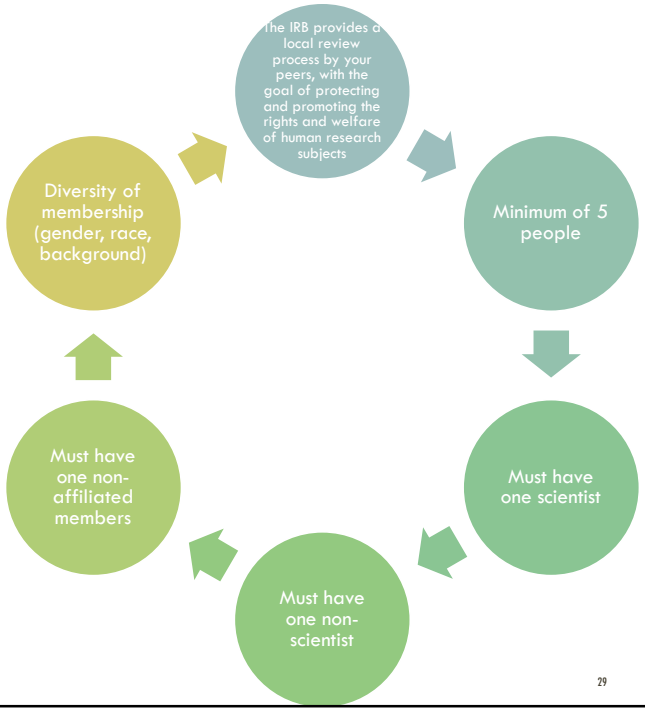
HOW MUST THE IRB BE CONSTITUTED?



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WHAT ARE THE TYPES OF IRB REVIEW?

Convened review (full committee): more than minimal risk; IRB must have a quorum of members to vote

Expedited review (single member): minimal risk (federal definition); review by Chairperson or designated IRB member

Exempt from the federal regulations: 4 exemptions require Limited IRB review

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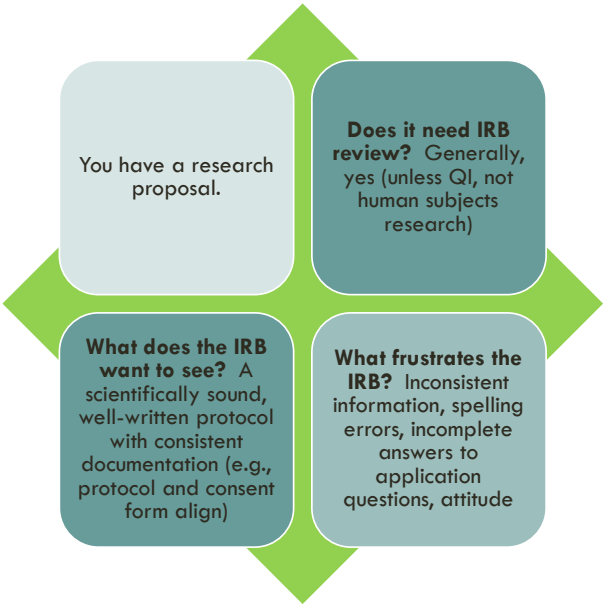
NAVIGATING THE IRB



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WHAT SHOULD BE INCLUDED IN YOUR PROTOCOL?

- Background and significance (including animal studies)
- Study hypotheses and objectives
- Overall study design
- Study procedures
- Subject selection (inclusion and exclusion)
- Recruitment process
- Consent process
- Risks and benefits
- Privacy and confidentiality of information
- Data collection and management
- Statistical analysis
- Data safety monitoring

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STUDY PROCEDURES

- In your protocol (and in your mind), differentiate between routine clinical care and research procedures.
- **Remember that you may make changes in clinical care without outside approval, but you must have IRB approval before changing your research procedures.** It doesn't matter if it is a minimal change to your research (e.g., extra blood draw, adding 5 minutes to a scan) or a significant change (using an investigational drug or device), if it is research, you must first submit a protocol amendment to the IRB.
- **In your protocol, also consider and describe:** stopping rules; what happens when the research ends; whether and how study results will be provided to participants; special issues such as genetics; whether primary physician may be contacted with results; future use of specimens; sharing of specimens.

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RISKS AND BENEFITS

Risks

- Describe research risks (not risks of clinical care)
- If possible, quantify the risks (one in twenty, small, often); describe in lay language
- Minimize study risks to the extent possible (screening, exclusion, medical monitor/DSMB)
- Remember associated risks (withdrawal from clinical medications, additional time under anesthesia, loss of confidentiality)

Benefits

- There is no benefit
- You may not benefit
- Do not include payments, psychological benefit of participating in research

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RADIOLOGY ISSUES

If "imaging" is included in the protocol:

- What is the purpose of the imaging?
- Is it research or standard of care?
- What is the imaging technique?
  - will contrast be used (include risks in the consent form)
  - is it experimental or FDA cleared
  - what is the dose of the exposure
  - where will it be done
- If images are clinical quality, how will incidental findings be handled?

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RECRUITMENT

Per Guidance, recruitment is the beginning of the consent process

How will you identify participants?

- Medical record review; former participants who agreed to be contacted for future research; referrals from other physicians; response to ads?

Who will contact participants and how, when and where will they be contacted?

- If participants have been identified through medical record review, contact should be from someone with a reason to know that information
- If participants are recruited in a waiting room or other public area, should have a process to allow them to provide information in a private area

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RECRUITMENT CONTINUED

- **Institutional policies differ** on who may contact and how contact is made (e.g., letter, cold call).
- Some Institutions have a **"front door" process**, asking everyone seeking clinical care if they may be contacted for future research.
- **Become familiar with your local policies** on recruitment and contact the IRB if you have questions.
- **Framework**: Would this person be surprised/concerned that you knew about their medical condition and were calling them?
- **For the IRB**: provide a detailed description of your recruitment process (who will contact; how, when and where participants will be contacted).

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CONSENT PROCESS

- **Consent is an on-going process** during the course of the research.
- **In order to be valid, consent must be**
  - **Informed**: The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information
  - **Voluntary and Free of Coercion**: provided "under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence"
- **Consent is required for research procedures, not standard of care**

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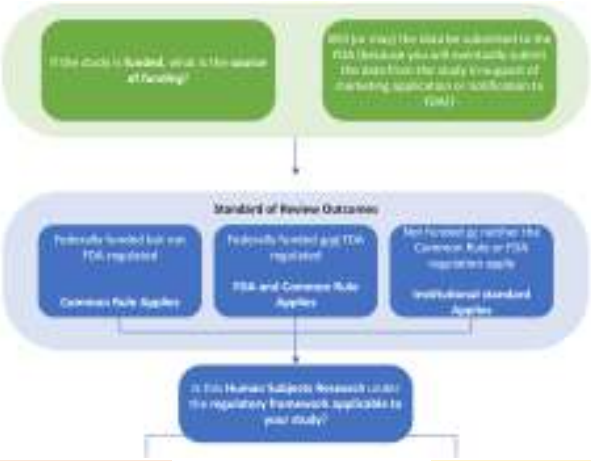
CKL2

DO I NEED TO OBTAIN INFORMED CONSENT?



Common Rule (and not FDA Regulated) or Unfunded/Funded but not by a Common Rule Agency

FDA Regulated or FDA Regulation and Common Rule

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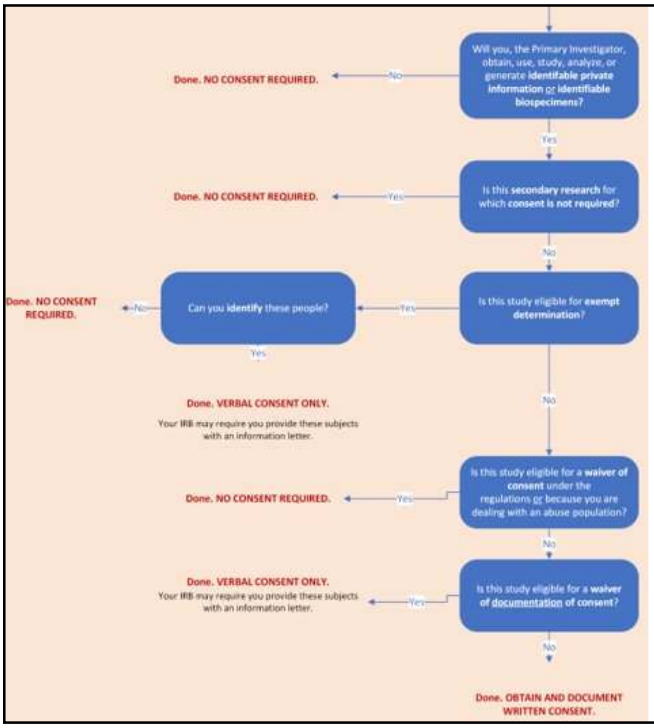

Analysis Under the RCR

Secondary Research for which Consent is Not Required:
Uses of identifiable private information or identifiable biospecimens, if at least one applies:
(i) The identifiable private information or identifiable biospecimens are publicly available;
(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under HIPAA for the purposes of "health care operations" or "research"

Research Eligible for an Exemption

1. Research in commonly accepted education settings meeting certain criteria
2. Research involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior if:
    1. Information is recorded by the investigator so that the identity of the subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    2. Disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects
    3. Information is recorded by the investigator so that the identity of the human subjects can readily be ascertained, and IRB conducts a limited review for privacy and confidentiality
3. Benign behavioral interventions meeting certain criteria
4. Research using or storing information in a repository meeting certain criteria

Consent Waiver
(i) Research is no more than minimal risk to the subjects;
(ii) Research could not practicably be carried out without the requested waiver or alteration;
(iii) If the research involves using identifiable private information/biospecimens, the research could not practicably be carried out without using the identifiable information/biospecimens
(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
(v) When appropriate, the subjects will be provided with additional information after participation.

Waiver of Documentation of Consent
(i) The only record linking the subject and the research would be the consent form and the principal risk would be potential harm resulting from a breach of confidentiality.
(ii) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

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Slide 39

CKL0 Will (or may) the data be submitted to the FDA...
Cooper, Kindra L., 2023-01-10T20:32:24.640

CKL1 In the blue boxes, can we remove the parentheses and keep the standard language in bold as the bottom line in each box?

Federally Funded but not FDA regulated
Common Rule Applies

FDA regulated OR Federally Funded AND FDA regulated
FDA and Common Rule Apply

Not Funded or Neither the Common Rule or FDA regulations apply
Institutional Standard Apply
Cooper, Kindra L., 2023-01-10T20:39:08.835

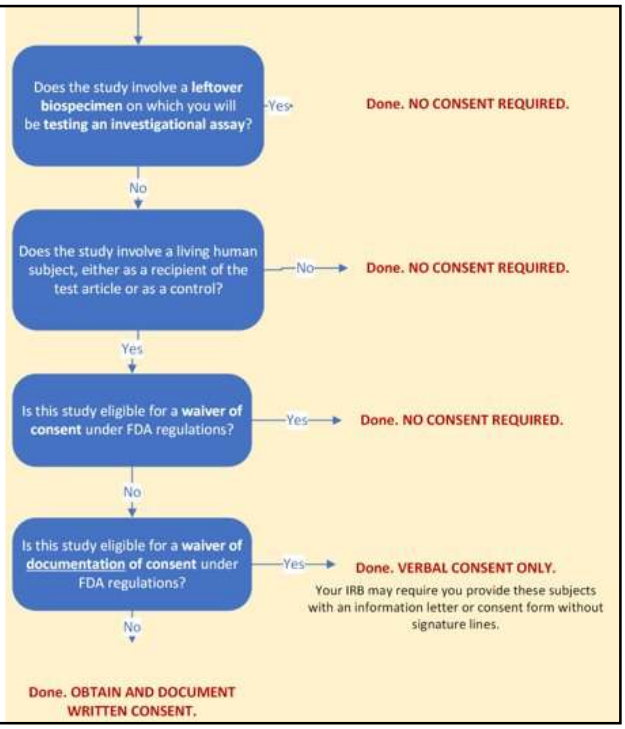
CKL2 Can we have the text in the pink and yellow boxes center aligned?
Cooper, Kindra L., 2023-01-10T20:39:41.123

Leftover Specimens:
FDA regulations do not speak to identifiability. Leftover specimens are human subjects. FDA has waived the requirement for informed consent for use of these specimens in companion diagnostic assay development.

In order for research to meet the definition of **human subjects research under the FDA regulations,** study must involve a live human (or leftover human tissue) and an FDA regulated drug, device, biologic, food, cosmetic, etc… If an investigator is testing an FDA regulated product without the use of human subjects, your study will be governed by other applicable FDA regs – not Parts 50 (informed consent) and 56 (Institutional Review Boards).

Waiver of Consent
(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.
(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
(3) Time is not sufficient to obtain consent from the subject's legal representative.
(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

Waiver of Documentation of Consent
(1) The IRB may, for some or all subjects, waive documentation of consent if the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or
(2) The research meets the definition of emergency research



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ELEMENTS OF CONSENT

There are 9 basic elements of informed consent and 9 additional elements (as applicable) Your Institution is likely to have a consent form template that must be used and includes regulatory requirements. The 9 basic elements of consent include:

(1) **A statement that the study involves research,** an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;

(2) A **description of any reasonably foreseeable risks or discomforts** to the subject;

(3) A **description of any benefits to the subject** or to others that may reasonably be expected from the research;

(4) A **disclosure of appropriate alternative procedures or courses of treatment,** if any, that might be advantageous to the subject;

(5) A **statement describing** the extent, if any, to which **confidentiality of records identifying the subjec**t will be maintained;

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CONSENT CONTINUED

(6) For research involving **more than minimal risk**, an **explanation as to whether any compensation and an explanation as to whether any medical treatments are available** if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of **whom to contact for answers to pertinent questions about the research and research subjects'** rights, and whom to contact in the event of a research-related injury to the subject;

(8) A statement that **participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time** without penalty or loss of benefits to which the subject is otherwise entitled; and

(9) **One of the following statements about** any research that involves the collection of **identifiable private information or identifiable biospecimens:**

- (i) 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; or
- (ii) 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.

DOCUMENTATION OF CONSENT

- Depending on the nature of the study, **documentation of consent may be provided in writing or verbally** (aka waiver of documentation of consent). **Waiver of documentation of consent is not the same was or waiver of consent.** The requirements for waiver are defined in the federal regulations.
- Consent documents (and recruitment materials) may not include handwritten changes or cross outs. **All changes must be prospectively reviewed and approved by the IRB.**
- **Consent language must be written "in language understandable to the subject"** (or the legally authorized representative.

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SAMPLE RADIATION RISK LANGUAGE

This research study includes exposure to radiation from x-rays or gamma-rays. This radiation exposure is for research purposes only and is not part of your medical care. The radiation exposure that you will get in this research study is ___ rem (a rem is a unit of absorbed radiation). This is less than the 0.3 rem that the average person in the U.S. gets each year from natural sources like the sun, air, food and soil. The radiation exposure described here is what you will get from the research study only. It does not include any exposure that you may have received or will receive from medical tests outside the study that are part of your medical care. Scientists disagree on whether radiation at these low levels is harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life. If you have questions about the total amount of radiation you will be receiving, you should ask your doctor.

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CONSENT LANGUAGE RE: RETURN OF RESULTS

The [type of imaging] you are having as part of this research study will be review by a qualified person just as it would if you were having the procedure done as part of your routine medical care. There is a possibility that we may see an abnormality that we did not expect to see in this study. This is called an "incidental finding". We will let you know if we see such an incidental findings. (Describe how subject will be contacted). If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

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YOU'VE SUBMITTED. NOW WHAT?

1. The application is received and recorded at the IRB office.
2. The application is assigned for staff review (prior to IRB review):
   - Usually there is an administrative and/or regulatory review by IRB staff prior to IRB review
   - The application may be returned to the research team for changes or if more information is needed prior to the IRB review

WHAT DOES THE IRB LOOK FOR?

RESEARCH TEAM QUALIFICATIONS AND TRAINING

COMPLETE APPLICATION

CLEAR PROTOCOL (DESCRIBING RESEARCH PROCEDURES AND SCHEDULE)

CONSENT FORM THAT MATCHES THE PROTOCOL

DRUG INFORMATION (INVESTIGATORS BROCHURE; PACKAGE INSERT)

DEVICE SPECIFICATIONS

LOCAL IRB APPROVAL FROM OTHER COUNTRIES (IF REQUIRED)

DEPARTMENTAL OR SCIENTIFIC REVIEW

PRE REVIEW REGULATORY CRITERIA

- Federal, state and local regulatory issues
- Institutional policy concerns
- Vulnerable population protections
- Conflict of interest issues
- Are ancillary reviews required?

Do you need to contact the ancillary committees directly or will your IRB manage these reviews?

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IRB REVIEW PROCESS

- Application is assigned to one member as the primary reviewer (may also have secondary reviewer)
- Application is listed on the IRB convened meeting agenda
- Agenda materials are provided to all IRB members prior to the meeting
- Primary reviewer should contact the researcher prior to the meeting with any questions
- Consider inviting the researcher to the meeting if there are many questions

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CRITERIA FOR IRB APPROVAL

- Risks are minimized
- Risks are reasonable when compared to benefits
- Selection of subjects is fair
- Informed consent (elements, documentation)
- When appropriate, data monitoring
- When appropriate, privacy and confidentiality are protected
- Additional safeguards for vulnerable populations

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REVIEW AT A CONVENED MEETING

- A quorum of members is required
- The IRB Chair should confirm whether any IRB members have a conflict of interest on any studies being reviewed
- Primary reviewer presents the study
- Study is discussed by all members
- Action is taken by a majority of the members: approve; approve with conditions; table/defer; disapprove
- Vote is recorded, with outstanding questions/concerns

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RESPONSES TO IRB CONCERNS

- An **outcome letter** will be sent to the principal investigator following the IRB meeting
- **Assume the IRB has reviewed your application and tabled it for further information.** In your response:
  - **Answer each query clearly** and **concisely**
  - **If you disagree** with an issue raised by the IRB, **respond thoughtfully and conservatively**

STUDY DISAPPROVAL

Reasons for disapproval:

- The IRB determines the **research design is not scientifically sound,** or the **risks outweigh the benefits,** or other significant concerns
- **Researcher can't provide satisfactory answers to** the **IRB's concerns**
- The **institution does not allow this type of research** (e.g., fetal research, drug abuse research using illegal drugs)
- **Researchers have the right to appeal** the disapproval and revise the application

POST APPROVAL: CONTINUING REVIEW

On-going IRB oversight:

- Annual review of research is required for FDA-regulated research and research conducted under the Old Common Rule
- For research conducted under the Revised Common Rule, continuing review is not required for research eligible for expedited review, research that has completed all interventions and is now in data analysis (with identifiable or deidentified data), research that has completed all interventions and now is limited to accessing follow-up clinical data
- Annual continuing review reports allow the IRB to monitor the on-going conduct of the study (include information on enrollment, deviations, problems, withdrawals, data safety monitoring)
- At the time of continuing review, the IRB determines whether the study may continue, changes are required, or should be stopped

POST APPROVAL: AMENDMENTS

Any changes to the research must be submitted to the IRB and approved prior to making the change, including:

- Protocol changes
- Consent form changes
- Changes in sample size
- Changes to the drug or device

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POST APPROVAL: UNANTICIPATED PROBLEMS

All **unanticipated problems involving risks to participants** should be reported to the IRB promptly (the IRB may have a specific time frame for reporting)

- Unanticipated given the nature of the study or occurring at a rate unanticipated by the protocol
- Related or possibly related to study participation
- Places the subjects or others at an increased risk of harm

Any **related deaths must be reported to the IRB promptly** – typically within 24-48 hours of the PI becoming aware of the death. Check your institutional policy.

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CLINICAL TRIALS REGISTRATION

- Clinical trials must be registered at a clinical trials registry that is electronically searchable and accessible to the public – in the U.S., clinicaltrials.gov has become the central registry.
- Check with your Institution to see who is responsible for registration.
- Definition: Any research study that prospectively assigns human participants to one or more health related interventions to evaluate effects on health outcomes.
- Most drug and biologic trials must be registered.
- Device trials with health outcomes must be registered.
- Both civil penalties and barriers on publication for trials not registered.
- Must register 21 days after first participant enrolled.
- Must update annually.
- Study results generally must be submitted within 12 months of Primary Completion Date; see definition at clinicaltrials.gov.

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WHAT DOES THIS MEAN FOR YOUR RESEARCH? FOUR KEYS TO IRB SUCCESS

UNDERSTANDING IRB VOCABULARY AND STANDARD OF REVIEW ARE KEY TO EARLY SUCCESS

- **Words and phrases codified in law have precise legal meanings**. Common vocabulary pitfalls: "low risk" v. "minimal risk," "exempt" or "exemption," "minimal risk" v. "nonsignificant risk." When in doubt, consult guidance at ORHP.gov and FDA.gov.
- **Standard of Review (SOR) determines which regulatory framework(s) apply to your research and the process of for IRB review.** SOR depends on five things:
  - **Source of funding**: Funding from a Common Rule Agency? Common Rule applies
  - **Data destination**: Will your data (now or later) be subject or provided to FDA? FDA regulations applies
  - **Degree of risk**: Minimal Risk or Greater than Minimal Risk? Review method will drive turn around time (TAT).
  - **Institutional Policies**: If neither the Common Rule nor the FDA regulations strictly apply to your research, what SOR has your institution adopted to govern non-Common Rule, non-FDA regulated research.

BE SENSITIVE TO SOURCES OF UNINTENDED RISK

The regulations require the IRB to assess risks of multiple harms – not just risks of clinical or medical harm

- Social or reputational harm, including risks of stigma and job loss
- Civil harms
- Criminal harms
- Risks to confidentiality and privacy

Language used to describe risks to subjects must be described in lay terms

REMEMBER, SCIENCE EVOLVES FASTER THAN LAW

- **2019/2020 updates to the Common Rule and planned future revisions to FDA regulations** are aimed at enhanced human subjects protections, modernization of the operational aspects of the regulations, and burden reduction. They do not address gaps in existing law governing drugs and devices, nor do they necessarily address evolving technology. When it comes to regulation of novel therapies, devices, or techniques, the IRB is forced to rely on guidance from regulators. Guidance documents necessarily lag behind the creation of the therapies, devices, or techniques to which they apply.
- If your **study design is based on an esoteric guidance document, site to that guidance** document in the IRB protocol.

PROTOCOL RISK AND INSTITUTIONAL SIZE HAVE IMPLICATIONS FOR IRB REVIEW

- **Greater than minimal risk research will pass through multiple hands** and receive review from **more than one specialty. Minimal risk research** will likely be **reviewed by a single reviewer,** who may or may not be a scientist.
- **Expansion of available exemptions** means **more research is available for review by a non-IRB member.**
- **When you don't know what you don't know, the unfamiliar is scary.** As a researcher, you may need to assume the role of educator with the IRB. You may also find yourself on an unfamiliar side of the autonomy/beneficence tug of war.

KEY TAKE AWAYS

✓Always keep your human subjects in the forefront of your thinking about your research

✓Get to know your IRB – its staff, procedures, requirements, standard of review

✓Remember the nature of the IRBeast – the IRB works in a highly regulated environment and that will control or influence many (perhaps most) of their decisions

✓ Do your homework before submitting to the IRB – have your protocol, consent form and related documents in good shape before asking the IRB to review them

✓ Understanding SOR and IRB vocabulary will set you up for early success, more rapid approvals.


THANK YOU