IRB Member Regulatory Training
What studies must follow FDA regulations?

All studies must follow HHS regulations, but some must also follow FDA regulations.

Clinical Investigations of a test article (studying safety and effectiveness) require FDA regulations to be followed.
- IND – Investigational New Drug
- IDE – Investigational Device Exemption

Use the Flow Chart to determine Exempt or Non-Exempt

- Exempt: Meets the criteria for exemption – Not required to follow 21 CFR 312 (Drugs) or 21CFR 812 (Biologics) – Exempt from subset of regulations, still follow rest of FDA regulations
- Non-Exempt: Apply for IND or IDE (only significant risk) → follow extra regulations
Regulatory Status of Investigational Drugs

Investigational Drug/Biologic

- IND Exempt
  - IND Exemption is approved by IRB; FDA approval is not needed

- Not IND Exempt
  - IND Application Required
    - IDE required; FDA approval is needed

Regulatory Status of Investigational Devices

Investigational Medical Device

- IDE Exempt
- Not IDE Exempt

  - Non-Significant Risk (NSR)
    - Abbreviated IDE is approved by IRB; FDA approval is not needed

  - Significant Risk (SR)
    - IDE required; FDA approval is needed
Drug/Biologic Determination Process

1. Describe the drug(s)/biologic(s) being used.
   Describe how it is used in the study.

2. Describe the sponsor/investigator's assessment of whether the drug would qualify for exemption or need to submit an IND application to the FDA.
   Explain whether or not you [the reviewers] agree with the sponsor/investigator's initial assessment.

3. If the IRB decides the drug is IND exempt:
   1. State the Panel's determination of IND exemption, and the rationale for the minutes.

   If the IRB decides the drug does not meet the exemption criteria:
   1. State the Panel's determination of IND required and the rationale for the minutes;
   2. Letter will inform the sponsor/investigator of the IND decision along with any other instructions regarding the IND.

Exemption criteria are listed on reverse side.

IND Application: If the IRB determines that drug does not meet the exemption criteria, the sponsor/investigator must submit an IND application to the FDA.
   - Documentation of the IND number (or the IND exemption, if applicable) from the FDA must be provided before the protocol can be approved.
IND Exemption Criteria

A clinical investigation of a *marketed* drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

1) The drug product is lawfully marketed in the United States.

2) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.

3) In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

4) The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

5) The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

6) The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).
Full Board Device Determination Process

1. Describe the medical device being used. Describe how it is used in the study.

2. Describe the sponsor's assessment of whether the device presents a significant or non-significant risk, or is IDE exempt. Explain whether or not you (the reviewers) agree with the sponsor's initial assessment.

3. If the IRB decides the device is IDE exempt:
   1. State the Panel's determination of IDE exempt, the category, and the rationale for the minutes.

   If the IRB decides that the device's use in the study is Non-Significant Risk:
   1. State the Panel's determination of NSR and the rationale for the minutes.

   If the IRB decides the device's use in the study is Significant Risk:
   1. State the Panel's determination of SR and the rationale for the minutes.
   2. Add a note to the Panel's letter informing the sponsor/investigator of the SR decision along with any other instructions regarding the IDE.

4. Proceed to review the study applying the criteria within 21 CFR 56.111 (45 CFR 46.111).

Medical Device: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: …
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or;
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.” (FD&C Act, 201(h))

The risk determination should be based on the proposed use of a device in an investigation and not on the device alone.

Exemption categories are listed on reverse side.

Non-Significant Risk: A NSR device investigation is one that does not meet the definition for a significant risk study.

Significant Risk: A SR device study is a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and:
1. is intended as an implant, or
2. is used in supporting or sustaining human life; or
3. is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
4. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
IDE Exemption Categories

21 CFR 812(c) provides exemptions from the Investigational Device Exemption (IDE) requirements; meaning 21 CFR 812 and the IDE requirements are not applicable when the device meets one of the criteria below:

1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

3) A diagnostic device, if the sponsor complies with applicable requirements of 809.10(c) and if the testing is:
   i. Is noninvasive,
   ii. Does not require an invasive sampling procedure that presents significant risk,
   iii. Does not by design or intention introduce energy into a subject, and
   iv. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety and effectiveness and does not put subjects at risk.

5) A device intended solely for veterinary use.

6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.
Federal Regulations

1. * Is this a Clinical Trial:
   - Yes
   - No
   - Clear

2. Is this an Applicable Clinical Trial that must be registered and reported to clinicaltrials.gov:
   - Yes
   - No
   - Clear

3. * Is this a FDA regulated study:
   - Yes
   - No
   - Clear

HELP
- FDA regulated research includes all clinical investigations involving a test article and a human.
- A test article means any drug (including a biological product for human use), medical device
What are some examples of FDA Regulated products?

*Could have multiple checked
Reviewing FDA Regulated Studies

FDA regulated studies must follow all HHS and FDA regulations (some are different)

1. Confirm if the study is FDA regulated (meets definition of Drug or Device)
2. If “YES,” determine exempt or non-exempt (flow charts)
3. Waivers
4. Determine Risk Level (full board vs. expedited)
5. Records/Reporting Requirements
6. Elements of Consent
Classification Activity

- Determine the difference in regulations by classifying them as HHS or FDA
**FDA vs. HHS Regulations – Human Subject Research**

**HHS**

**Research**: Systematic investigation, including research development, testing and evaluation, designed to contribute to generalizable knowledge

**Human Subject**: A living individual about whom an investigator conducting research obtains data through interaction or intervention with the individual or private identifiable information

**FDA**

**Research**: “Clinical Investigation” – any experiment that involves a test article and one or more human subjects

**Human Subject**: Any individual who is or becomes a participant in research, either as a recipient of the test article or the control – either healthy or a patient.
FDA vs. HHS Regulations – Cooperative Research

**HHS**

Cooperative Research: Projects which involve more than one institution – each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With approval from the department/agency head, and institution may enter into a joint review arrangement & rely on the review of another qualified IRB to avoid duplication of effort.

**FDA**

Cooperative Research: Institutions involved with multi-institutional studies may use joint IRB review, reliance upon the review of another qualified IRB, or similar arrangements aimed at the avoidance of duplication of effort.
Data Retention – Participants are allowed to withdraw data if the study allows (noted in IFC).

Data Retention – participants can’t withdraw data that has already been collected.
| **Waiver** - Full, some, documentation | **Waiver** – Only waiver is documentation of consent or EFIC, no waivers of parental permission/no waiver of doc of PP |
Confidentiality will be maintained

Can inspect records
FDA vs. HHS Regulations - Definitions

HHS
No definition of “family member,” or “ward”

FDA
Define “family member,” & “ward”
FDA vs. HHS Regulations - Consent

HHS

Consent does not need to be dated

FDA

Consent must be signed and dated.
EFIC

- **EFIC – Exception from Informed Consent**
  - *Greater than Minimal Risk:* Exception of general requirements for obtaining IFC in circumstances that are life threatening, not possible, time is not sufficient to obtain from LAR, not alternative method of therapy that provides equal or greater likelihood of saving the life
HIPAA

- **Health Insurance Portability and Accountability Act (HIPAA)** – Research involving access or use of Protected Health Information (PHI) is subject to compliance with HIPAA and must implement an appropriate pathway.
- Approve the minimum use of PHI
**PHI**

- **Protected Health Information (PHI):** Individually identifiable health information that is obtained or used for treatment, payment or health care operations within a covered entity.
  - Research studies using medical records as a source of person-identifiable research data
  - Intervventional clinical studies comparing safety and efficacy of treatments
  - Health information that is self reported by a subject that is maintained in an ACE is still PHI.
PHI Identifiers – Examples?

- Names
- All geographic subdivisions smaller than a state
- Some exceptions for 1st 3 digits of zipcode
- All elements of dates (except year) for dates directly related to an individual:
  - Birth date
  - Admission & discharge dates
  - Date of death
- All ages over 89 and all elements of dates (including year) indicative of such age
- Ages 90+ can be categorized into ≥90
- Telephone numbers
- Facsimile numbers
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web universal resource locators (URLs)
- Internet protocol (IP) address numbers
- Biometric identifiers, including fingerprints and voiceprints
- Full-face photographic images and any comparable images
- Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification
VCU Affiliated Covered Entity

- VCU Health System (VCUHS) and all satellite clinics
- School of Medicine
- School of Pharmacy
- School of Nursing
- School of Dentistry
- VCU Employee Health
- VCU Telecommunications
- VCU Audit & General Management
- VCU Police Services
- VCU Office of General Counsel
- VCU Office of Research and Innovation
HIPAA Pathways

- Review preparatory to research
- Signed participant authorization
- Waiver of authorization
- Partial waiver of authorization
- De-identified data
- Limited data set and data use agreement
- Research with decedents
Signed Authorization

- Standard for accessing/using PHI in research
- Risks to privacy & PHI disclosure
- Researchers may...
  - Combine the Authorization and the IFC into a single document; or
  - Utilize separate IFC and Authorization documents.
- Require certain elements – Use templates
- If the IFC includes optional activities (research registry for future use), HIPAA authorization must be clear that the subject is not required to provide authorization for both
Signed Authorization

- Appropriate HIPAA pathway?
  - If Authorization & IFC is one document → IRB approves entire document
  - When the Authorization is separate, the IRB will ensure the document has been submitted but **will not review** the content of the Authorization.
    - The investigator is responsible for ensuring the authorization contains all required elements.

- Example: Default – giving a survey and want to get data from medical record
  - Identifiers are allowed to **find and use/record**
  - Code Key is **allowed**
Waiver of Authorization (ALL)

- When a signed Authorization is not feasible (usually approvable if waiver of IFC is approved)
- Example: Chart review and you want to go back several times and get more data (need identifier to go back)
- Identifiers are allowed to find and use/record
- Code Key is allowed
Partial Waiver of Authorization for Recruitment

Recruitment by searching medical records within the VCU ACE.

*Kind of like a full waiver to collect contact information
- If an individual decides to enroll in a study → full signed Authorization is required
- Example: Using a clinic schedule or chart review to identify people who are eligible – write down contact info to contact them
- Identifiers are allowed to find
- **ONLY** use/record contact Information
- Code Key is allowed
Partial Waiver of Elements of Authorization

- Does not include all elements (including signature)
- Participants must still be provided with the information for the Authorization or an Authorization document.
  - Investigators should submit an Authorization form/language to the IRB (either combined with the informed consent form or a standalone document) that will be given or read to potential participants at the time of enrollment.
- Example: Telephone interview and person is giving PHI (don’t have time to tell every single part of HIPAA and won’t have them sign)
- Identifiers are allowed to find and use/record
- Code Key is allowed
Waivers

Look for justification:
- Use of PHI is no more than minimal risk
- A plan to protect & destroy (at the earliest opportunity) PHI
- An assurance that the PHI will not be reused or disclosed to any other person or entity (except as required by law)
- The research could not practicably be conducted without the waiver OR PHI

Approval:
- Full board review or expedited review if all of the criteria above are adequately addressed and the conditions are satisfied.
- The approved HIPAA pathway(s) will be documented in in RAMS-IRB.
Limited Data Set and Data Use Agreement

- A Limited Data Set and Data Use Agreement allow for the use of PHI without obtaining signed authorization or a waiver of authorization.

- Identifiers are allowed to find

- **ONLY** use/record:
  - Geographic information above the street level (e.g., city, state, zip code)
  - All dates or elements of dates (e.g., birth date, procedure date, admission date, age over 89)

- Code Key is **NOT** allowed

- **ONE TIME DATA COLLECTION**

- Requires a *Data Use Agreement* with the institution that is releasing the PHI
  - See WPP for specific provisions

- Reviewers should look for:
  - Applicability of a limited data set, ensuring that no unallowable identifiers will be used.
  - Submit a Data Use Agreement (use template when possible)
    - The Data Use Agreement will be signed by Michelle Stickler

- Example: Chart review and have to write zip code/date, but don’t need name or MRN
HIPAA De-identified Data

- Health information that has none of the 18 HIPAA identifiers associated with it is considered de-identified health information.
- De-identified data is not subject to HIPAA regulations.
- Review:
  - Verify that no identifiers will be recorded with research data and the de-identified data pathway is appropriate for the study.
- Example: Secondary Data - Chart Review – only need name or MRN to find person but not writing identifiers down
- Identifiers are allowed to find (so using PHI)
- NOT recording identifiers, so no longer PHI
- Code Key is NOT allowed
- ONE TIME DATA COLLECTION
Document Retention

- Documents pertaining to HIPAA covered research be maintained for a **minimum of 6 years** past the date of study closure with the IRB.
- Ensure this is in the data retention plan
Breach of PHI

- The event must be reported to the IRB as an Unanticipated Problem (Prompt Report) & Privacy Office.
  - Example: Loss of USB with PHI
- The IRB has the responsibility to review this breach.