

# Human Subjects Research Regulations

Staying in Compliance and Protecting  
Research Subjects

GW IRB Days

September 15-17, 2015

# Overview

- Differences in OHRP and FDA regulations
- When to identify if research is FDA regulated: off label use
- Review of Form 1572
- Review of FDA warnings (Form 483)
- How to prepare for review and monitoring

# Agencies

- *Office for Human Research Protections (OHRP)*: Provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS).
- *The Food and Drug Administration (FDA)*: Ensures that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective.
- *Institutional Review Boards (IRBs)*: A committee established to review and approve research involving human subjects. The purpose of the IRB is to ensure that all human subject research be conducted in accordance with all federal, institutional, and ethical guidelines.

# Regulations

- The Federal Policy for the Protection of Human Subjects or the “Common Rule” was published in 1991 and codified in separate regulations by 15 Federal departments and agencies;
- The HHS regulations, 45 CFR part 46, include four subparts: subpart A, also known as the Federal Policy or the “Common Rule”; subpart B, additional protections for pregnant women, human fetuses, and neonates; subpart C, additional protections for prisoners; and subpart D, additional protections for children;
- Each agency includes in its chapter of the Code of Federal Regulations [CFR] section numbers and language that are identical to those of the HHS codification at 45 CFR part 46, subpart A.

# OHRP vs. FDA

Similarities and differences

# Definition of Research

## OHRP

"...a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."

## FDA

"...any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration."

# Definition of Human Subject

## OHRP

"Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

## FDA

"Human subject" means 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 individual or a patient.

# Regulations on Human Subject Research

## OHRP

- Part 45, parts A, B, C, D.
- Regulations provide special protections for children, pregnant women/fetus/neonates, and prisoners.

## FDA

- Part 50 (protection of human subjects): Subpart A (definitions), Subpart B (informed consent), Subpart D (children) Note: No subparts for prisoners or pregnant women/fetus/neonates
- Part 54 (financial disclosure by clinical investigators)
- Part 56 (Institutional Review Boards)
- Part 11 (Electronic Records, signatures)
- Part 312 (Investigational New Drug Application)
- Part 809 (In Vitro Diagnostic products for human use)
- Part 812 (Investigational Device Exemption)



# Emergency Use: IRB Review

## OHRP

No special “emergency” IRB review procedure is provided.

## FDA

- FDA provides exemption from the prospective IRB review requirement for "emergency use" of test article in specific situations.
- FDA “Emergency Use” provides procedure for IRB clearance of investigational product use, when possible, prior to use in emergency clinical setting.

# Exempt Research

## OHRP

DHHS exempts certain categories of research and provides for a Secretarial waiver.

## FDA

- FDA provides for sponsors and sponsor-investigators to request a waiver of IRB review requirements (but not informed consent requirements).
- The FDA has a limited number of categories which are exempt (56.104/105)

# Waiver of Parent/Guardian Permission in Minimal Risk Studies

## OHRP

For minimal risk studies involving children, the IRB may waive the requirement for consent if the research meets the criteria of 46.116(d) or is designed for conditions or a population for which parent/guardian permission is not a reasonable requirement to protect the subjects (examples include neglected and abused children).

## FDA

Waiver of parental permission is not allowed for FDA regulated research.

# Waiver of Documentation of Informed Consent

## OHRP

OHRP allows for waiver or alteration of the requirement for a signed informed consent document in certain minimal risk studies and when the principal risk is a breach of confidentiality.

## FDA

- FDA does not permit waiver of documentation.
- Obtaining informed consent is “deemed feasible” except in two situations (clinical emergency and emergency research. 21 CFR 50.23, 50.24.

# Dating Consent Forms

## OHRP

OHRP regulations do not explicitly require consent forms to be dated.

\*GW IRB encourages this practice.

## FDA

FDA explicitly requires that consent forms be dated as well as signed by the subject or the subject's legally authorized representative.

\*GW IRB encourages the PI or designee to also sign and date document.

# Waiver of Informed Consent/Consent not Required

## OHRP

Waiver permitted under 46.116(d) if:

- The research involves minimal risk
- The waiver will not adversely affect the rights and welfare of subjects
- The research could not practicably be carried out w/out the waiver
- Where appropriate, subjects will be provided w/ additional information

## FDA

Exceptions to informed consent requirements 21 CFR 50.23:

- Subject is confronted with life-threatening situation necessitating use of test article
- Informed consent not possible because of an inability to communicate with, or obtain legally effective IC from the subject
- No time to obtain consent from LAR
- No alternative method of approved therapy available that provides equal or greater likelihood of saving subject's life
- IRB approves emergency research without requiring informed consent.

# When is My Study FDA Regulated?

Review determination  
Off-label drug and device use

# FDA Regulated

- It is the practice of GW IRB to review all studies that involve off label prescription drug, significant risk device, or tobacco product under full committee for the initial review;
- Subsequent reviews may be reviewed under expedited procedures if the committee makes this determination during the initial review process;
- All studies involving an IND, IDE, or 510(k) will always undergo full committee review and remain full committee.



# How Do I know if I need an IND?

- The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of an IND, if all of the following apply:
  - (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
  - (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
  - (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
  - (iv) The investigation is conducted in compliance with the requirements for review by an IRB (21CFR56) and the requirements for informed consent (21CFR 50); and
  - (v) The investigation is conducted in compliance with the requirements of 21CFR312.7 (Promotion and sale of investigational drugs).

# Minimal Risk

- Generally, a study may be determined to be minimal risk and reviewed under expedited procedures during initial review for the following situations:
  - Drugs used on label
  - Devices employed in an on label manner
  - Other studies that meet the criteria of Expedited categories #1 or #4 at initial review

# Expedited Category #1 and #4

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required.

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

# Off Label Drugs and Devices in Research

- “Off-label” use occurs when an FDA-approved drug, device, or biologic is utilized outside of its approved labeling;
- IRB oversight is only required when the drug or biologic is being used in a clinical investigation;
- The IRB may require literature to support the use of the drug, device, or biologic in an off label manner;
- Be sure to submit all labeling information (drug label, instruction manual for devices, FDA summaries, etc.) with the IRB application.

# Off Label Drugs and Devices in Research

- Even though the drug being used is currently on the market, it is important to be clear that it is being used for a different purpose in the context of the research;
- The consent document must state that the drug is not FDA approved for the disease or condition being studied;
- It is not appropriate to include wording such as “not currently approved” or “not yet approved” which implies that it will become FDA approved in the future.

# Off Label Drugs and Devices in Research

Standards for clinical care of patients

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Standards for academic research

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Standards for FDA regulated research

# FDA Forms

1572

483

# 1572- Investigator Agreement

- If your study is required to undergo FDA review (needs and IND), PIs will be required to complete Form FDA 1572, otherwise known as a Statement of Investigator;
- This document is the agreement between the PI and the FDA;
- FDA expects the PI to comply with Code of Federal Regulations, have knowledge of Clinical Investigator regulations and understanding of Clinical Investigator responsibilities;
- No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572.



# 1572- Investigator Agreement

## Commitments include:

- Conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- Personally conduct or supervise the described investigation(s).
- Inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- Report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
- Agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

# Expectations for Study Oversight

- Delegation of study tasks;
- Training of study staff;
- Supervision of conduct of ongoing study;
- Oversight of third parties involved in the study (e.g. outside labs specifically retained to conduct study assessments).

# Form FDA 483: Warning Letters

- Most FDA inspections are routine for studies that are pending New Drug Application review;
- However, directed, or for cause inspections can be initiated by suspicion of false or fraudulent data. This is data that may appear unrealistic, or if the sponsor alerts the FDA of serious problems;
- Warning Letters are issued only for violations of regulatory significance;
- Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected.

# Form FDA 483: Warning Letters

- A Warning Letter is the agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the Act);
- A Warning Letter is informal and advisory. It communicates the agency's position on a matter, but it does not commit FDA to taking enforcement action;
- For these reasons, FDA does not consider Warning Letters to be final agency action.

On September 28, 2012, the FDA issued a Warning Letter to Dr. Steven W. Boyce outlining violations observed during their inspection.

Violation 1: Failure to assure that an Institutional Review Board (IRB) complies with requirements of the 21CFR56 and 21CFR312.66 (Assurance of IRB review).

This citation was issued in response to enrollment of subjects after study expiration date of May 19, 2010. Dr. Boyce failed to obtain continuing review approval from the IRB. The initial response was that Dr. Boyce submitted the paperwork for renewal on April 7, 2010, but did not submit the required documentation stipulated by the IRB during the review process. Consequently, five subjects were enrolled under expired consent documents. Dr. Boyce maintained he was not aware of study expiration until August 30, 2010 (FDA, 2012).

Violation 2: Failure to maintain adequate case histories that record all observations, a violation of 21CFR312.62 (Recordkeeping and Record Retention).

This citation also stems from failure to obtain continuing review. Specifically, case histories include signed and dated consent forms. As the consent documents were expired at the time of enrollment for five subjects, this is a violation of 21CFR312.62(b), which states that investigators are required to prepare and maintain adequate and accurate case histories including case report forms and supporting data including, for example, signed and dated consent forms.

It was discovered during the FDA's inspection that a study coordinator has purchased a custom-made stamp and was using the stamp to falsely indicate that the consent documents had received IRB approval (FDA, 2012). This is not only a violation of federal regulations, it is unethical.

Violation 3: Failure to ensure the investigation is conducted according to the study plan, violation of 21CFR312.60 (General Responsibilities).

21CFR312.60 states that an investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations. During the FDA's inspection, nine subject records were reviewed. Out of the nine, seven did not receive study required ECGs at designated times. In addition, all nine subjects failed to receive designated assessments or assessments were performed prior to the stated time points.

Violation 4: Failure to obtain informed consent in accordance with 21CFR50 (Documentation of Informed Consent) and 21CFR.60 (General Responsibilities).

This violation is cited by the FDA as failure to comply with 21CFR50.27, which states that informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject. Dr. Boyce did not comply with the regulation by failure to obtain a dated consent document by one subject and by obtaining consent from five subjects under an expired document. This is also a violation of 21CFR312.60 which states that that an investigator is responsible for ensuring that an investigation is conducted according to the regulations.

## Form FDA 483: Case Study- Steven Boyce

# IRB and FDA Review and Monitoring

The Do's and Don'ts of Research

# The *DON'Ts* of Research

- Over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study, assessment of adverse events);
- Erase, white-out or obliterate original data entry;
- Accept suggested changes to study data without checking the source documents or without justification for such changes;
- Backdate the consent forms and signatures;
- Forget to obtain IRB approval of consent form revisions;
- Revise the protocol without obtaining the sponsor's written concurrence;
- Use staff as subjects in a study not having the condition(s) under investigation;
- Destroy study records.

# Preparing for an Inspection

- Section 505(k)(2) of the Food, Drug, and Cosmetic Act mandates that FDA shall have access to and copy and verify the required clinical study records;
- **21 CFR 312.68**“An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator...”



# Preparing for an Inspection- Questions that may be asked

- Delegation of authority: Who, when, where:
  - Screening of subjects
  - Interpreting screening results/admitting to the study
  - Informed Consent of subjects
  - Receipt of test article; handling; administration; return
  - Reporting (including safety reporting) /transcribing data
  - Clinical laboratory
  - Archiving study data

# Preparing for an Inspection- Risk for non-compliance

- Poor supervision and training of study staff;
- Insufficient investigator involvement in study conduct;
- Inappropriate delegation of study tasks to unqualified persons;
- Failure to adequately protect study subjects;
- Overworked investigator and study staff (e.g. too many subjects, complex study with large data collection, too many concurrent studies).

# Case Study: Lack of Supervision

## James Holland and Paul Kornak

- Study coordinator enrolled ineligible subjects in oncology trials;
- Coordinator altered source records and created fraudulent CRFs to make subjects appear eligible;
- Data manipulations should have been apparent to attentive clinician;
- Subject who was ineligible due to poor renal and liver function was enrolled, dosed, and died as a result;
- Study coordinator sentenced to 71 months in prison and debarred from any future involvement in FDA regulated research;
- Dr. Holland – 5 years probation, \$500k restitution to defrauded drug companies, disqualified.
- [http://www.nytimes.com/2005/02/06/nyregion/abuses-endangered-veterans-in-cancer-drug-experiments.html?\\_r=0](http://www.nytimes.com/2005/02/06/nyregion/abuses-endangered-veterans-in-cancer-drug-experiments.html?_r=0)

# The DO's of Research

- Select qualified staff and ensure adequate training and supervision:
  - Ensure staff are not performing tasks they are not qualified to do (e.g. assessing eligibility, performing physical exams, assessing adverse events)
  - Ensure oversight of sub-investigators and study staff

# The DO's of Research

- Address human factors in systems:
  - Hire experienced, qualified staff
  - Avoid conflicts of interest/financial incentives
  - Decrease number of times data are handled
  - Assess ability to comply with protocol visits; laboratory testing; electronic systems for data capture, archiving and transmission to sponsor; maintaining records, drug accountability, inspections by FDA

# The DO's of Research

- Create systems that limit opportunity for errors:
  - Simplify protocol and outcomes assessed
  - Be realistic about the amount of data to be collected
  - Standardize systems and formats where possible
  - Use validated instruments/definitions
  - Write down all procedures (SOPs)-Use checklists
  - Keep amendments to a minimum and check the CRFs and consent form against each change

# The DO's of Research

- Develop an integrated framework:
  - Data and Safety Monitoring Plan, Data Management Plan, Quality Assurance Plan, Data Analysis Plan
  - Insist on training and then test it
  - Think very carefully about unblinding procedures
  - Have a disaster plan (for staff turnover, floods, etc.)
  - Do beta-testing/dry-runs
  - Have weekly team meetings/calls
  - Audit yourself — be open and honest

# The DO's of Research

- Do real-time cleaning of the data;
- Pay attention to monitoring queries and respond promptly. Close loops!;
- Audit trail of changes should make clear what was changed, who changed it, and why it was changed;
- Evaluate need for system wide corrections and training.



# Wrapup

- Focus on the DO's of research for a smoother review, study, and monitoring visits;
- Familiarize yourself with the regulations and guidance;
- If you don't know where to find guidance documents, you may contact the IRB;
- This is a partnership! Be sure to always ask if you are uncertain.

# Resources

OHRP:

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

FDA:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56>

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312>

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812>

# Resources

1572 FAQs:

[www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf](http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf)

IND Guidance Documents:

<http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/guidancesinformationsheetsandnotices/ucm219433.htm>

Form FDA 483:

<http://www.fda.gov/iceci/inspections/ucm256377.htm>

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>

# Resources

Find Drug Information:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

Find Device Information:

<http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/>

# Thanks to...

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Presented by:

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Division of Good Clinical Practice Compliance

Office of Scientific Investigations

Office of Compliance, CDER

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