The ABCs of Human Research Protections
2015 HCCA Research Compliance Conference

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Objectives

1. Review the regulatory framework applicable to human research protections
2. Describe the responsibilities and requirements of the human research protection program
3. Identify common and high risk compliance areas related to human research protections

Regulations
Human Subject Protections: Applicable Regulations and Controls

- Human Subject Protections
  - 45 CFR 46
  - 21 CFR 50, 56, 312, 812
  - State law
  - Local institutional policy
  - AAHRPP accreditation standards
- Good Clinical Practice Compliance
  - ICH-GCP
  - State law
  - Local institutional policy
  - AAHRPP accreditation standards
- Conflicts of Interest
  - 42 CFR 50, subpart F
  - Local institutional policy
  - Institutional COI
- HIPAA
  - 45 CFR 164
  - Scientific Misconduct
  - 42 CFR 93
  - Local institutional policy
- Clinical Trial Billing
  - Medicare Coverage (HCPCS 310.1)
- Effort Reporting
  - OMB circulars
- Others
  - FDAAA 801 – Clinicaltrials.gov
  - Anti-Kickback Fraud and Abuse
  - International Research

Human Subject Protections: Core Regulations

Department of Health and Human Services (DHHS)
- 45 CFR 46

Food and Drug Administration (FDA)
- 21 CFR 50 – Informed Consent
- 21 CFR 54 – Financial Disclosure
- 21 CFR 56 – IRBs
- 21 CFR 312 – Investigational Drugs
- 21 CFR 812 – Investigational Devices

Common Rule Regulations

Subpart A: Basic HHS Policy for Protection of Human Research Subjects
Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
Subpart D: Additional Protections for Children Involved as Subjects in Research
Subpart E: Registration of Institutional Review Boards
Federal Regulatory Structure

Subpart A: Basic HHS Policy for Protection of Human Research Subjects

46.101: Applicability
46.102: Definitions
46.103: Assuring compliance with this policy
46.108: IRB functions and operations
46.109: IRB review of research
46.110: Expedited review
46.111: Criteria for IRB approval of research
46.112: Review by institution
46.113: Suspension or termination
46.114: Cooperative research
46.115: IRB records

46.116: General requirements for informed consent
46.117: Documentation of informed consent
46.118: Applications and proposals, lacking definite plans for involvement of human subjects
46.119: Research undertaken without the intention of involving human subjects
46.120: Evaluation and disposition of applications and proposal for research to be conducted or supported by a Federal Department or Agency
46.122: Use of Federal funds
46.123: Early termination of research support
46.124: Conditions

Subpart B: Research with Pregnant Women, Neonates, and Fetuses

45 CFR 46.201-207

46.204: Research involving pregnant women or fetuses
46.205: Research involving neonates
46.206: Research involving, after delivery, the placenta, the dead fetus or fetal material
46.207: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.
Subpart C: Research Involving Prisoners

45 CFR 46.301-306

46.304 - Composition of IRBs when prisoners are involved
46.305 – Additional duties of the IRB when prisoners are involved
46.306 – Permitted research involving prisoners

Subpart D: Research with Minors

45 CFR 45.404: Research not involving greater than minimal risk
45 CFR 45.405: Greater than minimal risk with prospect of direct benefit to individual subjects
45 CFR 45.406: Greater than minimal risk with NO prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder. (The risk is slightly greater than minimal)
45 CFR 45.407: Research not otherwise approved which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

The Subpart D determination made by the IRB dictates consent and assent requirements:
45 CFR 45.404: Consent of one parent, assent of participant
45 CFR 45.405: Consent of one parent, assent of participant
45 CFR 45.406: Consent of both parents, assent of participant
45 CFR 45.407: Consent of both parents, assent of participant

FDA Regulations

Food and Drug Administration
21 CFR 50 – Informed consent
21 CFR 56 – IRBs
21 CFR 312 – Investigational Drugs
21 CFR 812 – Investigational Devices
21 CFR 54 – Financial Disclosures by Investigators
**21 CFR 50: Protection of Human Subjects**

- **Subpart A** - General Provisions
  - 50.1 - Scope.
  - 50.3 - Definitions.

- **Subpart B** - Informed Consent of Human Subjects
  - 50.20 - General requirements for informed consent.
  - 50.23 - Exception from general requirements.
  - 50.24 - Exception from informed consent requirements for emergency research.
  - 50.25 - Elements of informed consent.
  - 50.27 - Documentation of informed consent.

- **Subpart C** [Reserved]

- **Subpart D** - Additional Safeguards for Children in Clinical Investigations
  - 50.50 - IRB duties.
  - 50.51 - Clinical investigations not involving greater than minimal risk.
  - 50.52 - Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.
  - 50.53 - Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition.
  - 50.54 - Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
  - 50.55 - Requirements for permission by parents or guardians and for assent by children.
  - 50.56 - Waivers.

**21 CFR 56: Institutional Review Boards**

- **Subpart A** - General Provisions
  - 56.101 - Scope.
  - 56.102 - Definitions.
  - 56.103 - Circumstances in which IRB review is required.
  - 56.104 - Exemptions from IRB requirement.
  - 56.105 - Waiver of IRB requirement.

- **Subpart B** - Organization and Personnel
  - 56.106 - Registration.
  - 56.107 - IRB membership.

- **Subpart C** - IRB Functions and Operations
  - 56.108 - IRB functions and operation.
  - 56.109 - IRB review of research.
  - 56.110 - Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
  - 56.111 - Criteria for IRB approval of research.
  - 56.112 - Review by institution.
  - 56.113 - Suspension or termination of IRB approval of research.
  - 56.114 - Cooperative research.

**21 CFR 312, 812, 54**

- **21 CFR 312** - Investigational Drug Exemptions
  - Subpart A - General Provisions
  - Subpart B - Investigational New Drug Application
  - Subpart C - Administrative Actions
  - Subpart D - Responsibilities of Sponsors and Investigators
  - Subpart E - Drugs Intended to Treat Life-threatening and Severely Debilitating Diseases
  - Subpart F - Miscellaneous
  - Subpart G - Drugs for Investigational Use in Laboratory Research Animals or in Vitro Tests
  - Subpart H - Reserved

- **21 CFR 812** - Investigational Device Exemptions
  - Subpart A - General Provisions
  - Subpart B - Application and Administrative Actions
  - Subpart C - Responsibilities of Sponsors
  - Subpart D - IRB Review and Approval
  - Subpart E - Responsibilities of Investigators
  - Subpart F - Reserved
  - Subpart G - Records and Reports

- **21 CFR 54** - Financial Disclosure by Investigators
  - 54.2 - Purpose
  - 54.3 - Definitions
  - 54.4 - Certification and disclosure requirements
  - 54.5 - Agency evaluation of financial interests
  - 54.6 - Recordkeeping and record retention
Institutional Policies

"unchecking the box" on the FWA

FDA & HHS regulations are not harmonized

- Scope – Applicability
- Definitions
- Exemptions
- Informed consent

Research Activity

FDA

HHS

Institutional Policies

Which set of regulations apply?
Which set of regulations apply?

**FDA:**
- Applies to all clinical investigations regulated by the FDA under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formula, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronics. 21 CFR 56.101(a)

**DHHS:**
- Applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States. 45 CFR 46.101(a)

**FDA and DHHS:**
- FDA and DHHS regulations apply when the research is subject to both FDA and DHHS regulation.

**Institutional Policies:**
- Institutional policies apply for all research but may “replace” DHHS regulation when the research is not subject to DHHS and FDA regulation. The terms of the organization’s FWA dictate requirements.

Foundations

Is IRB Review and Oversight Required?

1. New Activity
2. Human Research?
3. Is Institution Engaged?
4. Exempt?
5. Review by Expedited Procedure?
6. Review by Convened IRB?
Is the Activity Human Research?

New Activity → Human Research? → Is Institution Engaged?

Review by Convened IRB → Review by Expedited Procedure? → Exempt?

DHHS Definition of Research

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

45 CFR 46.102(d)

Systematic Investigation:

1. Utilization of statistical analysis and other scientific methods to collect and analyze data.
2. An activity that involves a prospective plan that incorporates data collection (quantitative or qualitative) and data analysis to answer a question.
3. Systematic Investigation is typically a predetermined method for studying a specific topic, answering a specific question(s), testing a specific hypothesis(es), or developing theory.
Generalizable Knowledge

**Generalizable Knowledge:**
- Knowledge that can be applied to populations outside of the population that is being studied.
- Activities designed (with intent) to develop or contribute to generalizable knowledge are those designed to draw general conclusions, inform policy, or generalize findings beyond a single individual or an internal program.
- Participants in the research may or may not benefit directly from the study, but a larger group is expected to gain from the knowledge obtained in the study.

| Is the project **DESIGNED** to contribute to generalizable knowledge? |

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Human Subject - DHHS

**Human Subject** means a living individual about whom an investigator conducting research obtains:
1. Data through intervention or interaction with the individual, or
2. Identifiable private information

45 CFR 46.102(f)

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Intervention & Interaction

**Intervention** includes both physical procedures by which data are gathered and manipulations of the subject or the subject’s environment that are performed for research purposes

**Interaction** includes communication or interpersonal contact between the investigator and the subject

**Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes.

Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining information to constitute research involving human subjects.
**FDA - Clinical Investigation**

**Clinical Investigation:** Any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the FDA, or is not subject to the requirements for prior submission to the FDA but the results of which are intended to be submitted to, or held for inspection, by the FDA as part of an application for a research or marketing permit.

21 CFR 56.102(c)

**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 human or a patient.

21 CFR 56.102(h)

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**Human Subject Research Determination**

- Is the project subject to FDA regulation?
- Is the project research as defined at 45 CFR 46.102(d)?
- Will the project involve human subjects as defined at 45 CFR 46.102(f)?

No

Yes

- IRB review NOT required

IRB review REQUIRED

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**Authority to determine HSR**

OHRP recommends:

- Institutions have policies that designate the individual or entity authorized to determine whether human subjects are involved in research.
- The person(s) authorized to make determination should be knowledgeable about the human subject protection regulations.
- The institution should ensure appropriate communication of such a policy to all investigators.
- Investigators should not be given authority to make an independent determination.

OHRP Guidance on Research Involving Coded Private Information or Biological Specimens, 2008
HSR determinations at the local level

At the local level:
- Investigators should know where they can obtain a HSR determination and when a HSR determination might be required.
- Institutions should create a systematic and transparent process to provide HSR determinations.
- Providing HSR determinations is not necessarily a function of the IRB committee.
- The person(s) authorized to make HSR determinations must be knowledgeable, and provide consistent and timely determinations.
- Institutions should create a process to distribute information related to HSR determinations to the IRB, HIMs, HIPAA privacy officer, compliance department, quality department, or other departments as they deem necessary.

Is the Organization Engaged in Research?

![Diagram of research process]

Engaged in Research

An institution is considered to be engaged in human subjects research when:
- Its employees or agents*:  
  - obtain data about living individuals for research purposes through intervention or interaction with them,  
  - obtain individually identifiable private information for research purposes, or  
  - obtain the informed consent of human subjects.  
- It receives a direct HHS award to support such research, even if all of the human subjects activities will be performed by agents or employees of another institution.

*Employees and agents, including students, are individuals performing institutionally designated activities and acting on behalf of the institution or exercising institutional authority or responsibility.

http://www.hhs.gov/ohrp/policy/engage08.html
Engaged in Research

An institution is NOT considered to be engaged in human subjects research when:

- Activities are limited to informing potential subjects about a research study.
- Activities are limited to providing written information about a research study, including:
  - how to contact the investigators for information and enrollment,
  - seeking and obtaining prospective subjects’ permission for investigators to contact them
- Institutions that permit use of their facilities for intervention or interaction with subjects by investigators from another institution.

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126432.htm
Is IRB Review and Oversight Required?

- **New Activity**
- **Human Research?**
- **Is Institution Engaged?**
  - **Exempt**
  - **Review by Expedited Procedure?**
  - **Review by Convened IRB**

**Exempt**
- Research meets one of the exempt categories per 45 CFR 46.101.

**Review by the Expedited Procedure**
- Research meets the requirements of 45 CFR 46.110
- Research meets one of the categories of research that may be reviewed by the expedited procedure

**Review by the Convened IRB**
- Research is not exempt
- Research does not qualify for review by the expedited procedure

**Exempt Research**

45 CFR 46.101(b): Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy (i.e. 45 CFR 46):

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices
2. Research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior
3. Research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior that is not exempt under #2 if human subjects are elected or appointed public officials.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Federal demonstration projects
6. Taste and food quality evaluation and consumer acceptance studies
Exempt Research

- The research project is human research
- Exempt research is exempt from the laws, regulations, codes, or guidance that govern the research and there are no required provisions to protect participants enrolled in the study
- The person(s) making the exempt determination should have authority to represent the organization
- The person(s) making the exempt determination should have no direct involvement in the activity he or she is examining
- The person making the exempt determination should be knowledgeable


Review by the expedited procedure

45 CFR 46.110: Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure.

(b) An IRB may use the expedited review procedure to review either or both of the following:

1. some or all of the research appearing on the list of expedited review categories and found by the reviewer(s) to involve no more than minimal risk,
2. minor changes in previously approved research during the period of one year or less for which approval is authorized.

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 performance of routine physical or psychological examinations or tests.

Expedited review categories

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 312) is not required. Research involving food or color additives that are regulated by the FDA for which a marketing permit has not yet been issued would fall into this category. (Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 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. (May not be allowed if randomization is involved in study.)
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   (a) from healthy, non-pregnant adults who weigh at least 110 pounds….
   (b) from other adults and children, considering the age, weight and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected….
3. Prospective collection of biological specimens for research purposes by noninvasive means.
4. Collection of data through noninvasive procedures routinely employed in clinical practice, excluding procedures involving x rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.
Expedited review categories

5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Categories 8 and 9 are for Continuing Review only and may be used only if the IRB has informed the PI in writing that future reviews may use the expedited review process.

8. Continuing review of research previously approved by the convened IRB as follows:
   (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research related interventions; and (iii) the research remains active only for long term follow-up of subjects; or
   (b) where no subjects have been enrolled and no additional risks have been identified; or
   (c) where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Review by the Expedited Procedure

- Review by the expedited procedure is not "review light."
- IRB must apply regulatory criteria for research approval
- Review conducted by "experienced" IRB member
- Reviewer cannot disapprove the research

Regulatory Criteria for Research Approval
Regulatory Criteria for Research Approval

45 CFR 46.111 / 21 CFR 56.111

(a) In order to approve research the IRB shall determine that all of the following requirements are satisfied:

1. Minimization of risks
2. Risk-benefit relationship
3. Equitable selection
4. Informed consent process
5. Informed consent documentation
6. Data monitoring
7. Privacy/confidentiality

(b) Additional safeguards for vulnerable populations

Criteria for Research Approval

- The regulatory criteria to approve research must be applied to all research reviewed by the IRB.
- The regulatory criteria to approve research is applicable to reviews of new submissions, continuing review applications, and modifications to IRB approved research.
- All eight components of the “111” criteria must be met for research approval.
- For reviews by the convened IRB, a formal determination by majority vote must be made and documented.
- For reviews by the expedited procedure, the designated reviewer must make and document a formal determination.
- Determinations require ethical judgments.
- All IRB members must have reviewed sufficient material related to the research to make a reasonable judgment.

45 CFR 46.111(a)(1) / 21 CFR 56.111(a)(1)

Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

During review of research, each IRB member must determine that:

- Risks to subjects are minimized by using procedures which are consistent with sound research design
- Risks to subjects are minimized because procedures do not unnecessarily expose subjects to risk, and
- Risks to subjects are minimized (whenever appropriate), by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Risk:
- Physical
- Psychological
- Social
- Economic
- Legal
Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

- IRB members must apply a risk-benefit (reasonable risk-anticipated benefit) analysis framed within the context of the importance of knowledge expected to result from the research
  - What are reasonable risks?
  - What are anticipated benefits?
  - What is the importance of the expected resultant knowledge?
- IRB members should apply their assessment to the risks and benefits of the research (as opposed to “standard of care” interventions)
- IRB members should not consider long-range effects of resultant knowledge

With regards to the protocol, the IRB must understand:
- The purposes of the research
- The scientific or scholarly rationale
- The procedures that will be performed
- Which procedures are being performed as part of research (versus standard of care)
- The risks and potential benefits of the research to participants

With regards to the resources, the IRB must assure that:
- Investigators have adequate time to conduct and complete the research
- Investigators have obtained funding to complete the research
- Investigators are qualified (credentialed) to conduct the required procedures
- Investigators have adequate and qualified staff
- Investigators have adequate facilities to conduct the research
- Investigators have access to a population that will allow recruitment of the necessary number of participants
- Availability of medical or psychosocial resources that participants may need as a consequence of research

Selection of subjects is equitable.
In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

What does equitable selection mean?
- Burdens (and anticipated benefits) of the research do not fall solely on one socioeconomic, vulnerable, or other special population.
- No population is unfairly targeted or excluded.

How does the IRB assess equitable selection?
- Protocol
- Inclusion/exclusion criteria
- Informed consent process
- Recruitment methodologies
- Advertisements
### 45 CFR 46.111(a)(4) / 21 CFR 56.111(a)(4)

Informed consent will be sought from each prospective subject or the subject’s legally authorized representative, in accordance with, and to the extent required by §46.116*.

**Process**

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### 45 CFR 46.111(a)(5) / 21 CFR 56.111(a)(5)

Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117*.

**Documentation**

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### 45 CFR 46.111(a)(6) / 21 CFR 56.111(a)(6)

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

**IRB Considerations:**
- What does “when appropriate mean?”
- What data is collected?
- Who collects data?
- Who reviews data?
- How is the data converted to meaningful information that investigators and the IRB need to protect participants?
- When is a DSMB necessary?
- DSMB Charter review?
When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Privacy: refers to persons and their interest in controlling access of others to themselves.
Confidentiality: refers to the agreement between the investigator and participant on how data will be managed and used.

IRB considerations regarding privacy:
- The time and place where participants will provide information
- The nature of the information they will give
- Who receives and uses the information?

IRB considerations regarding confidentiality:
- How will research data be collected, managed, secured, and disseminated?

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Vulnerable populations: Regulatory Subparts

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<th>FDA</th>
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<tr>
<td>Children</td>
<td>45 CFR 46.401-409</td>
<td>21 CFR 50.55-56</td>
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<td>Pregnant Women, Human Fetuses, and Neonates</td>
<td>45 CFR 46.201-207</td>
<td>21 CFR 50.55-56</td>
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Children:
- Research involving human subjects must be performed solely to benefit the individual subject.
- The risks to the individual subject must be outweighed by the prospects of direct benefit to individual subjects.
- The rights, welfare, and interests of the children must be protected.
- Informed consent must be obtained from children's legal guardians.

Pregnant Women, Human Fetuses, and Neonates:
- Research involving pregnant women or fetuses must be conducted with the consent of the pregnant woman and the neonate's legal guardian.
- The potential benefits to the mother and fetus must outweigh the potential risks.
- The research must be performed in the best interest of the mother and fetus.

Prisoners:
- Research involving prisoners must be conducted with the consent of the prisoner and the institutional authorities.
- The research must be approved by the institutional review board.
- The potential benefits to the prisoner must outweigh the potential risks.
- The research must be conducted in the best interest of the prisoner.

The IRB must apply the requirements of this subpart in addition to the other applicable regulatory requirements.
Informed Consent

Process of Informed Consent

21 CFR 50.20* General requirements for informed consent.

• Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative.

• An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

• The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

• No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

*References in this section of the presentation are tied to FDA regulation

Process of Informed Consent

• To many, the term informed consent is mistakenly viewed as synonymous with obtaining a subject’s signature on the consent form.

• Informed consent involves:
  • providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation,
  • facilitating the potential subject’s comprehension of the information,
  • providing adequate opportunity for the potential subject to ask questions and to consider whether to participate,
  • obtaining the potential subject’s voluntary agreement to participate, and
  • continuing to provide information as the clinical investigation progresses or as the subject or situation requires.

*2014 FDA Draft Guidance – Informed Consent Information Sheet 60
Process of Informed Consent

✔ To be effective, the process must provide sufficient opportunity for the subject to consider whether to participate. (21 CFR 50.20.)

✔ FDA considers this to include allowing sufficient time for subjects to consider the information and providing time and opportunity for the subjects to ask questions and have those questions answered.

✔ The investigator (or other study staff who are conducting the informed consent interview) and the subject should exchange information and discuss the contents of the informed consent document.

✔ This process must occur under circumstances that minimize the possibility of coercion or undue influence. (21 CFR 50.20.)

Basic Elements of Informed Consent

21 CFR 50.25 (a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

• 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 procedure to be followed, and identification of any procedures which are experimental.

• A description of any reasonably foreseeable risks or discomforts to the subject.

• A description of any benefits to the subject or to others which may reasonably be expected from the research.

• A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

• A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

• 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.

• 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.

• A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
Additional Elements of Informed Consent

21 CFR 50.25 (b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable
- Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent
- Any additional costs to the subject that may result from participation in the research
- The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research, which may relate to the subject’s willingness to continue participation, will be provided to the subject
- The approximate number of subjects involved in the study

Documentation of Informed Consent

21 CFR 50.27 (a): Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

21 CFR 50.27 (b): Except as provided in 56.109(k), the consent form may be either of the following:

1. A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject’s legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

2. A short form written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject’s legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

Documentation of Informed Consent

Alternative Methods of Obtaining Informed Consent (continued)

- Methods other than a face-to-face consent interview may be acceptable if those methods allow for an adequate exchange of information and documentation, and a method to ensure that the signer of the consent form is the person who plans to enroll as a subject in the clinical investigation or is the legally authorized representative of the subject.

- For example, the consent form may be sent to the subject or the subject’s legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject’s legally authorized representative can read the consent form during the discussion. After the consent discussion, the subject or the subject’s legally authorized representative can sign and date the consent form and return the document to the clinical investigator by facsimile, scanning the consent form and returning it through a secure e-mail account, or by posting it to a secure internet address.

- Alternatively, the subject may bring the signed and dated consent form to his/her next visit to the clinical site or mail it to the clinical investigator. The signed document should be filed with the subject’s case history.

- Although FDA regulations do not require the subject’s copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided.
Documentation of Informed Consent

Requirements for dating the IC document

- In addition to signing the consent form, the subject or the subject’s legally authorized representative must enter the date of signature on the form (21 CFR 50.27(a)) to allow confirmation that the subject or the subject’s legally authorized representative provided consent prior to participation in the clinical investigation, as required by 21 CFR 50.20.

- In those cases where the subject provides consent on the same day that he/she begins participation in the clinical investigation, the subject’s case history must document that the subject provided consent prior to participation in the research (see 21 CFR 312.62(b) and 21 CFR 812.140(a)(3)).

- The person signing the consent form must receive a copy of the consent form (21 CFR 50.27(a)), and the subject's case history should contain the signed and dated consent form. Although FDA regulations do not require the subject’s copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided.

Waiver or Alteration of Informed Consent

45 CFR 46.116(d) - An IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

45 CFR 46.116(c) – research or demonstration project

21 CFR 50.23 – Emergency Use of a test article (life-threatening situation)

21 CFR 50.24 – Planned emergency research without waiver of informed consent

Waiver of documentation of Informed Consent

45 CFR 46.117(c) - An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds either:

1. That the only record linking the subject and research would be the consent document

OR

2. Minimal risk research and involves no procedures for which written consent is normally required outside of the research context

21 CFR 50.109(c)(1) – The IRB may, for some or all subjects, waive the requirement that the subject, or the subject’s legally authorized representative, sign a written consent form if it finds 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 the research context
The Human Research Protection Program (HRPP)

Shared Responsibility to Minimize Risk

Human Research Protection Program

Core function of the IRB: Ethical Review of Research

**HRPP:** System wide approach toward synchronization of functions related to protecting human research participants.
Human Research Protection Program

- Research Participants
- Investigators
- IRB Office/Administrative personnel
- IRB Committees
- Scientific Review Committees
- Feasibility Assessment Committees
- Institutional Biosafety Committees
- Data and Safety Monitoring Committees
- Conflict of Interest
- Research Compliance
- Investigational Pharmacy
- Pre & Post Award
- Research Education & Training

Common and High Risk Compliance Areas

FDA: 2013 BIMO IRB

- Inadequate initial and/or continuing review
- Inadequate SOPs
- Inadequate membership rosters
- Inadequate meeting minutes
- Quorum issues
- Subpart D issues
- Inadequate communication with CI/institution
- Specific to devices – lack of or incorrect SR/NSR determination
FDA BIMO CI (2009-2013)

2013
- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – failure to report AEs and informed consent issues

2012
- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – including informed consent issues

2011
- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – including informed consent issues

2010
- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – including informed consent issues

2009
- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – including informed consent issues

FDA BIMO CI Five Year (2009 – 2013) Data

- N=3453
- NAI: 1797
- VAI: 1484
- OAI: 172

FDA for cause inspection criteria

- Suspicion of false or fraudulent data
- Evidence that a sponsor has rejected data from an investigator
- Evidence of delay in submitting adverse clinical findings
- Evidence of inadequately monitored clinical investigations
- Evidence of inadequate or inappropriate informed consent
- Evidence of delayed or inappropriate IRB approval
- Evidence that an investigator has a significant financial interest in the product
Center for Drug Evaluation & Research (CDER): Referral Related CI Inspections

Clinical Investigator Inspections:
Data Audit versus referral (CDER, FY 2012)

Referral Related CI Inspections (CDER, FY 2003 – FY 2012)

Referrals include complaints, required reports, IRB/Sponsor notifications, and other referrals (internal and external)

CDER CI Regulatory Actions

CI Regulatory Actions (CDER, FY 2003 – FY 2012)

Consequences of OAI:
- Warning Letter
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
- Notice of Opportunity for Hearing (NOOH)
- Consent Agreement (restricted agreement or full disqualification)
- Disqualification by Hearing or Commissioner
- Debarment

OHRP: Common Compliance Oversight Determinations

- Inadequate informed consent documents for specific research/lack of basic elements
- Lack of Appropriate Written IRB Policies and Procedures
- Protocol Changes prior to IRB review and approval
- Research Conducted without IRB Approval
- IRB Lacks Sufficient Information to Make Determinations Required for Approval of Research
- Failure of IRB to make and document required findings for waiver of informed consent
# AAHRPP: Top Findings

## Step 1 Materials
- Detailed individual conflict of interest policies and procedures
- Conducting convened IRB meeting (membership and attendance)
- Detailed non-compliance policies and procedures
- Defining policies and procedures for IRB suspensions, administrative holds, reporting requirements
- Policies and Procedures for determining the risks to prospective participants who are vulnerable

## Draft Site Visit Report
- Evaluation and feedback of IRB member and chair performance
- Conduct audits or surveys for HRPP compliance and make improvements
- Non-compliance procedures and determinations
- Contracts include notification of organization of study results when participant safety issues raised

## Common & high risk compliance areas

**IRB:**
- Inadequate review of research
- Incorrect utilization of approved with stipulations (conditions)
- Failure to provide Subpart determinations
- Disconnect between IRB review of research with COI management plans

**Institution:**
- Failure to provide human research determinations
- Disconnected management of noncompliance
- Inconsistent review and management of noncompliance
- Failure to reconcile MCA, CTA, and IC
- Failure to signal "Institutional Approval" of research

**Investigator:**
- Difficulty separating research from clinical practice
- General lack of appreciation for the requirements of informed consent for research
- General lack of appreciation for the importance of following the IRB approved protocol

## Inadequate Initial Review

**Failure to apply the regulatory criteria for research approval**
- Does the IRB apply the regulatory criteria for research approval for all research they review (initial submissions, continuing reviews, and modifications)?

**Compliance Risk:**
- Violates federal regulation

**Compliance Monitoring Considerations:**
- Does the IRB apply the regulatory criteria for research approval to all research?
- Are IRB members "knowledgeable"?
- Are determinations documented?
- If documented, where?
  - IRB minutes, checklists, etc.

**Compliance Monitoring Operations:**
- Review IRB meeting minutes
- Review IRB checklists
- Observe IRB meetings
- Interview IRB members and staff
Approval with stipulations

Incorrect utilization of Approved with stipulations (conditions)
Does the IRB approve with modifications correctly?

Compliance Risk:
• Violates federal regulation

Compliance Monitoring Considerations:
• Does the IRB grant approval contingent upon clarifications or modifications directly relevant to the determinations of the IRB?
  • Acceptable: On page 7 of the IRB, change LFT to liver function tests
  • Unacceptable: Clarify whether a DSMB will be convened

Compliance Monitoring Operations:
• Review IRB meeting minutes
• Observe IRB meeting
• Interview IRB members and staff

Failure to provide subpart determinations

Failure to provide Subpart requirements
Does the IRB provide Subpart determinations as required by regulation?

Compliance Risk:
• Violates federal regulation

Compliance Monitoring Considerations:
• Are subpart determinations provided by the IRB?
• Are subpart determinations documented?

Compliance Monitoring Operations:
• Review IRB meeting minutes
• Review IC documents
• Observe IRB meeting
• Observe IC process
• Interview IRB members, IRB staff, and investigators

Failure of IRB review of COI management plans

Failure of IRB review of COI management plans
Are COI management plans reviewed by the IRB?

Compliance Risk:
• Potential to conduct inadequate IRB review of research which would violate federal regulation

Compliance Monitoring Considerations:
• What role does the IRB hold with COI management?
• If COIs are managed separate from the convened IRB, does the IRB receive COI management plans when they review research?
• Is the IRB authorized to adjust COI management plans?

Compliance Monitoring Operations:
• Review IRB meeting minutes
• Review COI committee meeting minutes and management plans
• Interview IRB members
• Interview COI committee members
Failure to provide HSR determinations

**Failure to provide formal human subject research determinations**
Does the Institution support a formal process by which human research determinations are provided to investigators?

**Compliance Risk:**
- Violation of federal regulation - potential to conduct human research without IRB approval
- Potential violation of HIPAA Omnibus rule

**Compliance Monitoring Considerations:**
- Does a formal process exist by which investigators (and others) can obtain HSR determinations?
- Are determinations accurate?

**Compliance Monitoring Operations:**
- Evaluate HSR process
- Evaluate HSR/NHSR determinations
- Interview individuals responsible for providing determinations
- Interview investigators (and others) to evaluate their understanding of the process

Inconsistent review & management of noncompliance

**Inconsistent review of allegations related to noncompliance**
Are allegations of noncompliance consistently managed in accordance with institutional policy?

**Compliance Risk:**
- Potential to conduct inadequate IRB review of research which might lead to violation of federal regulation

**Compliance Monitoring Considerations:**
- What is the process by which allegations of noncompliance are triaged, reviewed, and managed?
- Are events related to noncompliance reviewed and managed in accordance with policy?
- Are determinations related to review documented?

**Compliance Monitoring Operations:**
- Evaluate documented reviews of allegations of noncompliance
- Are protocol deviations and violations managed in accordance with noncompliance policy?
- Are unanticipated problems involving risks to subjects and others managed in accordance with noncompliance policy?

Disconnected management of noncompliance

**Disconnected management of allegations related to noncompliance**
Is the IRB aware of allegations, determinations, and management of noncompliance?

**Compliance Risk:**
- Potential to conduct inadequate IRB review of research which might lead to violation of federal regulation
- Potential failure of IRB fulfilling their reporting requirements

**Compliance Monitoring Considerations:**
- What is the process by which allegations of noncompliance are triaged, reviewed, and managed?
- Is the IRB informed of allegations, determinations, management related to noncompliance?

**Compliance Monitoring Operations:**
- Evaluate noncompliance disclosure, review, management process
- Evaluate noncompliance, serious and continuing noncompliance determinations
- Evaluate compliance with reporting to federal regulatory agencies when determinations of serious and continuing noncompliance are made
- Interview individuals responsible for reviewing and providing determinations and management plans
- Interview IRB members and staff
Failure to reconcile the MCA, CTA, and IC

Failure to reconcile MCA, CTA, and IC (for qualifying clinical trials)

Does the institution synchronize the MCA, CTA, and IC?

Compliance Risk:
• Potential to provide inaccurate information to research participants
• Potential for Fraud and Abuse (violation of FCA)

Compliance Monitoring Considerations:
• Are MCA performed prior to negotiation of the study budget, CTA, and IRB review?
• Are the MCA used to negotiate budgets and write informed consent documents?
• What is the process to reconcile the MCA, CTA, and IC?
• Does the financial disclosure language of the IC match the terms of the CTA?
• Does the subject injury language of the IC match the terms of the CTA?

Compliance Monitoring Operations:
• Evaluate process of document synchronization
• Evaluate consistency between MCA, CTA, and IC from a representative sampling of clinical trials

Failure to signal institutional approval of research

Failure to signal institutional approval of research

Does the institution notify investigators when they can begin enrollment?

Compliance Risk:
• Risk of beginning research activities prior to IRB approval
• Risk of beginning research activities prior to finalizing contracts

Compliance Monitoring Considerations:
• Does a process exist by which investigators are notified when the Institution has approved the research?

Compliance Monitoring Operations:
• Evaluate process of Institutional Approval
• Interview investigators and administrators

Informed Consent

Informed consent

Do investigators understand the requirements of obtaining informed consent?

Compliance Risk:
• Potential violation of federal regulation

Compliance Monitoring Considerations:
• Do investigators understand the regulatory requirements around informed consent in research?
• Do investigators understand the differences between informed consent process and documentation of IC?
• Do investigators understand the difference between assent and consent?
• Do investigators understand the process of documentation of informed consent with the short form (when applicable and allowed per institutional policy)?

Compliance Monitoring Operations:
• Observe the IC process
• Evaluate informed consent documents
• Interview investigators and research coordinators
Failure to follow the IRB approved protocol

Do investigators follow the IRB approved protocol?

Compliance Risk:
• Violation of federal regulation (21 CFR 312.60)

Compliance Monitoring Considerations:
• Do investigators understand the differences between clinical practice and research?
• Do investigators understand their requirement to follow the IRB approved protocol?
• Do investigators know when they may deviate from the IRB protocol without obtaining IRB approval?
• Do investigators understand their reporting responsibilities when they deviate from the protocol?

Compliance Monitoring Operations:
• Evaluate protocol deviations and violations
• Interview investigators

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