






A Primer on Human Research Protection Regulations for the Compliance Professional
2017 HCCA Research Compliance Conference

Scott Lipkin, DPM
Managing Director – Clinical Research & Compliance

 **Objectives**

- Review the regulatory framework applicable to human research protections
- Describe the responsibilities and requirements of the human research protection program
- Identify changes to the current HHS regulations in light of the updated final rule

2

 **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
- **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 (NCD 310.1)
- **Effort Reporting**
 - OMB circulars
- **Others**
 - FDAAA 801 – Clinicaltrials.gov
 - NIH – Single IRB of Record
 - Anti-Kickback Fraud and Abuse
 - International Research

Human Subject Protections: Core Regulations

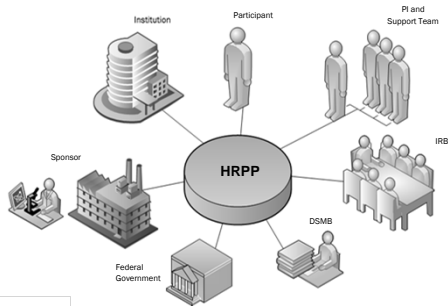
Department of Health and Human Services (DHHS)
• 45 CFR 46



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



Shared Responsibility to Minimize Research 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.

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

Updated Final Common Rule



If/When FINAL RULE IS IMPLEMENTED:
Effective Date: January 19, 2018
Compliance Date for single IRB: January 20, 2020

- 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

<https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf>

Unchecking the Box is Not Necessary Under the Updated Final Rule

- Eliminate the requirement to designate an IRB on the FWA
- Eliminate the requirement to provide a statement of ethical principles
- Eliminate the need to provide an up to date list of IRB members on the FWA
- Establish authority of Common Rule departments and agencies to enforce compliance directly against IRBs (that are operated by an assured institution)
- Eliminate the requirement that grant applications undergo IRB review prior to submission

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

- 46.101: Applicability
- 46.102: Definitions
- 46.103: Assuring compliance with this policy
- 46.107: IRB membership
- 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 A: Basic HHS Policy for Protection of Human Research Subjects

Updated Sections under the Final Common Rule

- 46.101: Applicability
- 46.102: Definitions
- 46.103: Assuring compliance with this policy
- 46.104: Previously reserved, now assigned as Exempt Research
- 46.107: IRB membership
- 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 approval 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 subjects' 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 - Wards

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 operations.
 - 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.

- Subpart D--Records and Reports
- 56.115 - IRB records.
- Subpart E--Administrative Actions for Noncompliance
- 56.120 - Lesser administrative actions.
 - 56.121 - Disqualification of an IRB or an institution.
 - 56.122 - Public disclosure of information regarding revocation.
 - 56.123 - Reinstatement of an IRB or an institution.
 - 56.124 - Actions alternative or additional to disqualification

21 CFR 312, 812, 54


<p>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 Illnesses Subpart F: Miscellaneous Subpart G: Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests Subpart H: Reserved Subpart I: Expanded Access to Investigational Drugs for Treatment Use</p>	<p>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</p> <p style="text-align: center;">21 CFR 54 Financial Disclosure by Investigators</p> <p>54.1: Purpose 54.2: Definitions 54.3: Scope 54.4: Certification and disclosure requirements 54.5: Agency evaluation of financial interests 54.6: Recordkeeping and record retention</p>
---	--

22

Harmonization?

FDA & HHS regulations are not harmonized

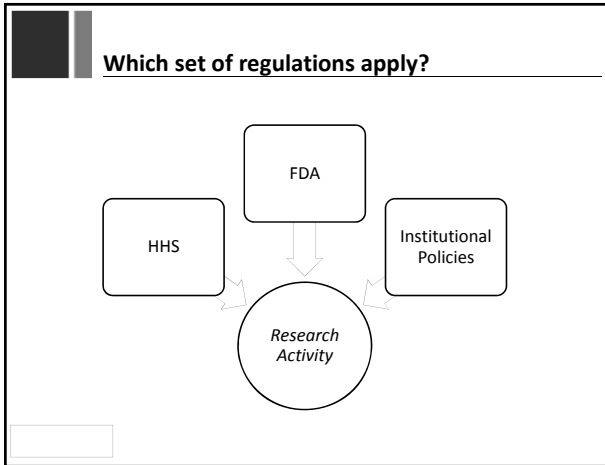
- Scope – Applicability
- Definitions
- Exemptions
- Informed consent



<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm>

Harmonization – 21st Century Cures Act

Protection of Human Research Subjects [Section 3023]
 Harmonization of the differences between the HHS and FDA Human Subject Regulations
 Requirement to modify the two sets of regulations to reduce regulatory duplication and unnecessary delays, to facilitate multisite research, and to incorporate local considerations, community values, and protections of vulnerable populations.



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 formulas, 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 State. *45 CFR 46.101(a)*

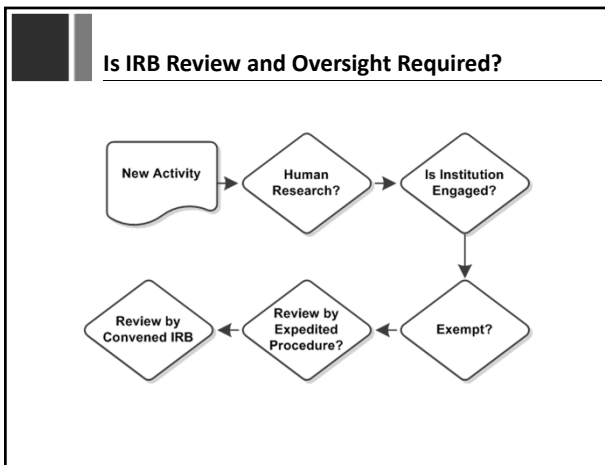
FDA and DHHS:

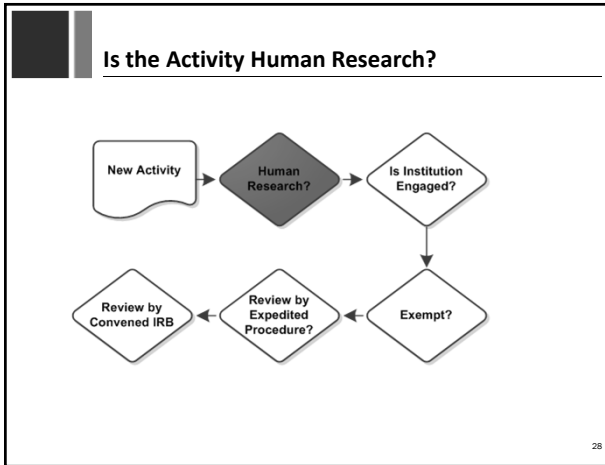
- FDA and DHHS regulations apply when the research is subject to both FDA and DHHS regulation.

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 organizations FWA dictate requirements.

26





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)

When evaluating a project it is useful to think of the research definition as a requirement for two key elements:

1. The project involves a **systematic investigation**
2. The **design**—meaning goal, purpose, or intent—of the investigation is to develop or contribute to **generalizable knowledge**

29

Systematic Investigation

Systematic Investigation:

- Utilization of statistical analysis and other scientific methods to collect and analyze data.
- An activity that involves a prospective plan that incorporates data collection (quantitative or qualitative) and data analysis to answer a question.
- 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.

30

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?

31

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)

32

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.

33

Human Subject - DHHS

Current: *Human Subject* means a living individual about whom an investigator conducting research obtains:

- Data through intervention or interaction with the individual, or
- Identifiable private information

Updated under the Final Rule

Updated: *Human Subject* means a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and stores, uses, studies, or analyzes the information or biospecimens; or
- Obtains, stores, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

34

DHHS Definition of Research

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

Updated under the Final Rule

Updated: *Research* means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. For purposes of this part, the following activities are deemed not to be research:

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship,
- Public health surveillance activities,
- criminal justice or criminal investigative activities,
- Activities that support intelligence, homeland security, defense, or other national security missions.

35

FDA - Clinical Investigation

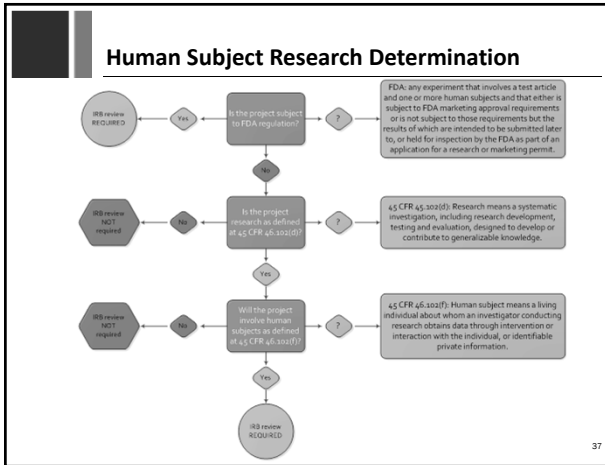
Clinical Investigation: Any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the FDA , or is not subject to the requirements for prior submission to the FDA but the results of which are intended to be submitted to, or 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(e)

36



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

38

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.

39



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/faq/assurance-process/engaged-in-research.html>
<http://www.hhs.gov/ohrp/policy/engage08.html>

41

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.hhs.gov/ohrp/policy/faq/assurance-process/engaged-in-research.html>
<http://www.hhs.gov/ohrp/policy/engage08.html>

42

Engaged in Research

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

Institutions (including private practices) not selected as a research site whose employees or agents provide clinical trial-related medical services that are dictated by the protocol and would typically be performed as part of routine clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial investigators (e.g., medical history, physical examination, assessment of adverse events, blood test, chest X-ray, or CT scan) provided that all of the following conditions also are met:

- the institution's employees or agents do not administer the study interventions being tested or evaluated under the protocol;
- the clinical trial-related medical services are typically provided by the institution for clinical purposes;
- the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and
- when appropriate, investigators from an institution engaged in the research retain responsibility for:
 - overseeing protocol-related activities; and
 - ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.

<http://www.hhs.gov/ohrp/policy/faq/assurance-process/engaged-in-research.html>
<http://www.hhs.gov/ohrp/policy/engage08.html>

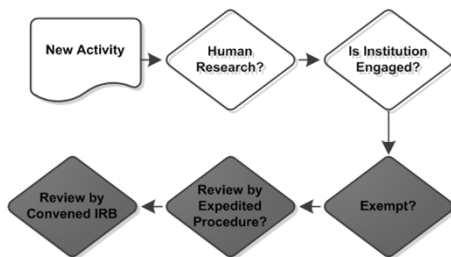
43



<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126432.htm>

44

Is IRB Review and Oversight Required?



Exempt	<ul style="list-style-type: none"> • Research meets one of the exempt categories per 45 CFR 46.101.
Review by the Expedited Procedure	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Research is not exempt • Research does not qualify for review by the expedited procedure

46

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. Educational Research
2. Interactions: educational tests, surveys, 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

47

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

AAHRPP Evaluation Instrument, January 2013; Elements 6.2.A and 6.2.B
48

Exempt Research

Updated under the Final Rule

New: 45 CFR 46.104(d):

1. Educational Research
2. Interactions: educational tests, surveys, observation of public behavior
3. Benign behavioral interventions
4. Secondary research when informed consent is not required
5. Federal research and demonstration projects
6. Taste and Food quality evaluation and consumer acceptance studies
7. Storage or maintenance when broad consent is required
8. Secondary research when broad consent is required

49

Exempt Research

Updated under the Final Rule

New:

- ❖ Storage or maintenance when broad consent is required
- ❖ Secondary research when broad consent is required

LIMITED IRB REVIEW

50

Broad Consent

Broad Consent:

- Obtaining prospective consent for unspecified future research from a subject for storage, maintenance, and secondary research use of identifiable private information and identifiable biospecimens.
- Broad consent is an optional alternative that an investigator may choose instead of having the IRB waive the requirement for informed consent, or obtaining consent for a specific study when conducting the research on nonidentified information and nonidentified biospecimens.
- Broad consent must include:
 - The information required in 45 CFR 46.116(b)(2), (b)(3), (b)(5), (b)(8), and when appropriate (c)(7) and (c)(9)
 - General description of research that will be conducted (reasonable person standard)
 - Description of data or biospecimens, whether sharing will occur, and who might use it
 - Period of time for storage/maintenance and for research use
 - Notification of details for future research
 - Return of clinically relevant results
 - Contact information

51

Limited IRB Review

Limited IRB Review:

- The IRB does not need to make the determinations §.111(a)(1)–(7), but must make the following determinations:
 - Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of §.116(a)(1)–(4), (a)(6), and (d);
 - Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with §.117; and
 - If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- Limited IRB review may occur by the expedited procedure

52

Exempt Research & Subparts Under the Final Rule

Subpart B:

- all exemptions apply

Subpart C:

- exemptions do not apply (except if the research incidentally includes prisoners)

Subpart D:

- research under exemption #3 not allowed
- research under exemption #2 allowed under limited circumstances

53

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.

54

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..... or
 - (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.

55

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.

56

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

57

Review by the Expedited Procedure

Updated under the Final Rule

New:

1. Limited IRB review is added to the list of categories allowable for expedited review
2. Statement that the HHS Secretary will evaluate and update the list of categories allowable for expedited review every eight years

58

IRB Continuing Review Changes

Updated under the Final Rule

New:

- Continuing Review no longer required for research that:
 - Eligible for expedited review
 - Approved by limited IRB review
 - That has progressed to data analysis and/or long-term follow-up

59

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

60

Criteria for Research Approval

- Minimization of risks
- Risk-benefit relationship
- Equitable selection
- Informed consent process
- Informed consent documentation
- Data monitoring
- Privacy/confidentiality
- Vulnerable populations

- ✓ 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 and/or 21 CFR 56.111 61

Vulnerable Populations: Regulatory Subparts

	FDA	DHHS	References
Children	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	45 CFR 46.401-409 21 CFR 50.55-56
Pregnant Women, Human Fetuses, and Neonates		<input checked="" type="checkbox"/>	45 CFR 46.201-207
Prisoners		<input checked="" type="checkbox"/>	45 CFR 46.301-306

✓ The IRB must apply the requirements of the subparts in addition to the other applicable regulatory requirements.

Children

46.404- Research not involving greater than minimal risk
 46.405- Greater than minimal risk but the prospect of direct benefit to individual subjects
 46.406- No prospect of direct benefit but likely to yield generalizable knowledge about the subject's disorder and the risk represents a minor increase over minimal risk
 46.407- Research not otherwise approvable which present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

Pregnant Women, Human Fetuses and Neonates

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 approval which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

62

Criteria for IRB Approval of Research

Updated under the Final Rule

New:

- Added limited IRB review as §.111(a)(8)
- New description of vulnerable populations
 - Updated to remove pregnant women but Subpart B remains unchanged
- HHS Secretary to issue guidance on privacy and confidentiality

63

Process of Informed Consent

21 CFR 50.20 and 45 CFR 46.116 General requirements for informed consent.

- 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.** (excluding waiver)
- 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.

64

Basic Elements of Informed Consent

45 CFR 46.116(a) and 21 CFR 50.25 (a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, 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.

65

Additional Elements of Informed Consent

45 CFR 46.116(b) and 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:

1. 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
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
3. Any additional costs to the subject that may result from participation in the research
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
5. 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
6. The approximate number of subjects involved in the study

66

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 with waiver of informed consent

67

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 56.109(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

68

Informed Consent

Updated under the Final Rule

New:

- General changes
- Basic elements
- Additional elements
- Broad consent
- Waiver of informed consent
- Screening, recruiting, determining eligibility
- Posting of the informed consent document

69

Informed Consent
Updated under the Final Rule

New:
 General changes

- The prospective subject or the legally authorized representative must be provided with the information that a *reasonable person* would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.
- Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.
- The informed consent document must provide sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

70

Informed Consent
Updated under the Final Rule

New:
 Basic elements

- Added one additional element for research that involves collection of identifiable private information or identifiable biospecimens:
 - A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
 - A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

71

Informed Consent
Updated under the Final Rule

New:
 Additional elements

- Added three additional elements to be used when appropriate:
 - Biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
 - A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
 - For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)

72

Informed Consent
Updated under the Final Rule

New:
 Additional elements

- Added three additional elements to be used when appropriate:
 - Biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
 - A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
 - For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)

73

Informed Consent
Updated under the Final Rule

New:
 Waiver

- IRB cannot waive informed consent if a subject previously refused broad consent
- Elements of broad consent cannot be altered

74

Informed Consent
Updated under the Final Rule

New:
 Screening, recruiting, determining eligibility

- IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if :
 - Investigator obtains information by communicating with the subject or LAR or
 - Investigator is accessing records or stored biospecimens

75

Informed Consent


Updated under the Final Rule

New:

Posting of clinical trial consent form

- Applies to federally funded clinical trials
- One version of the IRB approved informed consent must be posted to a federal website (clinicaltrials.gov?)
- Redaction possible
- Must be posted after the clinical trial is closed to recruitment or within 60 after the last study visit by any subject

76



QUESTIONS:

Scott Lipkin, DPM, CIP
Managing Director – Health Solutions
Scott.Lipkin@fticonsulting.com
484.793.2854
