FTI CONSULTING

A Primer on Human Research Protection Regulations for the Compliance Professional

2017 HCCA Research Compliance Conference

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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

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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

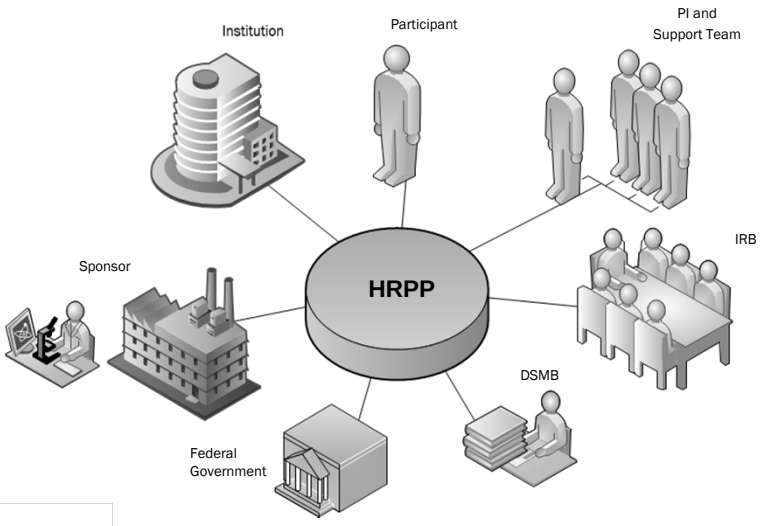
Department of Health and Human Services (DHHS)

- 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



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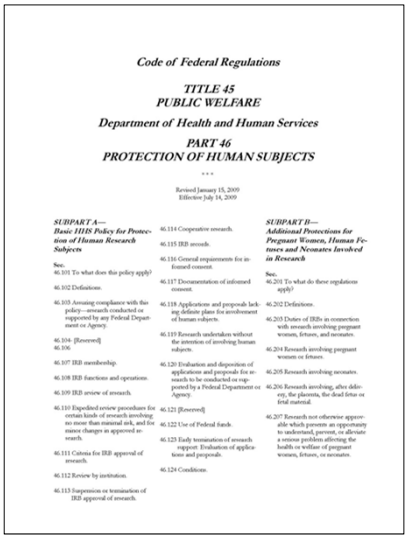
Human Research Protection Program

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



Code of Federal Regulations

TITLE 45
PUBLIC WELFARE
Department of Health and Human Services
PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised January 15, 2009
Effective July 14, 2009

SUBPART A—Basic HHS Policy for Protection of Human Research Subjects

Sec.
46.101 To what does this policy apply?
46.102 Definitions.
46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
46.104–[Reserved]
46.106
46.107 IRB membership.
46.108 IRB functions and operations.
46.109 IRB review of research.
46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
46.111 Criteria for IRB approval of research.
46.112 Review by institution.
46.113 Suspension or termination of IRB approval of research.
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 proposals for research to be conducted or supported by a Federal Department or Agency.
46.121 [Reserved]
46.122 Use of Federal funds.
46.123 Early termination of research support: Evaluation of applications and proposals.
46.124 Conditions.

SUBPART B—Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Sec.
46.201 To what do these regulations apply?
46.202 Definitions.
46.203 Duties of IRBs in connection with research involving pregnant women, 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 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 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

Federal Register / Vol. 82, No. 12 / Thursday, January 19, 2017 / Rules and Regulations 7149

DEPARTMENT OF HOMELAND SECURITY
6 CFR Part 46
DEPARTMENT OF AGRICULTURE
7 CFR Part 1c
DEPARTMENT OF ENERGY
10 CFR Part 745
NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
14 CFR Part 1230
DEPARTMENT OF COMMERCE
15 CFR Part 27
SOCIAL SECURITY ADMINISTRATION
20 CFR Part 431
AGENCY FOR INTERNATIONAL DEVELOPMENT
22 CFR Part 225
DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT
24 CFR Part 60
DEPARTMENT OF LABOR
29 CFR Part 21
DEPARTMENT OF DEFENSE
32 CFR Part 219
DEPARTMENT OF EDUCATION
34 CFR Part 97
DEPARTMENT OF VETERANS AFFAIRS
38 CFR Part 16
ENVIRONMENTAL PROTECTION AGENCY
40 CFR Part 26
DEPARTMENT OF HEALTH AND HUMAN SERVICES
45 CFR Part 46
RIN 0937–AA02

NATIONAL SCIENCE FOUNDATION
45 CFR Part 690
DEPARTMENT OF TRANSPORTATION
49 CFR Part 11
Federal Policy for the Protection of Human Subjects
AGENCY: Department of Homeland Security; Department of Agriculture; Department of Energy; National Aeronautics and Space Administration; Department of Commerce; Social Security Administration; Agency for International Development; Department of Housing and Urban Development; Department of Labor; Department of Defense; Department of Education; Department of Veterans Affairs; Environmental Protection Agency; Department of Health and Human Services; National Science Foundation; and Department of Transportation.
ACTION: Final rule.
SUMMARY: The departments and agencies listed in this document announce revisions to modernize, strengthen, and make more effective the Federal Policy for the Protection of Human Subjects that was originally promulgated as a Common Rule in 1991. This final rule is intended to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators. The revisions are an effort to modernize, streamline, and enhance the current system of oversight.
DATES: This rule is effective on January 19, 2018. The compliance date for this rule, except for § ___.114(b) (cooperative research), is January 19, 2018. The compliance date for § ___.114(b) (cooperative research) is January 20, 2020.
ADDRESSES: Jerry Menikoff, M.D., J.D., OHRP, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.
FOR FURTHER INFORMATION CONTACT: Jerry Menikoff, M.D., J.D., Office for Human Research Protections (OHRP), Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852; telephone: 240–453–8300 or 1–866–447–4777; facsimile: 301–402–2071; email: jerry.menikoff@hhs.gov.
SUPPLEMENTARY INFORMATION:
Preamble
Executive Summary
I. The Rationale for Modernizing the Common Rule
II. To What Does This Policy Apply? Scope and Applicability of the Regulations
III. Definitions for Purposes of this Policy
IV. Changes to Compliance with this Policy
V. Exempt Research
VI. Protection of Identifiable Private Information and Identifiable Biospecimens
VII. IRB Review; Streamlining and Modification to Reflect Increased Knowledge and Addition to Reflect Increased Knowledge and Modification to References to Vulnerability
VIII. IRB Functions and Operations
IX. IRB Review of Research
X. Expedited Review Procedures
XI. Criteria for IRB Approval of Research
XII. Cooperative Research
XIII. IRB Research
XIV. General Requirements for Informed Consent
XV. Documentation of Informed Consent
XVI. Applications and Proposals Lacking Definite Plans for Involvement of Human Subjects
XVII. Research Undertaken Without the Intention of Involving Human Subjects
XVIII. Conditions
XIX. Regulatory Impact Analysis
XX. Environmental Impact
XXI. Paperwork Reduction Analysis
XXII. Tribal Consultation Statement
Final Regulatory Text
Executive Summary
Purpose of the Regulatory Action
Individuals who are the subjects of research may be asked to contribute to the generation of knowledge. Science is the research enterprise, which benefits society at large. U.S. federal regulations governing the protection of human subjects in research have been in existence for more than three decades. The Department of Health, Education, and Welfare first published regulations for the protection of human subjects in 1974, and the Department of Health and Human Services (HHS) revised them in the early 1980s. During the 1980s, HHS began a process that eventually led to the adoption of a revised version of the regulations by 15 U.S. federal departments and agencies in 1991. The purpose of the revisions was to promote uniformity and understanding of and compliance with human subject protections as well as to create a uniform body of regulations across federal departments and agencies (subpart A of 45 Code of Federal Regulations [CFR] part 46), often referred to as the "Common Rule" or "Protection of Human Subjects Regulations." Those regulations were last amended in 2005, and have remained unchanged until the issuance of this final rule.

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

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

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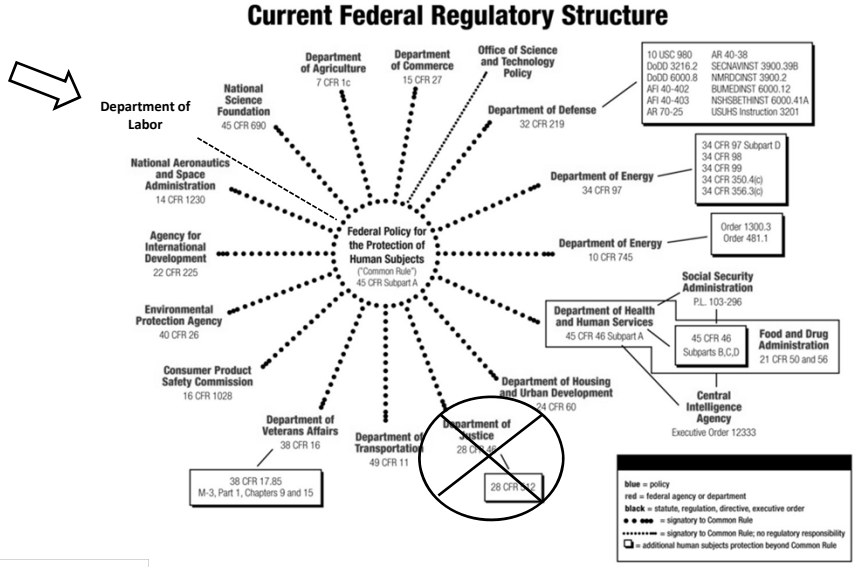
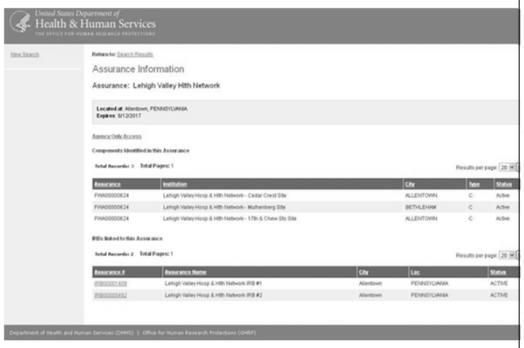
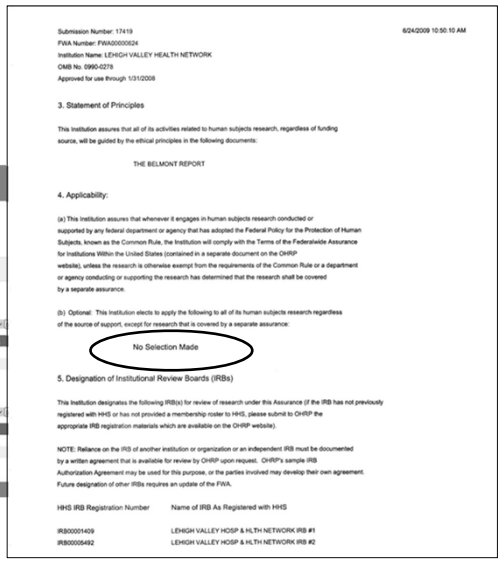
Federal Regulatory Structure



Scope of your Institutions Federalwide Assurance

“unchecking the box” on the FWA





Submission Number: 17419 6/24/2009 10:50:10 AM
FWA Number: FWA00000624
Institution Name: LEHIGH VALLEY HEALTH NETWORK
OMB No. 0990-0278
Approved for use through 1/31/2008

3. Statement of Principles

This institution assures that all of its activities related to human subjects research, regardless of funding source, will be guided by the ethical principles in the following documents:

THE BELMONT REPORT

4. Applicability:

(a) This institution assures that whenever it engages in human subjects research conducted or supported by any federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule, the Institution will comply with the Terms of the Federalwide Assurance for Institutions Within the United States (contained in a separate document on the OHRP website), unless the research is otherwise exempt from the requirements of the Common Rule or a department or agency conducting or supporting the research has determined that the research shall be covered by a separate assurance.

(b) Optional: This institution elects to apply the following to all of its human subjects research regardless of the source of support, except for research that is covered by a separate assurance:

No Selection Made

5. Designation of Institutional Review Boards (IRBs)

This institution designates the following IRB(s) for review of research under this Assurance (if the IRB has not previously registered with HHS or has not provided a membership roster to HHS, please submit to OHRP the appropriate IRB registration materials which are available on the OHRP website).

NOTE: Reliance on the IRB of another institution or organization or an independent IRB must be documented by a written agreement that is available for review by OHRP upon request. OHRP's sample IRB Authorization Agreement may be used for this purpose, or the parties involved may develop their own agreement. Future designation of other IRBs requires an update of the FWA.

HHS IRB Registration Number	Name of IRB As Registered with HHS
IRB00001409	LEHIGH VALLEY HOSP & HLTH NETWORK IRB #1
IRB00005492	LEHIGH VALLEY HOSP & HLTH NETWORK IRB #2

Unchecking the Box is Not Necessary Under the Updated Final Rule

- The prior option that enabled institutions with an active FWA to “check the box” will be eliminated.
- Institutions can voluntarily extend the regulations to all research as they apply flexibility permitted under the regulations (equivalent protections)

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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

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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
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46.122: Use of Federal funds
46.123: Early termination of research support
46.124: Conditions

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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

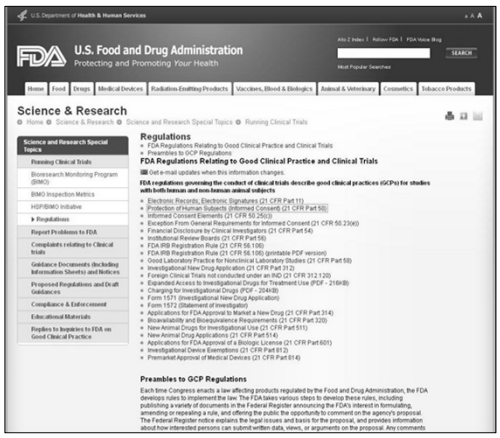
21 CFR 50 – Informed consent

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

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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 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

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

54.1: 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

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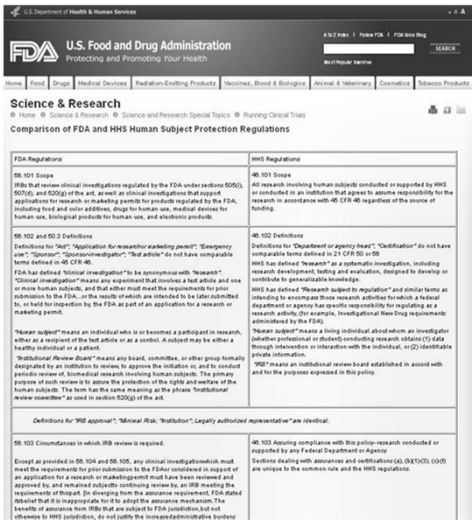
Harmonization?

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.

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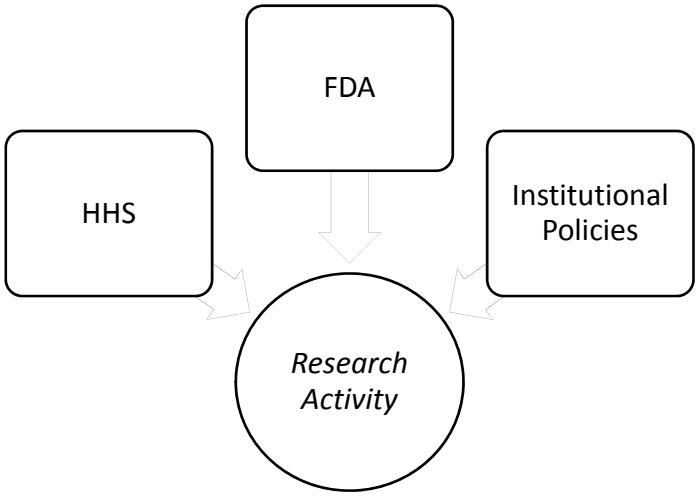
Which set of regulations apply?



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 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.

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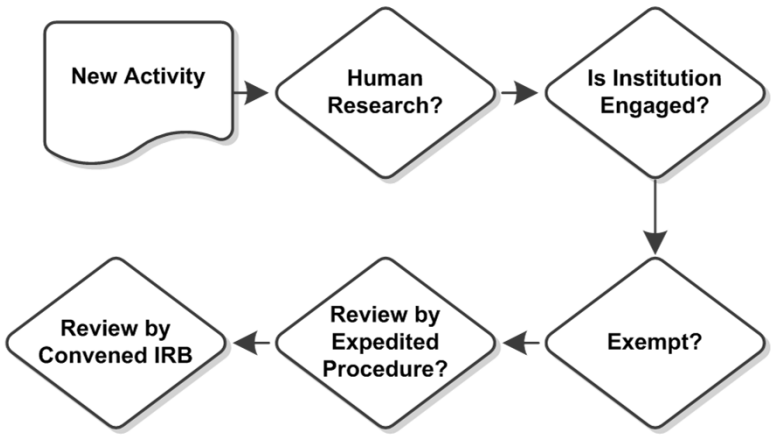
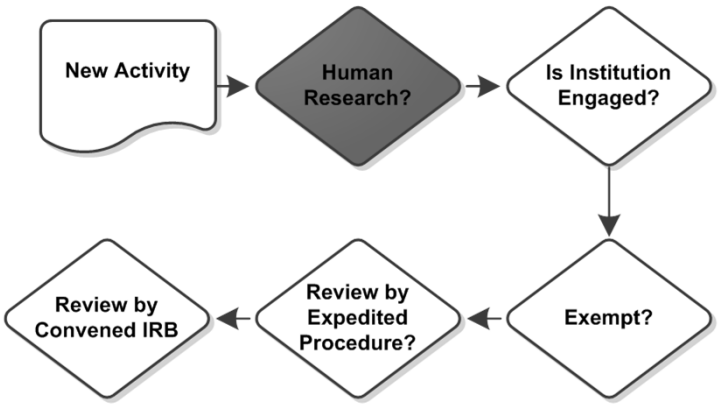
Is IRB Review and Oversight Required?



Is the Activity Human Research?



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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***

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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.

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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.

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Human Subject - DHHS

Updated under the Final Rule

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: 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.

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DHHS Definition of Research

Updated under the Final Rule

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

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.

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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)

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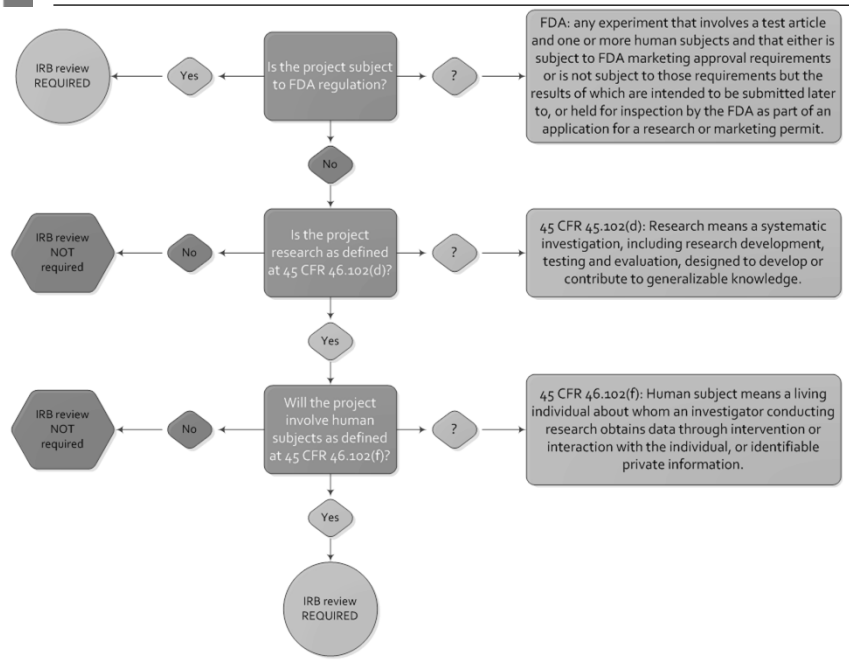
Human Subject Research Determination



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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

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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.

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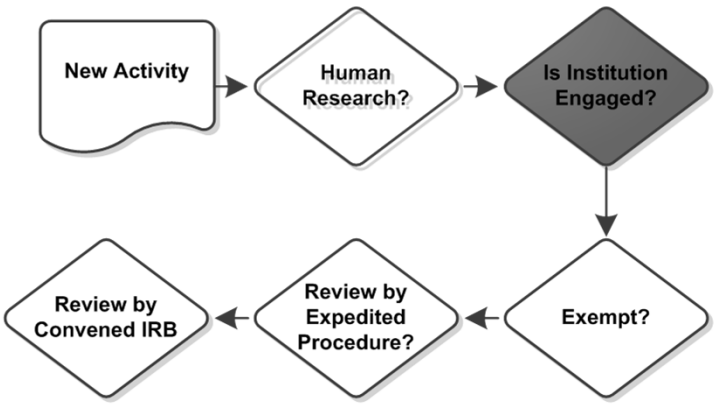
Is the Organization Engaged in Research?



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

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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

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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

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

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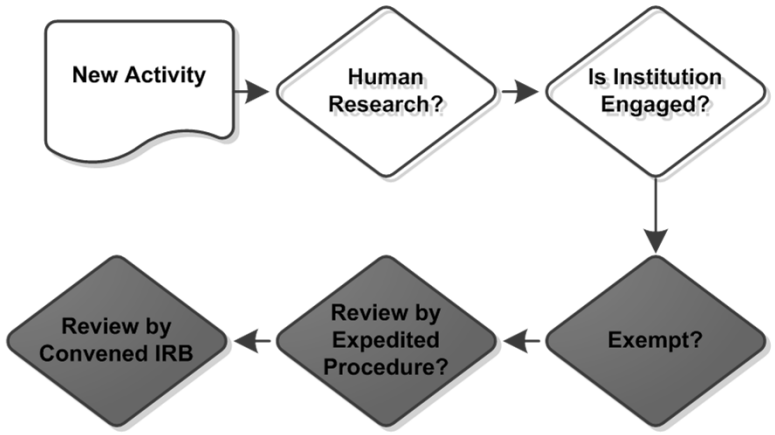
Is IRB Review and Oversight Required?



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

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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

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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 II.2.A and II.2.B

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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

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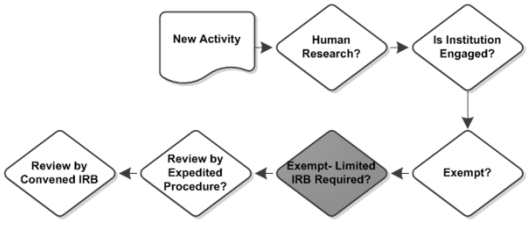
Exempt Research

Updated under the Final Rule

New:

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

LIMITED IRB REVIEW



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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

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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

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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

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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.

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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.

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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.

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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

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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

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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

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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

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Vulnerable Populations: Regulatory Subparts

	FDA	DHHS	References
Children	☑	☑	*45 CRF 46.401-409* *21 CFR 50.55-56*
Pregnant Women, Human Fetuses, and Neonates		☑	*45 CFR 46.201-207*
Prisoners		☑	*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.

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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

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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.

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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.

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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

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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 wit waiver of informed consent

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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

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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

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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.

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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.

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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

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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

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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

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QUESTIONS:

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