Auditing Human Subjects Research

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Discussion Topics

- Primary Goal of Auditing Human Subjects Research
- Federal Requirements of the Department of Health and Human Services (DHHS), FDA, and Institutions Federal Wide Assurance (FWA) and Responsibilities
- Identifying Noncompliance-Conducting Audits
- Audit Ready

Why Conduct Audits of Human Subject Research?

Definition

- Auditing is a formalized method of review which is always independent of the function being audited and where the auditor has no clear interest in the findings and/or overall outcome of the audit. Monitoring is usually an informal method of self review.

Primary Goal

- The primary goal of an audit is to evaluate a research study to ensure that the rights and welfare of human participants are protected, and the research complies with federal regulations, state laws, and institutional policies.

Benefits

- Determine the adequacy of internal controls
- Promote best practices for controls
- Ensure compliance with policies and regulations
- Identify operational inefficiencies and waste –Assess efficient and responsible use of resources
- Verify validity and integrity of data
- Assure the rights and welfare of participants are protected

Reference: Research Compliance Professional's Handbook, second edition, 2013 Healthcare Compliance Association

Federal Requirements of the United States Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and Institution's Federal Wide Assurance (FWA) and Responsibilities

Reference: **21 CFR Parts 50 and 56**
Informed Consent; Standards for Institutional Review Boards for Clinical Investigations; [Docket No. 87N-0032] 56 FR 28025

FDA-U.S Food and Drug Administration

- FDA is charged by statute with ensuring the protection of the rights, safety, and welfare of human subjects who participate in clinical investigations involving articles subject to section 505(i), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i), 357(d), or 360j(g)), as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

56.102 and 50.3 Definitions

- FDA has defined *"clinical investigation"* to be synonymous with *"research". "Clinical investigation"* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA...or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.
- *"Human subject"* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.
- *"Institutional Review Board"* means any board, committee, or other group formally designated by an institution to review, to approve the initiation or, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase *"institutional review committee"* as used in section 520(g) of the act

- The FDA **regulates** clinical **studies** conducted on **drugs, biologics, devices, diagnostics**, and in some cases dietary supplements and food additives.

Federal Requirements of the Department of Health and Human Services (DHHS), United States Food and Drug Administration (FDA), and Institutions Federal Wide Assurance (FWA) and Responsibilities

Reference: **https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials**

FDA Regulations Governing Human Subject Protection & the Conduct of Clinical Trials

- Electronic Records; Electronic Signatures (21 CFR Part 11)
- Regulatory Hearing Before the Food and Drug Administration (21 CFR Part 16)
- Protection of Human Subjects (Informed Consent) (21 CFR Part 50)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Institutional Review Boards (21 CFR Part 56)
- Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR Part 58)
- Investigational New Drug Application (21 CFR Part 312)
- Applications for FDA Approval to Market a New Drug (21 CFR Part 314)
- Bioavailability and Bioequivalence Requirements (21 CFR Part 320)
- New Animal Drugs for Investigational Use (21 CFR Part 511)
- New Animal Drug Applications (21 CFR Part 514)
- Applications for FDA Approval of a Biologic License (21 CFR Part 601)
- Investigational Device Exemptions (21 CFR Part 812)
- Premarket Approval of Medical Devices (21 CFR Part 814)

* ICH GCP (E6(R2))- Good Clinical Practice

Federal Requirements of the United States Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and Institutions Federal Wide Assurance (FWA) and Responsibilities

DHHS- Department of Health and Human Services

- The Office for Human Research Protections (OHRP) is the department within DHHS that provides leadership in the protection of the rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP provides clarification and guidance, maintains regulatory oversight, and provides advice on ethical and regulatory issues in biomedical and behavioral research.

DHHS Definitions:

- "Research": a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
- a human subject is "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 uses, studies, or analyzes the information or biospecimens; OR Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
- "Research Subject to Regulation" those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration).
- "Institution": Any public or private entity or agency [that is engaged in research].

OHRP Recommends answering the following questions to determine if DHHS regulations apply:

- (1) Does the activity involve *research* under 45 CFR 46.102(d)? (If yes, proceed to the second question.)
- (2) Does the activity involve *human subjects* under 45 CFR 46.102(f)? (If yes, proceed to the third question.)
- (3) Is the activity *exempt* under 45 CFR 46.104 (d) (*2018 requirements*)?
- If the answer to the first two questions is "yes", and the answer to the third question is "no", then the HHS regulations apply; otherwise, the HHS regulations do not apply.

Reference: **21 CFR Parts 50 and 56**
Informed Consent; Standards for Institutional Review Boards for Clinical Investigations; [Docket No. 87N-0032] 56 FR 28025

Federal Requirements of the United States Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and Institutions Federal Wide Assurance (FWA) and Responsibilities

Reference: **https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/index.html**

DHHS Regulations Governing Human Subject Protection & the Conduct of Clinical Trials

Note: Although the FDA is an HHS agency it regulates clinical investigations of products under its jurisdiction, such as drugs, biological products, and medical devices. FDA is not considered a Common Rule agency because its regulations differ from the Common Rule.

The Code of Federal Regulations at 45 CFR 46 describes the DHHS requirements for the protection of human subjects. The DHHS regulations require that research involving human participants:

- be subject to oversight by an IRB to ensure that the rights and welfare of research participants are protected, and
- meets regulatory and institutional requirements.

45 CFR 46 subpart B, additional protections for **pregnant women, human fetuses**, and **neonates**; subpart C, additional protections for **prisoners**; and subpart D, **additional protections for children.**
DHHS Subpart E, describes the requirements and processes for **registration of the IRB.**

Federal Requirements of the United States Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and UMB Institutions Federal Wide Assurance (FWA) and Responsibilities

Reference: **21 CFR Parts 50 and 56**
Informed Consent; Standards for Institutional Review Boards for Clinical Investigations; [Docket No. 87N-0032] 56 FR 28025

DHHS Regulations Governing Human Subject Protection & the Conduct of Clinical Trials

The Common Rule: §46 Subpart A is known as the Common Rule. The Common Rule describes the basic DHHS policy for the protection of human research subjects **and is codified according to the agencies that are official signatories (i.e., codified in their own CFR sections).**

The following federal agencies have signed onto the Common Rule:

1. Department of Agriculture (7 CFR 1C)
2. Department of Energy (10 CFR 745)
3. National Aeronautics and Space Administration (14 CFR 1230)
4. Department of Commerce (15 CFR 27)
5. Consumer Product Safety Commission (16 CFR 1028)
6. Agency for International Development (22 CFR 225)
7. Department of Housing and Urban Development (24 CFR 60)
8. Department of Justice (28 CFR 46)
9. Department of Defense (32 CFR 219)
10. Department of Education (34 CFR 97)
11. Department of Veterans Affairs (38 CFR 16)
12. Environmental Protection Agency (40 CFR 26)
13. National Science Foundation (45 CFR 690)
14. Department of Transportation (49 CFR 11)
15. Department of Health and Human Services (45CFR46)
16. Office of the Director of National Intelligence (CR-EO12333)
17. Central Intelligence Agency (CR-EO12333)
18. Department of Homeland Security (6CFR46)
19. Social Security Administration (20CFR431)
20. Department of Labor(29CFR21) NEW!

Federal Requirements of the United States Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and Institutions Federal Wide Assurance (FWA) and Responsibilities

Reference: **https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/index.html**

FWA- Federal Wide Assurance

Before an institution engages in federally funded research, *i.e.*, research that is funded or supported by a Common Rule federal agency, the institution must sign a Federal Wide Assurance ("FWA") and submit it to the HHS Office for Human Research Protections ("OHRP"). An FWA is a contract between an institution proposing to conduct federally funded research and the federal government, via HHS, whereby the institution commits to the federal government that the institution (via its employees and agents) will comply with **45 C.F.R. § 46** when conducting FWA covered research.

Through DHHS FWA, Institutions assure that whenever they become engaged in human subjects' research conducted or supported by any U.S. federal department or agency that has adopted the U.S. Federal Policy for the Protection of Human Subjects (also known as the Common Rule), unless the research is otherwise exempt from the requirements of the Common Rule or the department or agency conducting or supporting the research determines that the research shall be conducted under a separate assurance. Institutions may elect to apply this assurance to all human subjects' research regardless of the source of support, except for research that is covered by a separate assurance.

NOTE: Engaged in Human Research

In general, an institution is considered engaged in Human Research when the Institution's employees or agents for the purposes of the Human Research obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about or identifiable biospecimens from the subjects of the research; or (3) the informed consent of human subjects for the research.

Federal Requirements of the United States Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and Institutions Federal Wide Assurance (FWA) and Responsibilities

Reference: **https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/index.html**

FWA- Federal Wide Assurance

Terms of Agreement

- ✓ Institutions assure compliance with the Federal Policy for the Protection of Human Subjects ('Common Rule').
- ✓ Research must be guided by the 'Ethical Principles' for Human Subjects Research [Belmont Report].
- ✓ Institutions assure compliance with all applicable federal, state, local, institutional policies, regulations, and written procedures
- ✓ Institutions must have written policies and procedures
- ✓ Scope of IRB(s) responsibilities must be defined
- ✓ Informed Consent Requirements
- ✓ Education and Training

All of the Institution's human subjects research activities, regardless of whether the research is subject to the U.S. Federal Policy for the Protection of Human Subjects (also known as the Common Rule), will be guided by a statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution. This statement of principles may include (a) an appropriate existing code, declaration (such as the World Medical Association's Declaration of Helsinki), or statement of ethical principles (such as the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research), or (b) a statement formulated by the institution itself.

Identifying Noncompliance

What is Non-Compliance?

Any failure to follow federal regulations[45CFR46-including any applicable subparts; Any other applicable code of federal regulations], IRB requirements , determinations or provisions made through its approval of a human subject research study, institutional policies and procedures related to human subject research, state laws, and local laws.

- Noncompliance can be as a result of performing acts that violate requirements
- Noncompliance can be as a result of inaction (failure to act when required)

Types of Noncompliance

As defined by UMB HRPO

Serious Noncompliance

- Non-Compliance that adversely affects the rights or welfare of subjects.
- Department of Defense (DOD) research: failure of a person, group, or institution to act in accordance with Department of Defense (DOD) Instruction 3216.02 and its references such that the failure could adversely affect the rights, safety, or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject's willingness to participate in research; or damage or compromise the scientific integrity of research data.
- Veterans Administration (VA) research: any failure to adhere to requirements for conducting Human Research that might reasonably be regarded as:
- Presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or
- Substantively compromising the effectiveness of a Veterans Administration (VA) facility's human research protection program (HRPP).

Identifying Noncompliance

Examples of Serious Noncompliance

- Conducting human subject research involving interactions/interventions without IRB approval
- Conducting non-exempt human subject research without IRB approval
- Enrolling a subject who did not meet the inclusion/exclusion criteria, resulting in increased risk of harm
- Failing to obtain/ document informed consent
- Allowing IRB approval to expire and continuing research activities during the period of expiration
- Major research protocol deviations that may place participants at risk from research procedures

Types of Noncompliance

As defined by UMB HRPO

Continuing Noncompliance

- A pattern of Non-Compliance that indicates a deficiency likely to result in further Non-Compliance or a circumstance in which an investigator fails to cooperate with investigating or correcting Non-Compliance.
- For Veterans Administration (VA) research Continuing Non-Compliance includes a persistent failure to adhere to the legal and policy requirements governing Human Research.

Noncompliance (minor)

- Actions/Activities associated with human research conduct or oversight that fail to comply with the IRB approved research plan, federal regulations, or applicable institutional policies that do not:
  - ✓ result in harm or increase the risk of harm to the participant
  - ✓ Cause a negative change in the welfare of the participant
  - ✓ Significantly impact the integrity of the data
  - ✓ Result from deliberate/reckless misconduct by a member of the research team

Identifying Noncompliance

Examples of Continuing Noncompliance

- Failure to obtain IRB approval prior to recruitment and involvement of human subjects
- Inadequate or non-existent procedures for the informed consent process
- Inadequate supervision for research procedures
- Failure to follow recommendations made by the IRB
- Failure to report adverse events or unanticipated problems to the IRB
- Failure to report protocol changes
- Failure to provide ongoing progress reports
- Failure to report protocol deviations
- Multiple minor noncompliance issues

Identifying Noncompliance

Examples of Noncompliance

- Changes made to study team members without IRB approval (not including PI)
- Change in research questionnaires/surveys without IRB approval
- Protocol deviations (e.g., laboratory test out of study window; study visits out of study window/schedule)
- Changing study procedures that do not result in increased risks/harm/ welfare of participants (e.g., changing schedule visits without IRB approval)
- Failing to follow reporting requirements
- Failure to follow corrective/preventive actions

Auditing Examples

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

Please incorporate all signature lines (below) which are applicable to your study and delete all others.

NOTE: The participant and person obtaining consent signature lines are required for all research studies.

Bradley Louis Sutton

Participant's Signature

Date: August 28, 2020

Freddie Skipper

Witness*

Date: August 30, 2020

Maria Mac Fallen, MD, FACCS

Investigator or Designee Obtaining Consent Signature

Date: August 28, 2020

Deviations

- Signature date of witness is inconsistent with signature dates of participant and Investigator/designee obtaining consent.
- IRB approval is valid January 21, 2020 through July 21, 2020.
- Informed consent document is invalid.

Regulatory Reference

Common Rule: Although the HHS regulations at 45 CFR 46.117 do not require the consent form to be dated at the time it is signed, OHRP recommends that it be dated so that the IRB and others can document that informed consent was obtained prior to a subject's participation in the research.

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

Auditing Examples

Eligibility Criteria For Cov-19 Related Study
Inclusion Criteria

- Age ≥ 18 years
- Positive test for the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as determined by Polymerase Chain Reaction (PCR) in any respiratory specimen
- Hospitalized for COVID-19
- Weighing at least 50 kilograms (kg)
- Oxygen (O2) saturation ≤ 94% on room air or requiring O2 supplement or Radiographic evidence of pulmonary infiltrates for COVID-19
- The interval between COVID-19 symptoms onset and randomization is no more than 10 days

Exclusion Criteria

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal
- Positive serum pregnancy test at screening for women of childbearing potential or currently breastfeeding
- Known hypersensitivity to the study drug, metabolites, or formulation sulfobutylether-beta-cyclodextrin (SBECD)
- Not willing to be admitted to hospital
- Inability to understand and sign the written informed consent

Deviations

- Participant was enrolled into a study but did not meet eligibility criteria.
- These deviations are categorized as intentional protocol deviations according to OHRP.

Regulatory Reference:
FDA- ICH GCP E6 (R2) 4.5.1; 2.1; ; FDA 21 CFR §56.108(a)(4); 21 CFR §56.108(b); 21 CFR §812.150.
[DHHS 45 CFR §46.103(b)(4)

Patient 1ACOV **STATUS: ENROLLED**

VISIT 1(SCREENING) Date: 11 07 2020 (DD MM YYYY)

INFORMED CONSENT
Written informed consent must be given before any study procedures take place or any current therapy is discontinued for the purpose of participation in this study
Has the subject freely given written informed consent? Yes [x] No [ ]

DEMOGRAPHIC DATA
Age (yrs.) 19 Sex: Female [x] Male [ ]
Height (m): 1.8
Weight (lbs.): 105

MEDICAL DIAGNOSIS
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Inconclusive
(Determined by Rapid Test-Antigen NAAT)

VITAL SIGNS
Pulse Rate: 95 beats/min
BP: 121/85 mm Hg
Saturated O2: 95%

LABORATORY RESULTS

Test	Results on Admission	Reference Value
Urea nitrogen (mg/dL)	92*	8-22
Creatinine (mg/dL)	6.8	0.7-1.3
Phosphorus (mg/dL)	3	2.5-4.3
Hematocrit (%)	25.1	36-48
Platelet count (10^3/mm^3)	316	150-450
Alkaline phosphatase (ALP) (U/L)	450*	40-129
Aspartate transaminase (AST) (U/L)	336*	8-48
Alanine Transaminase (ALT) (U/L)	330*	7-55

HOSPITAL ADMISSION STATUS: Admitted (Day1)

Audit Ready

Who can audit my research?

- OHRP (Office for Human Subject Research Protections, DHHS)
- FDA (U.S. Food and Drug Administration)
- DOD (Department of Defense)DEA (Drug Enforcement Agency)
- NIH (National Institutes of Health and applicable agencies)
- VA (U.S. Department of Veterans Affairs)
- Other federal/state agencies
- Private Sponsors
- Local IRB/HRPO
- Institutions- Compliance Offices (e.g., OAC)

Audit Ready

Audit Triggers

- **For Cause-Reported Concerns**

✓ This audit is initiated out of concerns of noncompliance that may result in an increased risk to participant safety or well-being, infringements of the rights of participants, or questions with regards to the integrity of research data.

✓ This type of audit is usually directed by the IRB/Institution Official/Agency/Sponsor in response to concerns.

✓ The review will usually focus on all aspects of the research e.g., the roles and responsibilities of research team members, regulatory and IRB compliance, consent form elements, recruitment, eligibility and consenting process, case report forms (CRFs) for protocol adherence, source documentation and data collection verification, adverse events (reportable/serious adverse events and non-reportable), data storage and access, drug/device accountability, and sample storage.

- **Routine-Random/Spot Audit**

✓ This audit is initiated to fulfill compliance commitments e.g., assurances, MOAs(memorandum of understanding),

✓ This type of audit will usually focus on a defined aspect of the research conduct e.g., review of regulatory documents, recent AE/SAE submissions and modifications, informed consent documentation, eligibility criteria, follow-up reviews from corrective action plans, and data confidentiality and file security.

✓ This type of audit is usually directed by the IRB/Institution Official/Agency/Sponsor to ensure compliance.

Audit Ready

Audit Triggers

- **Follow-Up Audit**

✓ This type of audit occurs when a research study has previously been audited and corrective actions were required as a result of the audit.

✓ A follow-up audit is a focused on reviewing corrective actions that were implemented in response to previously identified problems.

✓ Follow-up audits may be directed by the IRB/Agency/Institution Official/Sponsor to occur within a specific time frame following the initial audit.

- **Post Approval Monitoring Audit**

✓ This type of audit is usually educational- it provides an opportunity to educate investigators and research staff on federal, state, local laws, and institutional policies in the areas of research record keeping and study management.

Audit Ready

Be Prepared

- ✓ Understand your research protocol (e.g., procedures, study intervention schedules, research members' responsibilities etc.,)
- ✓ Understand which regulations, policies, and laws apply to your study
- ✓ Take note of your obligations (e.g., reporting requirements, submissions, training requirements etc.,)
- ✓ Maintain Good Documentation Practices [Refer to Good Clinical Practices Regulations-ICH GCP E6(R2)]:
  - Retain all correspondence from sponsors, monitors, IRB (e.g., Letters, faxes, emails, memos, telephone contacts
  - Maintain study subjects' files
  - Retain all test articles and accountability records
  - Retain shipping receipts, screening and enrollment logs, dispensing logs
  - Maintain regulatory binder (include training and qualification certificates for all research team members, all protocol versions, case reports form templates,
  - Document all deviations including reasons,
  - Document adverse events, and unexpected events
  - Document the informed consent process

Audit Ready

Be Prepared

- ✓ Maintain knowledge of current regulatory/policy requirements
- ✓ Cooperate with Auditors-provide all requested records, accommodate reviews/audits
- ✓ Conduct periodic reviews of research study files (case report forms, regulatory binder etc.,)
- ✓ Consult and adhere to your institutional/departmental policies regarding research
- ✓ Consult with compliance departments/agency/sponsor regarding compliance issues when necessary
- ✓ Conduct self-reviews
- ✓ Encourage research team members to participate in research related continuing education opportunities

References:

- Research Compliance Professional's Handbook, second edition, 2013 Healthcare Compliance Association
- 21 CFR Parts 50 and 56
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- https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/index.html
- https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/index.html
- University of Maryland, Baltimore (UMB)-HRP0-001-SOP definitions

Graphics:

https://hpbbnews.com/2017/02/03/there-is-no-one-size-fits-all-model-to-happiness-at-work/#prettyPhoto

ask questions icon

foire-questions-automobiles.jpg