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Application: All Locations, Domestic and International

PROTECTION OF HUMAN SUBJECTS IN RESEARCH AND CLINICAL INVESTIGATIONS

SECTIONS:

1. PURPOSE AND SCOPE

This policy affirms the Centers for Disease Control and Prevention's (CDC)[1] commitment to protecting the rights and welfare of all human subjects in research and clinical investigations with which CDC is associated. The policy provides direction on implementing human subjects research and clinical investigation requirements outlined in U.S. Department of Health and Human Services' (HHS) regulations and guidelines issued by the HHS Office of Human Research Protections (OHRP).

This policy applies at all locations, domestic and international, and to all Centers, Institute, and Offices (CIOs) and Business Services Offices, which are hereafter called "CDC Components[2]" unless otherwise noted. The policy applies to all CDC employees[3] and, as appropriate, non-employees[4] who serve in the following capacities on human subjects research and clinical investigations: Principal (PI) and Lead CDC investigators; study staff;[5] supervisors, managers, and team leads of PIs;[6] Associate Directors for Science;[7]

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[1] References to CDC also include the Agency for Toxic Substances and Disease Registry (ATSDR).

[2] More information on CDC organizational nomenclature is available at: https://sbi.cdc.gov/DOA/pdf/orgnom.pdf

[3] For the purposes of this policy, the term "employees" consists of members of the civil service, Commissioned Corps officers, and locally employed staff. For more information on these categories, refer to "Employee Categories (Updated July 2018)," available at: http://intranet.cdc.gov/ocio/docs/systems-tools/EmployeeCategoryHelp_July_2018.pdf.

[4] For the purposes of this policy, the term "non-employees" includes individuals who provide consistent services to CDC or maintain a regular presence on a CDC facility, or have been issued a physical or logical access credential and are funded by CDC-managed appropriations. As used in this policy, non-employees include groups of individuals such as guest researchers, contractors, Intergovernmental Personnel Act (IPA) personnel, or students. For more information on these categories, refer to "Non-Employee Categories (Updated July 2018)," available at: http://intranet.cdc.gov/ocio/docs/systems-tools/Non-EmployeeCategoryHelp_July_2018.pdf.

[5] Study staff include all individuals engaged in the conduct of human subject research and clinical investigations working under the direction of the PI. More information on engagement is available at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html.

[6] For the purposes of this policy, supervisors and managers also refer to employees with responsibility for administrative supervision over PIs, such as branch chiefs, division directors, and Component directors.

[7] This category includes equivalent scientific oversight roles at branch, division, and Component levels.

human research protection coordinators;[8] institutional review board (IRB) members; the CDC Institutional Official for the protection of human subjects; the Human Research Protections Lead (HRP Lead); and other program employees.[9]

2. BACKGROUND

CDC is governed by ethical principles and applicable regulations in the discharge of our responsibilities for protecting the rights and welfare of human subjects of research and clinical investigations conducted, supported, or sponsored as an operating division of HHS. This policy provides CDC-specific direction to accompany the HHS regulations.

3. POLICY

A. Protection of Human Subjects

CDC must comply with the HHS Policy for Protection of Human Research Subjects outlined in 45 C.F.R. §§ 46.101-46.505 and Policy for the Protection of Human Subjects outlined in 21 C.F.R. §§ 50, 56, 312 and 812. If any provision of this policy conflicts with the regulations, the regulations prevail.

Common Rule

Subpart A (45 C.F.R. §§ 46.101-46.124) incorporates the Federal Policy for the Protection of Human Subjects or the "Common Rule," which is a set of identical provisions that multiple federal departments and agencies have codified in their own regulations. The Common Rule provides basic requirements for IRBs, informed consent, and Assurances of Compliance.

Additional Regulatory Requirements

The other subparts (45 C.F.R. §§ 46.201-46.505) of the HHS regulations outline additional protections for certain subjects (e.g., pregnant women, minor children, prisoners) and requirements for IRB registration.

Federal Drug Administration

The Food and Drug Administration (FDA) is an agency within HHS that regulates clinical investigations of products under its jurisdiction, such as drugs, biological products, and medical devices. FDA regulations are published as part of chapter 21 of the C.F.R. and FDA's human subject protection regulations are in parts 50, 56, 312, and 812. The FDA regulations provide basic requirements for IRBs, informed consent, investigational new drug applications (INDs) and investigation device exemptions (IDEs).

Belmont Report

The Belmont Report, which heavily influenced the Common Rule, outlines basic ethical

[8] This category includes Human Research Protection Coordinators or equivalent human research analyst roles at branch, division, and Component levels.
[9] This includes other employees at the team, branch, division, or Component level with responsibilities in CDC's human research protection program, such as extramural research program office staff, contracting officers, grants officers and project officers.

principles for research involving human subjects. All of CDC's research activities involving human subjects, whether subject to the HHS regulations or not, will be guided by the ethical principles described in the Belmont Report (e.g., respect for persons, beneficence, justice).

B. Determining When the Requirements Apply

Because HHS and FDA requirements only apply to certain activities under specific circumstances, CDC must appropriately determine and document when it must comply with the regulations and when it is not required to comply.

Research Involving Human Subjects

45 C.F.R. § 46.102(l) defines research for purposes of HHS policy as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." Importantly, the regulation notes that "[a]ctivities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities." Although not exhaustive, the regulation specifies that the following activities are deemed not to be research:

- Scholarly and journalistic activities (refer to 45 C.F.R. § 46.102(l)(1))
- Public health surveillance activities (refer to 45 C.F.R. § 46.102(l)(2))
- The collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes (refer to 45 C.F.R. § 46.102(l)(3))
- Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions (refer to 45 C.F.R. § 46.102(l)(4))

45 C.F.R. § 46.102(e)(1) defines human subject as:

> [A] living individual about whom investigators (whether professional or student) conducting research:
>
> (i) Obtain information or biospecimens through intervention or interaction with the individual, and use, study, or analyze the information or biospecimens; or
>
> (ii) Obtain, use, study, analyze, or generate identifiable private information or identifiable biospecimens.

Clinical Trials

45 C.F.R. § 46.102(b) states that a clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. For each clinical trial conducted or supported by a Federal department or agency, specific requirements at 45 C.F.R. §46.116 (h) must be met.

The HHS OHRP has issued additional guidance to help determine when the regulations apply. CDC will follow HHS guidance and any additional guidance posted on the CDC Human Research Protection Office's (HRPO) site, which is available at: https://intranet.cdc.gov/os/osi/hrpo/policies-regulations/index.html.

Clinical Investigations

21 C.F.R. § 56.102(c) defines a clinical investigation as:

> [A]ny 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] under section 505(i) or 520(g) of the act or need not meet the requirements for prior submission to the [FDA] under these sections of the act, but 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. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

21 C.F.R. § 312.3(b) further defines an "experiment" for purposes of investigational new drugs as:

> [A]ny use of a drug except for the use of a marketed drug in the course of medical practice.

21 C.F.R. § 812.3(h) articulates the scope of "investigation" for purposes of investigational devices to mean:

> [A] clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

21 C.F.R. § 56.102(e) defines human subject as:

> [A]n 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.

The requirements addressing investigational new drugs at 21 C.F.R. §312.3(b) and those addressing investigational devices at 21 C.F.R §812.3(p) further articulate that a "subject" includes a "human who participates in an investigation, either as a recipient of the investigational new drug or as a control," or "an individual on whom or on whose specimen an investigational device is used," including as a control.

C. Assuring Protections

Human subjects research should be guided by principles for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution. Mechanisms such as assurances and registrations are used to describe the ethical codes, regulations and policies governing an institution in the discharge of its responsibilities. When human subjects research is conducted or supported by HHS or an IRB in the U.S. reviews FDA-regulated clinical investigations, there are specific requirements that must be met before the research can begin.

Assurance of Compliance under the HHS Requirements

An assurance of compliance is a written document submitted by an institution (not an Institutional Review Board) that is engaged in non-exempt human subjects research conducted or supported by HHS. The assurance of compliance from OHRP is called a Federalwide Assurance (FWA). Under an FWA, an institution commits to HHS that it will comply with the requirements set forth in 45 C.F.R. § 46, as well as the Terms of Assurance. The FWA is the only type of assurance of compliance accepted and approved by OHRP. Other types of assurance documents issued by other departments, agencies, or governments generally do not satisfy HHS requirements.

FWAs are only required for research subject to the Common Rule. Clinical investigations under FDA regulations do not require institutional assurances of compliance.

Registration of IRBs under the HHS and FDA Requirements

Both the HHS and FDA require IRB registration in certain circumstances.

The HHS regulations at 45 C.F.R. § 46, subpart E, require all IRBs to register with HHS if they will review human subjects research conducted or supported by HHS and are to be designated under an assurance of compliance approved for Federalwide use (i.e., an FWA) by OHRP. FDA requires each IRB in the United States (U.S.) that reviews FDA-regulated studies to register in accordance with 21 C.F.R. § 56.106.

IRB registration information for HHS and FDA regulated research is entered into the same registration system maintained by HHS OHRP for FWAs.

CDC Institutional Review Boards

The Common Rule and FDA regulations require that IRBs review and have the authority to approve, require modifications of, or disapprove all research activities subject to those requirements. The regulations outline general requirements for IRBs, such as membership, functions and operations, review of research, criteria for approval of research, and the suspension or termination of research. Both HHS regulations outline additional (e.g., registration) or research subject-specific (e.g., minor children) requirements for IRBs.

IRBs are responsible for protecting the rights and welfare of research subjects in all research under their purview, whether conducted by CDC or by an outside institution relying on a CDC IRB. Board actions must comply with ethical norms, legal, and policy-related requirements, including federal human research regulations, guidance, and HHS and CDC policy. This policy expressly releases CDC IRB members from any perceived responsibility to protect CDC, its programs, or its investigators, except where such protections are in the interests of research subjects or compliance with ethical norms and legal and policy-related requirements.

IRB oversight includes reviewing and approving CDC research that is subject to HHS or FDA human subjects research protection regulations before the research begins. CDC officials may not permit CDC investigators to conduct research that is disapproved, suspended, or terminated by the IRB of record, or for which IRB approval has lapsed.

More information about CDC IRBs is available at:
https://intranet.cdc.gov/os/osi/hrpo/processes/index.html.

CDC Institutional Official for Human Research Protections

The HHS regulations require each institution engaged in the conduct of human subjects research or clinical investigations subject to the requirements assure compliance with the regulations. The CDC Director has delegated this authority to the CDC Institutional Official for the protection of human subjects.

The Institutional Official is authorized to set the tone for the agency by promoting an institutional culture of respect and conscience, so that the ethical conduct of human research is supported at the highest levels of the organization. The Institutional Official is also authorized to respect, support, and defend the autonomy of CDC's IRBs and other IRBs of record to act within their purview.

CDC Human Research Protection Office (HRPO)

Acting under the Institutional Official's authority, the HRPO leads CDC in protecting the rights and welfare of those who participate in CDC-conducted and -sponsored research. The lead of HRPO serves as the HRP Lead for CDC. Key responsibilities of the Institutional Official for the IRBs have been redelegated to the HRP Lead. The HRP Lead oversees daily operations of IRBs and the CDC Human Research Protection Program and serves as the primary point of contact for correspondence with HHS OHRP on human subjects' research.

CDC Human Research Protection Standard Operating Procedures (SOPs)

HRPO issues standard operating procedures (SOPs) that outline specific procedures or processes that CDC Components must follow to protect human subjects. The SOPs address topics such as (1) management and procedures for the audits of research determinations; (2) the management of the functions of the CDC IRBs; (3) the review procedures for the actions of the CDC IRB; (4) HRPO internal processing procedures; and (5) training for IRB members. These procedures are published at:
http://intranet.cdc.gov/os/osi/hrpo/processes/sops/index.html.

D. Protecting Privacy and Confidentiality

CDC must comply with other applicable regulations, including the Privacy Act of 1974; the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule; statutory provisions for the issuance of certificates and assurances of confidentiality under sections 301(d) and 308(d) of the Public Health Service Act [42 U.S.C. §§ 241(d) and 242m(d), respectively]; or other legal or policy requirements listed in Section 5.

4. RESPONSIBILITIES

A. CDC Component Associate Directors for Science or Equivalent Position

- Determine when the regulatory requirements for human research protections apply for activities planned by the Component
- Ensure that the research uses procedures consistent with sound research design sufficient to yield the expected knowledge

- Confirm that the resources necessary to protect subjects are present before permitting the research study to begin
- Assess investigators' conflicts of interest
- Ensure funding announcements, proposals, and awards address any applicable human subjects research protections requirements in accordance with Scientific Requirements for Contracts, Grants, and Cooperative Agreements
- Ensure receipt of valid certification from the recipient institution of IRB approval in accordance with 46 C.F.R. § 103 prior to disbursement of funds

B. CDC Institutional Official

- Exercises delegated authority to ensure CDC complies with HHS Human Research Protections, this policy, CDC SOPs on human research protections, and laws, policies, and regulations listed in Section 5
- Maintains awareness of changes in laws, regulations, policies, or standards on the protection of human subjects that may impact research conducted or supported by CDC
- Oversees the CDC HRPO and HRP Lead

C. CDC Human Research Protections Lead

- Exercises delegated authority to ensure CDC complies with HHS Human Research Protections, this policy, CDC SOPs on human research protections, and laws, policies, and regulations listed in Section 5
- Maintains awareness of changes in laws, regulations, policies, or standards on the protection of human subjects that may impact research conducted or supported by CDC
- Manages day-to-day operations of the CDC HRPO
- Maintains comprehensive knowledge of CDC's human research protection program
- Ensures CDC SOPs on human research protections are updated

D. Office of Financial Resources' (OFR) Grants Management Officer or Contract Officer

- Assures any applicable human subjects research protection requirements are in the funding announcement and terms and conditions of award
- Verifies receipt of valid certification from the recipient institution of IRB approval in accordance with 45 C.F.R. § 46.103 prior to authorizing disbursement of funds or issuing contract awards for human subjects research activities
- Ensures funds relating to the conduct of research involving human subjects will be restricted until the awardee provides certification, if certification is not obtained prior to award issuance

E. CDC IRB Members

- Exercise the oversight responsibilities outlined in the HHS Human Research Protections, this policy, and provide guidance for development of CDC SOPs on human research protections

F. CDC Component Employees and Non-Employees

- Comply with the applicable regulations for the protection of human research subjects, this policy, and CDC SOPs on human research protections
- Comply with directions from IRBs, as applicable

5. REFERENCES

A. 21 C.F.R. §§ 312.1-312.320 (2019) – Investigational New Drug Application
B. 21 C.F.R. §§ 50.1- 50.56 and §§ 56.101-56.124 (2019) – FDA Protection of Human Subjects
C. 21 C.F.R. §§ 812.1- 812.150 (2019) – Investigational Device Exemptions
D. 42 U.S.C. 242m (2019) – General Provisions Respecting Effectiveness, Efficiency, and Quality of Health Services
E. 45 C.F.R. §§ 46.101-505 (2019) – HHS Protection of Human Subjects
F. CDC. Delegation of Authority, "Protection of Human Research Subjects (Institutional Official – Human Research Subjects," dated May 22, 2018, https://sbi.cdc.gov/doa/download.aspx?doaID=329
G. Health Insurance Portability and Accountability Act of 1996 (HIPAA) Pub.L.104–191, https://www.govinfo.gov/content/pkg/PLAW-104publ191/html/PLAW-104publ191.htm.
H. HHS. *Engagement of Institutions in Human Subjects Research*, dated October 16, 2008, https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html.
I. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. April 18, 1979, https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html.

6. ACRONYMS AND ABBREVIATIONS

CIO – Centers, Institute, and Offices
FWA – Federal Wide Assurance
HHS – U.S. Department of Health and Human Services
HRP – Human Research Protections
HRPO – Human Research Protection Office
IO – Institutional Official
IRB – Institutional Review Board
OHRP – Office for Human Research Protections
OFR – Office of Financial Resources
OS – Office of Science
PI – Principal Investigator
SOP – Standard operating procedure

7. DEFINITIONS

CDC Component – Organizational entities of CDC that are comprised of Centers, Institute, and Offices, and Business Services Offices, as outlined in Organizational Nomenclature Used in Delegations of Authority.