USAID
FROM THE AMERICAN PEOPLE

Protection of Human Subjects in Research Supported by USAID

A Mandatory Reference for ADS Chapter 200

New Edition Date: 12/26/2006
Responsible Office: GH
File Name: 200mbe_122606

Protection of Human Subjects in Research Supported by USAID

1. Introduction and Purpose

Along with many other Federal Agencies, USAID has adopted the Common Federal Policy for Protection of Human Subjects (sometimes referred to as the "Common Rule") as USAID regulation (referred to herein in this document as the Policy – see **22 CFR 225**). The Policy sets standards for the protection of human research subjects that USAID follows when research activities supported by USAID involve human subjects. Safeguarding the rights and welfare of human subjects involved in research supported by USAID is the primary responsibility of the organization to which support is awarded. No research involving human subjects may be undertaken unless the research is approved as outlined in the Policy. The Policy sets forth detailed guidance that allows for some latitude in adaptation of the Policy to the specific situation of each agency, including administrative procedures and interpretation.

This document is a companion to the Policy. Its purpose is to describe how the Policy is implemented and interpreted by USAID. It is intended especially to help Cognizant Technical Officers (CTOs), Technical Advisors (TAs,) Mission staff, and USAID recipients to understand and apply the Policy when supporting or conducting research involving human subjects. CTOs, TAs and Mission staff are the first line of responsibility in assessing applicability of the Policy to a particular research project. For Bureaus/Missions with research activities covered by the Policy, they are responsible for reading the Policy and for ensuring that those organizations receiving USAID funds for research are adhering to requirements set forth in the Policy. USAID's Cognizant Human Subjects Officer (CHSO or successor) assists with guidance and interpretation of the Policy. The CHSO, located in USAID/Washington, is appointed by the Assistant Administrator Global Health (AA/GH). Ultimate Agency authority for decisions regarding human subjects' protection has been delegated to the CHSO.

2. Basic Principles of Human Research Subjects Protection

(a) The 1979 report, of the President's Commission for the Study of Ethical Programs in Medicine and Biomedical and Behavioral Research, or "Belmont Report", laid out much of the ethical principles for the Common Rule. Human subjects' considerations are essential to the design and implementation of research projects. USAID strongly supports vigorous efforts to protect human subjects as provided for by the Policy. Much of the Policy itself is primarily oriented towards experimental biomedical research, but some other types of research are included (see section 5 for application of the Policy to various other types of research, and for exemptions).

(b) Human subjects research rests on three pillars of protection:

(1) Review of the research by a properly constituted ethical committee or Institutional Review Board (IRB);

(2) A meaningful assessment of risks and benefits by the IRB; and

(3) A meaningful informed consent procedure for research subjects.

(c) Trust in the honest, conscientious judgment of the human beings who serve on IRBs is pivotal to the entire system of protection of research subjects. Indeed, the system recognizes that there is no simple formula to apply to ethical decisions, and instead it vests the major responsibility of ethical decision making with the IRB. IRB actions must be based on ethical principles (such as outlined in the Belmont Report.) IRB board members should fully recognize that ethical decisions involve a *balance* among such principles (such as respect for persons, beneficence, and justice) and the importance of the knowledge that may reasonably be expected to result from proposed research (the requirement for which is itself grounded in the principle of beneficence.)

In order to carry out its mandate, institutions conducting research and IRBs are empowered with very wide discretion *within* the bounds of the Common Rule. Recognizing the wide range of situations under which research may occur, the IRB should strive, *above all else,* to do "the right thing" as it sees it. The regulation allows for considerable flexibility to serve that purpose. In the interest of promoting human subjects protection, it is important for institutions and IRBs to take a facilitative, collegial, and educational approach to investigators, rather than a burdensome adversarial one. The IRB should encourage investigators to embrace ethical behavior by acting to facilitate ethical research and it should not be seen as an obstacle to the conduct of research. To that end, institutions and IRBs should promote education efforts for researchers and other staff, and they are encouraged to use their broad discretion to adopt creative administrative and other means to reduce administrative burden and maximize attention to the most important ethical issues.

(d) The Policy recognizes that foreign countries may often present special situations and it provides mechanisms to help deal with these (see **22 CFR 225.101(h)**). As provided for in the Policy, USAID will accept legitimate foreign procedural systems, for example, an institution which complies with the guidelines of the World Medical Assembly Declaration, as long as they are determined to provide protection "at least equivalent" to the Policy. Substantive application of the "three pillars" should generally satisfy this requirement. (See “at least equivalent” procedure below.) As noted in **22 CFR 225.101(g)**, the research must also conform to legal and other requirements governing research with human subjects in the country where it is conducted.

(e) USAID's implementation of the Policy recognizes the highly diverse situations and methodologies for conducting research and seeks to avoid undue burden that might be imposed by its application, while protecting human subjects. It emphasizes practicality, flexibility, and common sense. In cases where all or part of the research is subcontracted to another institution, the prime contractor/recipient is responsible for complying in detail with the Policy. Because USAID conducts no research itself directly, no need is foreseen for an internal USAID IRB *per se* to review research proposals. For research other than experimental biomedical research, generally the primary issue is protection of privacy rather than direct physical harm.

3. Definitions, Interpretation, and Guidance re. Certain Terms and Concepts in the Policy

(a) Research – The Common Rule defines research as
".. a systematic investigation including research development, testing and evaluation designed to develop or contribute to generalizable knowledge."

Further, as described in the Belmont Report "...the term 'research' designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or to contribute to generalizable knowledge....Research is usually described in a formal protocol that sets forth an objective and a set of procedures to reach that objective."

Thus, a key aspect of research is that there be a systematic design *in advance*, generally utilizing a scientific approach or protocol, for the definite purpose of contributing to *generalizable knowledge.* Research can include a wide variety of activities, including the following:

- Experiments,
- Observational studies,
- Surveys,
- Tests, and
- Recordings designed to contribute to generalizable knowledge.

It generally does not include such operational activities as the following:

- Medical care;
- Quality assurance;
- Quality improvement;
- Certain aspects of public health practice, such as routine outbreak investigations and disease monitoring;
- Program evaluation;
- Fiscal or program audits;
- Journalism;
- History;
- Biography;
- Philosophy;
- "Fact-finding" inquiries such as criminal, civil and congressional investigations,
- Intelligence gathering; and
- Simple data collection or data collection for other purposes.

However, some of these activities may include or constitute research in the specific circumstance where there is clear advance intent to contribute to generalizable knowledge with a formal scientific protocol.

(b) Human Subject – This means a *living individual* about whom an investigator obtains

(1) data through intervention or interaction, or

(2) identifiable private information.

(c) Intervention – This includes physical procedures and manipulations of the subject or the subject's environment *for research purposes.*

(d) Interaction – This includes communication between the investigator and the subject.

(e) Private information includes information about behavior in which an individual can reasonably expect that no observation is taking place, or information for specific purposes (such as a medical record) that individuals can reasonably expect will not be made public. Private information must also be readily individually identifiable (i.e. the subject's identity is or may be *readily* ascertained by the investigator or the subject's identity readily associated with the information.)

Thus, simple observational studies of public behavior (including television and internet chat rooms) do not involve human subjects, as defined, because there is no intervention or interaction and the behavior is not private. Also, studies based on data otherwise collected for non-research purposes do not constitute human subjects research unless individual identity is readily identifiable. Examples include: programmatic data such as service statistics, school attendance data, crime statistics, election returns, vital statistics, and pathologic specimens collected for therapeutic purposes (where such information does not readily identify individuals.)

(f) Exemptions – Certain research is exempt under the Policy. Ordinarily, institutions can make the determination that an activity is exempt, but the CHSO has final authority:

(1) Survey and certain similar research – 22 CFR 225.101(b)(2). The Common Rule exempts survey and certain similar research, except in situations where *each* of two things occurs: first, the information would allow subjects to be identified (either directly or through identifiers linked to the subject), and second, "any disclosure of the human subject's responses outside the research could *reasonably* place the subject at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation." Thus, survey and similar research under formal human subjects protection is "covered" only when *both* privacy/confidentiality might be compromised through identification *and* the nature of the information disclosed is very sensitive. In determining whether there might be a reasonable risk of damage related to divulging the sensitive information, etc., it is not enough that there be merely some hypothetically possible risk that can be construed. Rather, the risks resulting from disclosure must be readily appreciable and significant.

(2) Research involving the collection or study of existing data or specimens – 22 CFR 225.101(b)(4).
"Existing" means existing at the time the research is conducted. "Existing" includes sources such as vital records routinely created on an ongoing basis without alteration, even though some may be created after the start of the research. This research is exempt 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. Thus, the key point is how the data are recorded. The research would remain exempt if the investigator had access to identifiable information (such as medical records) but did not record identifiers. Moreover, consistent with the definition of human subject, identification needs to be *readily* ascertainable. Research would remain exempt, for example, if identity is linked only by legitimate encryption or other procedures that make it very difficult for investigators to identify individuals.

(3) Public Benefit or Service Programs – 22 CFR 225. (101)(b)(5). This exemption to study, evaluate, or otherwise examine public service or benefit programs is broadly written. However, the exemption is generally interpreted to be limited to research on the process or outcomes of service delivery (e.g., programmatic research or operations research.)

(g) Informed consent to promote communication and understanding – (22 CFR 225.116 and 117): Recognizing that communication is an imperfect human process, in the interest of better human subjects protection, it is important to recognize the informed consent process as a process of communication and not just a legal requirement. The consent form should not be confused with the informed consent process. In the interest of good communication, the process should promote: simple understandable language, emphasis on the required and most important information, and avoidance of "information overload," without large amounts of additional information of marginal use to the consent process. The process should also promote good communication techniques, such as active listening, individualizing, and requesting restatement by the subject.

(h) Waiver or Alteration of Informed Consent – 22 CFR 225.116 (d) provides conditions for waiving or altering the informed consent procedure for research involving no more than minimal risk. A key condition is that "The research could not be practicably carried out without the waiver or alteration." The determination that the research could not be practicably carried out is not a matter of mere inconvenience to the research process. Rather, there need be a plausible concern that either the conduct or the findings of the research might be adversely affected by the consent process. An adverse effect might include a substantial delay or increase in cost. Examples of situations where waiver or alteration of informed consent may often be justified are minimal risk (and non-exempt) social science methods involving deception, and surveys and cultural anthropology where implementation of all or part of the informed consent process might offend or raise unwarranted suspicions among respondents, thereby adversely affecting the research. Certain medical record review research is another common example where consent may not be practicable. **22 CFR 225.117 (c)** allows for waiver of a signed consent form under certain circumstances, but does not otherwise alter the consent requirements *per se*.

(i) Minimal Risk – As defined in the Common Rule this "... means that the probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." In making this assessment, the risk/harm/discomfort of daily life or routine tests in their *totality* should be weighed against those of the research, not necessarily whether any specific risk/harm discomfort in the research matches that of daily life or such tests. Moreover, it means the risks/harm/discomfort encountered *inherent to the daily lives of the population or class of research subjects involved* and the additional risk/harm/discomfort added by the research. Thus, a treadmill test of low intensity might be minimal risk for the population in general, but more than minimal risk for research conducted with a group of cardiac patients. Likewise, measuring blood levels of a drug with serious side effects among a group of patients already receiving it for therapy might be considered minimal risk, whereas administering the same drug solely for research purposes and measuring it among the healthy population could be more than minimal risk. This standard should not be interpreted to mean that additional highly risky or potentially harmful interventions are considered minimal risk for certain severely ill patients simply because such patients are subject to such interventions as part of their treatment. Many non-exempt surveys may be

considered minimal risk since they do not exceed the harm or discomfort of certain psychological examinations or tests or those ordinarily encountered in daily life.

(j) Multiple Site Research – 22 CFR 225.114 addresses cooperative research. Each institution is responsible for safeguarding subjects' rights and following appropriate procedures. However, institutions may rely on the review of another *qualified* IRB. The types of research, the levels of risk, and the kinds of sites where cooperative research takes place vary widely and the need for considerable adaptability is recognized. For example, the mere fact that research occurs at a certain place (such as a health department, school, or supermarket) does not mean that "place" would be considered a research institution. If a site is only opening its doors to researchers or data abstractors, or is merely providing data, it is not considered a research institution. While it is not necessary that every site or every institution provide its own IRB review (an IRB may be "remote" from the site of the actual research), it is important that the IRB review and oversight that is conducted is explicitly considered competent and cognizant of the conditions and situations in the sites under its purview. One specific mechanism is a cooperative amendment to assurances of institutions participating in cooperative research, which can be agreed to by those institutions, and approved by the sponsoring agency, to document the terms of reliance on another institution's IRB.

(k) Continuing Review and Promoting More Active Oversight – IRBs must conduct continuing review of covered research at least annually. IRBs have considerable latitude in what the review entails. The key concept is that the review be substantive and meaningful. In some cases it may involve a complete review of the entire protocol by the full IRB together with any additional changes, events, and findings. It may also include observations of the research or the consent process. In other instances, IRBs may adopt more expeditious procedures, for example relying on findings of a principal reviewer or on research progress reports. The IRB may consider a biomedical or other intervention study closed when all active participation of the subjects has ended and the investigator is no longer accessing private identifiable information. Once a study is closed, it is a good idea to have reasonable ongoing procedures in place as appropriate and practicable, to protect confidentiality and to provide feedback of relevant emerging information to subjects.

As with any undertaking, a sense of priority is important in dealing with human subjects research, and institutions are encouraged to exercise more active oversight beyond the minimum requirement of the Common Rule for certain higher risk research, as appropriate. More active oversight could include such activities as the following:

- Special educational outreach to investigators and other appropriate stake holders,
- Site visits and observations of research activities,
- Research participant interviews as appropriate,
- Ongoing IRB briefings of research progress,
- Timely monitoring and evaluation of untoward events, and
- Data monitoring and safety boards.

(l) Promoting Ethical Behavior in Areas Exempt from the Policy – Even though certain classes of research are exempt under the Common Rule, they should not be considered exempt from common ethical standards. For example, a certain survey may be exempt, but it is common courtesy and otherwise generally reasonable to ask permission and provide some simple information to

respondents. Likewise, research on existing specimens might not record identifiers and thus be exempt, but researchers should still strive to protect individual privacy. The interest in promoting ethical behavior outside the common rule is not intended as a mandate for more structured procedures, but rather to advance a cultural norm of ethical behavior for research and non-research activities alike, to be exercised with discretion by institutions and individuals.

4. Application in Various Research Locations

(a) Research in the U.S. – When research takes place in the U.S., it must conform to all aspects of the Policy. Recipient institutions may be of two categories:

(1) Many have a "Federal-wide Assurance" of Compliance (FWA) issued and administered by the Department of Health and Human Services (DHHS) that applies to all Federally-funded research. Under the FWA, the implementation procedures and interpretations of the respective Federal funding agency govern its application.

(2) If no FWA exists, the institution must provide an acceptable "assurance" to USAID describing how it will comply with the Policy (see section 8 below).

(b) Research in Foreign Countries – There are generally three mechanisms by which USAID supports research in foreign countries:

(1) The primary funding recipient is a U.S.-based institution, with the research carried out in another country. In this situation, the primary recipient is responsible for complying or assuring compliance in detail with the Policy as described above under either an FWA or USAID-approved assurance governing the research. USAID encourages, but does not require, the host-country collaborators of U.S.-based institutions to use an in-country IRB.

(2) The recipient is a United Nations (U.N.) agency (e.g. the World Health Organization (WHO)) .

(3) The primary recipient is a host country government or non-government institution.

In the last two cases, there are three ways acceptable standards can be applied:

(i) An FWA or a USAID-specific assurance as with U.S. institutions.

(ii) Access to an appropriate USAID-accepted research system, such as through a WHO/ Council for International Organizations of Medical Science (CIOMS)-approved Ethical Committee (see section 4(a) below) either directly or through a collaborative arrangement.

(iii) An alternative human subjects system can be employed if it can be determined (by the AA/GH or designee) to be "at least equivalent" to the Policy (as delineated in section 5 below).

5. Determination that Alternative Protection Procedures are "at Least Equivalent" to the Policy

(a) **22 CFR 225.101(h)** describes the use of alternative protection of human subjects systems when research is conducted outside the U.S. It specifically cites the example of "...a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human subjects is internationally recognized." Research supported through or adhering to the standards established by United Nations agencies, such as WHO, is considered to qualify as affording such "at least equivalent" protection.

(b) To make a determination that another system besides (a) above provides “at least equivalent" protection, a justification memorandum is required for an individual or class of research activities which is cleared by the Agency's CHSO (designee or successor) and is signed by the AA/GH (or designee.) Such a justification memorandum must describe how the alternative system provides the "three pillars" of protection described above under section 2(b)(1-3). In assessing equivalency, the general concept should be whether the system provides a level of protection that is equivalent overall when viewed in toto and not whether any specific component (e.g. the precise make-up of the IRB equivalent) is identical. Each determination of "at least equivalent" protection, including the determination for a class of activities, will be published in the Federal Register or otherwise in accordance with **22 CFR 225.101(h)**.

6. Applicability of the Policy to Various Types of Research and Research-Related Activities

The following listed activities are guidelines for helping to assist in determining applicability of the Policy to a particular activity. They are not intended to be totally inclusive.

(a) **Experimental Biomedical Research –** The Policy clearly applies to experimental biomedical research related to prevention, transmission, treatment, or curing of human diseases and to prevention of pregnancy; including the following:

- Vaccine and drug development;
- Clinical trials of new drugs, devices, and vaccines; and
- Experimental studies of disease transmission involving human subjects.

(b) **Survey Research/Demographic Data Collection**

(1) Survey research in which no individual identifiers are collected or in which the data collected are not highly sensitive is exempt **(See 22 CFR 225.101(b)(2) & (3))**. Research with identifiers involving highly sensitive questions is not exempt, for example, surveys of high-risk sexual behavior and of HIV infection. Surveys generally considered exempt would include typical censuses, surveys of reproduction and contraceptive use, and standard nutrition surveys.

(2) Studies, such as surveys involving anthropometry and the gathering of human material through relatively non-invasive means, can be exempt as described in section 6(b)(1) above. Examples include such relatively benign procedures as collection of hair, nail clippings, external secretions, saliva, breast milk, oral, rectal or genital swabs, data via physical sensors applied to the surface of the body, etc. In and of itself, collection of such materials does not remove exemption. However, if such gathering of human material is more invasive, such as blood sampling, then this research is not exempt.

(3) Anthropologic/ethnographic research is considered survey research as broadly defined and the same rules apply. Clearly, informed consent in this context is often unnecessary, impractical, and may be waivable (See section 7(a) below).

(c) Epidemiologic Research – A number of epidemiologic studies are seen as survey research and treated accordingly **(22 CFR 225.101(b)(2))**. As described above (section 6(b)(1)), when no individual identifiers are collected or when data are not highly sensitive, this research is exempt. Epidemiologic approaches include the following:

(1) Case-Control and Cohort Studies. Generally treat as survey research.

(2) Surveillance. **22 CFR 225.101(b)(4)** exempts research involving existing publicly available data, records and specimens or if the investigator does not record data in an identifiable manner. Also, epidemiologic surveillance is often carried out as public health practice and not for the purpose of contributing to generalizable knowledge and thus does not meet the definition of research.

(3) Other epidemiologic studies utilizing existing data or specimens. Generally exempt under **22 CFR 225.101(b)(4)**.

(4) Outbreak Investigations. These are often carried out as a public health practice and often may not meet the definition of research. Otherwise treat as survey research, but recognize the need for expedited procedures (See section 7(b) below).

(d) Operations Research – Operational/operations research or service delivery research includes research on service delivery systems for the purpose of understanding how they function and how to improve efficiency and effectiveness. It includes making alterations or making observations of how services are provided among acceptable alternatives (e.g., comparing differences in clinic hours or evaluating the impact of adding new services.) It is generally exempt under **22 CFR 225.101(b)(5)**, which exempts research on public benefit or service programs. Nevertheless, operations research in highly sensitive areas involving issues of privacy, such as sensitive sexual behavior, may need special attention regarding matters such as confidentiality and often formal protection procedures should be applied. When research into service delivery includes working with staff, and involves gathering information about staff or otherwise having staff perform additional or different work than would ordinarily be part of what could reasonably be expected as part of their normal job or as part of normal service delivery improvement, then such data gathering about staff is also exempt.

(e) Research on Diagnostic Tests – Research to develop or assess diagnostic tests on blood, urine, etc., while not well-delineated in the Policy, can span several research categories.

(1) Research on existing specimens is generally exempt if sources are publicly available or subjects cannot be identified.

(2) Research on newly collected materials may be treated as survey research, but otherwise will not qualify for exemption per **22 CFR 225.101 (b) (2 or 3)** if it includes invasive procedures, such as blood collection.

(3) Research on existing standard of care diagnostic methods (e.g. comparing two techniques for diagnosing Chlamydia, both of which are commonly used in programs) may be treated as operations research.

(4) Other diagnostic research, such as a new test versus an existing test, may be considered experimental biomedical research when the results of such testing will potentially lead to important treatment changes for the individual.

(f) Education Research – Education research involving special subjects, such as children and mentally disabled individuals, is covered by the Policy. Much educational research is exempted under **22 CFR 225.101(b)(1)**, including research in educational settings involving normal educational practices.

7. Balancing Protection with Burden

(a) Recognizing the importance and contribution of research to prevent much human mortality and morbidity, implementation of the Policy at USAID is intended to provide adequate protection of human research subjects, while avoiding imposition of undue burden on the research process and people. Common sense, practicality, and flexibility are essential, especially in areas other than experimental biomedical research (the original focus of development of the Policy) where there is no issue of causing appreciable physical harm. In the area of epidemiologic research, for example, informed consent may not be necessary nor practical and might pose a major impediment to conducting the research. **22 CFR 225.116** and **22 CFR 225.117** describe appropriate mechanisms for altering or waiving the informed consent procedure, which requires IRB approval. It might also well be reasonable in many instances of survey research for the informed consent procedure to consist simply of a legitimate statement that participation is voluntary and that information will be kept confidential. In circumstances where consent is required, but written consent is inappropriate in a given culture or population, verbal consent may be appropriate, but it must be witnessed and documented in writing.

(b) Additional situations call for practicality. For example, where a series surveys or other similar research activities are highly standardized or systematized, review and approval of such research as a group or class by an IRB may be appropriate. Likewise, it may be reasonable to review and approve certain outbreak investigations as a class, in advance, because of the emergency nature of such research.

8. Right of Access of USAID Officials to Records

To implement and monitor human subjects research activities properly, it is essential that USAID reserve the right to speak with subjects and inspect any relevant records, and to prohibit research which presents unacceptable risks. Appropriate language to that effect must be included in contracts, grants, and other support documents, as well as in informed consent documents.

9. Compliance

(a) All research activities involving human subjects that are funded by USAID must adhere to the procedures set forth in the Policy, or have a system that provides "at least equivalent" protection which has been approved by the AA/GH or designee. Compliance with USAID human subjects procedures is the primary responsibility of the organization receiving USAID support. To help ensure observance of USAID's human subjects procedures by such recipients, appropriate language must be included in funding documents, when appropriate.

(b) Unless the research is conducted under an applicable Federal-wide Assurance (FWA) or qualifies as affording "at least equivalent" protection as described in section 5 above, the recipient must provide USAID with a satisfactory written "assurance" that it will comply with the requirements set forth in the Policy. An assurance such as from a primary USAID-supported institution can also cover the activities of collaborating institutions. As described in **22 CFR 225.103(b)(1)**, the assurance must include: a statement of principles governing the institution's responsibilities, designation of one or more IRBs, a list of IRB members, written procedures which the IRB will follow, and written procedures for ensuring prompt reporting of unanticipated problems to the IRB. Assurances may be for a single research project or for multiple projects.

200mbe_122606_cd46