Chapter 4
Federalwide Assurances

This chapter describes the University of Southern California (USC) Federalwide Assurances of compliance maintained with the Office for Human Research Protections (OHRP)/Department of Health and Human Services (DHHS). The University is required to enter into this agreement because it receives federal funding for research involving human subjects.

4.1 Federalwide Assurance (FWA)

A Federalwide Assurance (FWA) is a binding written agreement between USC and OHRP. It states that the University is guided by the ethical principles of the Belmont Report and will comply with federal regulations 45 Code of Federal Regulations Part 46, or simply 45 CFR 46 for all federally funded human subjects research. The UPIRB and the HSIRB each have FWAs with OHRP (click here to view).

USC complies with requirements stipulated by other federal agencies when they serve as sponsors or have oversight of research conducted at USC. For a list of applicable federal regulations, refer to Appendix M.

The USC IRBs are registered in the OHRP/FDA IRB database.

4.2 Specific FWA Requirements

FWA requirements must be met before OHRP/FWA is issued. These requirements pertain to the Institution, the intuitional official, and the IRBs:

- All human subjects research conducted under the auspices of USC will be guided by the ethical principles of The Belmont Report
- The FWA applies to all federally funded research in which USC is engaged. Refer to Section 4.5 – Engagement in Research
- The FWA requires compliance with the Federal Policy for Protection of Human Subjects (45 CFR 46)

- The USC IRBs have written procedures for reporting unanticipated problems involving risks to subjects or others, serious or continuing noncompliance with federal regulations or IRB requirements and suspension or termination of IRB approval. USC must also ensure that a qualified person or persons determine research is exempt from IRB review. Finally, the USC IRBs have clear written procedures for conducting IRB initial and continuing review; approving research; reporting IRB findings to the investigator and Institution; determining which projects require review more than annually; how the IRBs ensure that changes to ongoing research are reported promptly and are not initiated without IRB review and approval (except when necessary to eliminate apparent immediate hazards to subjects)

- The FWA grants authority to the IRBs to approve, require modifications to or disapprove covered human subject research

- The FWA expects detailed informed consent requirements for research conducted under the auspices of USC

- The FWA requires that USC secure assurances from other Institutions participating in collaborative research with University investigators when applicable

- The FWA requires that the University secure written agreements of commitment relevant to human subject protection policies and USC IRB oversight if the investigator is not an employee or agent of the University and the USC IRB agrees to review the research

- The FWA requires that the University provide the IRB with resources and professional and support staff sufficient to carry out their responsibilities under the assurance

- The FWA recommends that the Institutional Official, IRB Administrator(s) and IRB Chair(s) complete a training module detailing major responsibilities of these individuals

- The FWA recommends that the University establish educational training and oversight mechanisms to ensure that research investigators, IRB members and staff and other appropriate personnel maintain continuing knowledge of, and comply with, relevant ethical principles, relevant federal regulations, OHRP guidance, other applicable guidance, state and local laws and University policies for the protection of human subjects

- The FWA details the conditions under which the FWA must be renewed

4.3 Responsibilities Defined under the FWA

The Federalwide Assurance also describes the responsibilities of the Institution, the Designated Institutional Official, the Institutional Review Boards and the investigator, which are detailed below. All investigators at USC are expected to conduct research in accordance with the provisions of the Federalwide Assurance and ensure that the rights and welfare of the individuals involved are protected. Faculty members who assign or supervise research conducted by students are responsible for overseeing the research to ensure that students adequately safeguard the rights and welfare of subjects and conduct the research as approved.

Investigator Responsibilities

The investigator is responsible for acquiring the appropriate knowledge regarding human subject protections, ethics, federal regulations, training, and monitoring to conduct his/her proposed research. The PI must assure that key study personnel are adequately trained and knowledgeable regarding human subject protections, ethical considerations, and federal regulations applicable to the proposed research. The PI is responsible for complying with the training, monitoring, and human subject research guidance as outlined in the FWA and USC IRB policies and procedures.

IRB Committee Responsibilities

The IRB Committee is to review all human subjects research activities and document findings regarding ethical considerations, scientific merit, adherence to federal regulations and IRB policies and procedures. The IRB Committee must review and

monitor ongoing human subjects research for adherence to the Federal regulations and IRB policies and procedures.

IRB Staff Responsibilities

In addition to routine IRB staff duties, the OPRS/ IRB staff will participate in ongoing auditing (refer to Section 19.3 – Audits and Assessment) and monitoring activities to assure adherence to the federal regulations. The IRB staff will participate in the revisions of the IRB policies and procedures as applicable.

IRB Administration Responsibilities

All information provided under Federalwide Assurances must be updated at least every five years, even if no changes have occurred, in order to maintain an active Assurance approved by OHRP. Amendments to the Assurance are to be reported promptly to OHRP. This includes changes to IRB Committee rosters, IRB Chair/Vice Chair, or a legally recognized entity of USC. USC will maintain policies and procedures reflecting the current practices of the IRB in conducting reviews and approvals under its Assurance. These policies and procedures will be maintained and kept current by the USC OPRS. They will be reviewed and revised as needed at least every three years. Changes in policy are to be finalized by the Executive Director of OPRS.

The IRB's budget will be reviewed annually, by the Executive Director of OPRS, and the Vice President of Research and modified, as necessary, to accommodate the volume and type of research reviewed, education, space, facilities, and staff.

4.4 FWAs and the "Unchecked Box"

As discussed in Section 4.1 – Federalwide Assurance (FWA), a Federalwide Assurance is a binding agreement between USC and OHRP, the federal agency responsible for human subjects protection. It states that the University is guided by the ethical principles of the Belmont Report and will comply with federal regulations 45 CFR 46 for all federally funded human subjects research.

FWAs may include research that is not federally funded but this is optional.

When this option is selected, the assurance is inclusive of all research regardless of funding source as well as unfunded research. Institutions that select this option often face substantial regulatory burdens without the benefit of additional human subjects protection. Further, regulations for human subjects research primarily address biomedical research. Adapting regulations to social behavioral research often results in additional hurdles with little, if any, benefit to subjects.

USC, like many universities and Institutions, has also chosen to limit the scope of its FWA. The choice to do so is commonly referred to as "unchecking the box" in reference to the box (Item 4b in an FWA) that is filled in when not federally funded studies are included in FWAs. "Unchecking the box" does not eliminate the ethical requirement for IRB review of human subjects research but rather places the responsibility for oversight of non-federally funded and unfunded research with the Institution. The Human Subjects Research protections are equivalent whether the box is unchecked. Reporting requirements, however, may vary.

Unfunded projects for which Subpart A is not applied are all minimal-risk. These projects are all reviewed under the USC Flexibility Policy or are reviewed similar to Subpart A criteria.

4.5 Engagement in Research

The USC IRBs define engagement in research according to OHRP's 2008 guidance on the engagement of Institutions in research and OHRP's 2011 Correspondence on "Non-engaged Scenarios".

An Institution becomes "engaged" in human subjects research when its employees or agents (all individuals performing institutionally-designated activities or exercising institutionally-delegated authority or responsibility, including faculty and students):

- Intervene or interact with living individuals for research purposes
- Obtain individually identifiable private information for research purposes [45 CFR 46.102(d),(f)]
- Obtain the informed consent of human subjects

An Institution is automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases the awardees Institution bears ultimate responsibility for protecting human subjects under the award.

IMPORTANT NOTE: The USC IRBs require review by a USC IRB and by the IRB(s) at other location(s) (if the other Institution is "Engaged in the Research") regardless of funding, unless an IRB Authorization Agreement (IAA) is required or obtained.

Examples of Engaged Research

(For more examples see the OHRP 2008 Guidance for Engaged Research):

In general, Institutions are considered engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would need to hold or obtain OHRP-approved FWAs and certify IRB review and approval to HHS) when the involvement of their employees or agents in that project includes any of the following:

- Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (awardee Institutions), even where all activities involving human subjects are carried out by employees or agents of another Institution

- Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures. Examples of invasive or noninvasive procedures include drawing blood; collecting buccal mucosa cells using a cotton swab; administering individual or group counseling or psychotherapy; administering drugs or other treatments; surgically implanting medical devices; utilizing physical sensors; and utilizing other measurement procedures [See scenarios B.(1), B.(2), and B.(3) in OHRP guidance for limited exceptions]

- Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment. Examples of manipulating the environment include controlling environmental light, sound, or temperature; presenting sensory stimuli; and orchestrating environmental events or social interactions [See scenarios B.(1) and B.(3) in OHRP guidance for limited exceptions]

- Institutions whose employees or agents interact for research purposes with any human subject of the research. Examples of interacting include engaging in protocol dictated communication or interpersonal contact; asking someone to provide a specimen by voiding or spitting into a specimen container; and conducting research interviews or administering questionnaires [See scenarios B.(1), B.(2), B.(3), and B.(4) in OHRP guidance for limited exceptions]

- Institutions whose employees or agents obtain the informed consent of human subjects for the research

- Institutions whose employees or agents obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research. It is important to note that, in general, Institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects research are considered engaged in the research, even if the Institution's employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:

    - observing or recording private behavior

    - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another Institution

    - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators

In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. [See scenarios B.(1), B.(2), B.(3), B.(7), B.(8), B.(9), and B.(10) in OHRP guidance for limited exceptions.]

Examples of NOT Engaged Research

(For more examples see the OHRP 2008 Guidance for Engaged Research):

Institutions would be considered **not** engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS) if the involvement of their employees or agents in that project is **limited to one or more** of the following. The following are scenarios describing the types of institutional involvement that would make an Institution **not** engaged in human subjects research; there may be additional such scenarios:

1. Institutions whose employees or agents perform commercial or other services for investigators provided that **all** of the following conditions also are met:

    a. the services performed do not merit professional recognition or publication privileges

    b. the services performed are typically performed by those Institutions for non-research purposes

    c. the Institution's employees or agents do not administer any study intervention being tested or evaluated under the protocol

    The following are some examples, assuming the services described would not merit professional recognition or publication privileges:

    - an appropriately qualified laboratory whose employees perform routine serum chemistry analyses of blood samples for investigators as a commercial service
    - a transcription company whose employees transcribes research study interviews as a commercial service
    - a hospital whose employees obtain blood through a blood draw or collect urine and provide such specimens to investigators as a service
    - a radiology clinic whose employees perform chest x-rays and send the results to investigators as a service

2. 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 (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:

    a. the Institution's employees or agents **do not** administer the study interventions being tested or evaluated under the protocol

    b. the clinical trial-related medical services are typically provided by the Institution for clinical purposes

    c. the Institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research

    d. when appropriate, investigators from an Institution engaged in the research retain responsibility for:

        i. overseeing protocol-related activities

        ii. 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

    Note that Institutions (including private practices) not initially selected as research sites whose employees or agents administer the interventions being tested or evaluated in the study—such as administering either of two chemotherapy regimens as part of an oncology clinical trial evaluating the safety and effectiveness of the two regimens—generally would be engaged in human subjects research (see scenario B.(3) in OHRP guidance for a limited exception). If such an Institution does not have an FWA, its employees or agents may be covered by the FWA of another Institution that is engaged in the research through an Individual Investigator Agreement. See http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf.

3. Institutions (including private practices) not initially selected as a research site whose employees or agents administer the study interventions being tested or

evaluated under the protocol limited to a one-time or short-term basis (an oncologist at the Institution administers chemotherapy to a research subject as part of a clinical trial because the subject unexpectedly goes out of town, or is unexpectedly hospitalized), provided that all of the following conditions also are met:

a. an investigator from an Institution engaged in the research determines that it would be in the subject's best interest to receive the study interventions being tested or evaluated under the protocol

b. the Institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research

c. investigators from the Institution engaged in the research retain responsibility for:

   i. overseeing protocol-related activities

   ii. ensuring the study interventions are administered in accordance with the IRB-approved protocol and

   iii. ensuring appropriate arrangements are made for reporting protocol-related data to investigators at the engaged Institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol **and**

   iv. an IRB designated on the engaged Institution's FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an Institution not selected as a research site

4. Institutions whose employees or agents:

   a. inform prospective subjects about the availability of the research

   b. provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects' consent for the research or act as representatives of the investigators

c. provide prospective subjects with information about contacting investigators for information or enrollment and/or

d. seek or obtain the prospective subjects' permission for investigators to contact them

An example of this would be a clinician who provides patients with literature about a research study at another Institution, including a copy of the informed consent document, and obtains permission from the patient to provide the patient's name and telephone number to investigators.

5. Institutions (schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by investigators from another Institution. Examples would be a school that permits investigators from another Institution to conduct or distribute a research survey in the classroom; or a business that permits investigators from another Institution to recruit research subjects or to draw a blood sample at the work site for research purposes.

6. Institutions whose employees or agents release to investigators at Institution identifiable private information or identifiable biological specimens pertaining to the subjects of the research. Note that in some cases the Institution releasing identifiable private information or identifiable biological specimens may have institutional requirements that would need to be satisfied before the information or specimens may be released, and/or may need to comply with other applicable regulations or laws. In addition, if the identifiable private information or identifiable biological specimens to be released were collected for another research study covered by 45 CFR part 46, then the Institution releasing such information or specimens should:

   a. ensure that the release would not violate the informed consent provided by the subjects to whom the information or biological specimens pertain (under 45 CFR 46.116), or

   b. if informed consent was waived by the IRB, ensure that the release would be consistent with the IRB's determinations that permitted a waiver of informed consent under 45 CFR 46.116 (c) or (d)

   Examples of Institutions that might release identifiable private information or identifiable biological specimens to investigators at another Institution include:

- schools that release identifiable student test scores
- an HHS agency that releases identifiable records about its beneficiaries and
- medical centers that release identifiable human biological specimens

Note that, in general, the Institutions whose employees or agents **obtain** the identifiable private information or identifiable biological specimens from the releasing Institution would be engaged in human subjects research. [See scenario A. (6) in OHRP guidance]

7. Institutions whose employees or agents:

    a. obtain coded private information or human biological specimens from another Institution involved in the research that retains a link to individually identifying information (such as name or social security number), and

    b. are **unable** to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, for example:

        i. the Institution's employees or agents and the holder of the key enter into an agreement prohibiting the release of the key to the those employees or agents under any circumstances

        ii. the releasing Institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the Institution's employees or agents under any circumstances, or

        iii. there are other legal requirements prohibiting the release of the key to the Institution's employees or agents

For purposes of this document, *coded* means that:

- identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (the code), and

- a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens

Although this scenario resembles some of the language in OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens, it is important to note that OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens addresses when research involving coded private information or specimens is or is not research involving *human subjects*, as defined in 45 CFR 46.102(f) (see http://www.hhs.gov/ohrp/policy/cdebiol.html). As stated in Section II of the OHRP guidance, the Guidance on Engagement of Institutions in Human Subjects Research should only be applied to research projects that have been determined to involve human subjects and that are not exempt under HHS regulations at 45 CFR 46.101(b).

8. Institutions whose employees or agents access or utilize individually identifiable private information **only** while visiting an Institution that is engaged in the research, provided their research activities are overseen by the IRB of the Institution that is engaged in the research.

9. Institutions whose employees or agents access or review identifiable private information for purposes of study auditing (a government agency or private company will have access to individually identifiable study data for auditing purposes).

10. Institutions whose employees or agents receive identifiable private information for purposes of satisfying U.S. Food and Drug Administration reporting requirements.

11. Institutions whose employees or agents author a paper, journal article, or presentation describing a human subjects research study.

Investigators should review all information included in the OHRP 2008 Guidance and 2011 Correspondence on "Non-engaged Scenarios". For additional questions or further clarification, investigators can contact the IRB.

IRB Approval at a Non-USC Site Engaged in Research

USC faculty/staff/students conduct research at other sites, both domestic and international. When USC is engaged in research with another Institution, alternative arrangements for IRB review may be used (see Section 4.6 – IRB Authorization Agreements and Appendix J – IRB Requirements for Research with Other Sites).

If non-USC sites are engaged in research (45 CFR 46) and have their own IRB(s) or equivalent ethics board, the USC IRB expects the non-USC sites to obtain their own IRB review for research carried out at their site, unless an IRB Authorization agreement is sought or obtained.

When conducting research at a non-USC site, USC investigators are required to provide the following information in the iStar application:

- Site name and address
- Description of activities that will take place at the site
- Whether the non-USC site has an IRB
- Confirmation of the IRB's and/or equivalent authority's approval to conduct the research
- Approved informed consent form(s) and recruitment documents, if appropriate

Helpful Link

- OHRP Guidance on Engagement of Institutions in Human Subjects Research http://www.hhs.gov/ohrp/policy/engage08.html

4.6 IRB Authorization Agreements

An IRB Authorization Agreement is an arrangement in which one Institution relies on another Institution's IRB for initial approval and continued oversight of specified research.

IRB Authorization Agreements are required in the following circumstances:

- Non-USC site without its own IRB relies on USC's IRB:

    - Under the terms of the USC Federalwide Assurance, when research is conducted at a non-USC site without its own IRB and the site agrees to rely on the USC IRB review and approval, an IRB Authorization Agreement must be signed by both Institutions

      Note: an IRB Authorization Agreement is not required if the research is not federally funded and is not subject to FDA regulations, unless the outside Institution requests an Agreement. If requested by the outside Institution, USC will comply with the request. Additionally, USC may require an IRB Authorization Agreement at its discretion

- USC is "engaged" in the research, the risk occurs at the non-USC site, and the site has its own IRB:

    - When USC is engaged in the research, (USC may be the recipient of Federal funding) and the greatest level of risk to study subjects occurs at the non-USC site, USC may agree to rely on the non-USC site for IRB approval and continued oversight. This requires an IRB Authorization Agreement between USC and the non-USC site and includes the same information noted above. This policy assumes the IRB at the non-USC site will have the required reviewer expertise. If it does not, the IRB with the required reviewer expertise will be selected from among the engaged Institutions. Any IRB reserves the right to conduct its own review. An alternative option, if OHRP permits on a case-by-case basis, is for USC to waive the engagement obligation under 45CFR46 and forego any responsibility for approval and continued oversight of the research.

      Note: an IRB Authorization Agreement is not required if the research is not federally funded and is not subject to FDA regulations, unless the outside Institution requests an Agreement. If requested by the outside Institution, USC will comply with the request. Additionally, USC may require an IRB Authorization Agreement at its discretion.

- When conducting multi-site research sponsored by the Department of Defense (DOD), a formal agreement between Institutions is required to specify the roles and responsibilities of each party.

IRB Directors facilitate the IRB authorization agreement process and are responsible for:

- executing the authorization agreements
- sending a copy of the agreement to the IRB at the non-USC site
- sending a copy of the agreement to the USC PI to include the agreement in their IRB application

The Office of Research maintains copies of signed IRB Authorization Agreements.

For help or more information, contact the appropriate IRB office.

Helpful Links

- IRB Authorization Agreement (long form)
  https://oprs.usc.edu/files/2013/01/IRB_Authorization_Agreement_020411_Clean.doc
- IRB Authorization Agreement (short form)
  http://oprs.usc.edu/files/2013/01/IRB_Authorization-1.doc
- Required IRB Documents for Research with Other Sites
  https://oprs.usc.edu/files/2013/02/IRB-Required-Documents-for-Research-with-Other-Sites.pdf

Chapter 5:

Conflicts of Interest

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