Wayne State University Human Investigation Committee	
Subject	Initial Protocol Submission Requirements
Form Date	July 2008 (Rev. 07/19/10)
Approvals	General Counsel 11/17/06, Steering Committee 12/07/06, Administrative Approval 03/06/07, General Counsel 03/14/08. Administrative Approval 07/14/08, General Counsel 07/17/08, Administrative Approval 09/30/10

Background

All research that involves human participants must be reviewed and approved by the Wayne State University (WSU Institutional Review Board (IRB) prior to the implementation of research in accordance with the Department of Health and Human Services (DHHS) regulations at 45 CFR 46.108(b), the Veteran's Administration (VA) regulations at 38 CFR 16.108(b), and the Food and Drug Administration (FDA) regulations at 21 CFR 56.108(b). The Wayne State University Institutional Review Board uses the primary and secondary reviewer system [OHRP Guidance 71] and conducts continuing review of approved research at intervals appropriate to the degree of risk, but not less than once a year. Based on the determination of level of risk, the IRB may require additional review at more frequent intervals. The date for continuing review will be based on the date of IRB approval. [VHA 12005 7(b)]. The IRB criteria for review are based on the type of protocol being submitted and will comply with regulations or guidance for a specific federal agency (e.g., ICH-GCP, Department of Defense, the Department of Education, the Department of Energy, the Environmental Protection Agency, etc.). Investigators should consult the applicable regulation for additional information and/or counsel (NOTE: The HIC website (Sections 16 "References") provides a link to these federal agencies and more). The website also provides the latest information on new/updated policies and procedure, federal regulations, etc. HIC contact numbers are also available on the website for those who require additional education and training.

Scope

This Policy/Procedure applies to all behavioral or biomedical human subject research activities by WSU employees, faculty, and students or by individuals who are members of WSU affiliate institutions.

Definitions

Generalizable knowledge - Determination as to whether the activity will contribute to "generalizable knowledge" is often based on whether the data will be disseminated by means of publication or presentation. This should not be the sole factor used to make a determination, however. In general, OHRP gives guidance that if the data will be used to draw conclusions related to a larger entity, then the activity is considered "research."

Human participant (subject)

1. Under DHHS regulations "human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information.
2. Under FDA regulations "human subject" means an individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be either a healthy individual or a patient. For research involving medical devices a human subject is also an individual on whose specimen are investigational device is used.
3. *Experimental subject (as defined by the Department of Defense)* – "An activity for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32CFR.210.102 (f) reference (c). Examples of interventions or interactions include, but are not limited to: a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose."

Note: Investigators conducting human participant research must satisfy DHHS regulations [45 CFR 46], FDA regulations [2 CFR 50 and 56], and VA regulations [38 CFR 16] regarding the protection of human subjects [participants]in research, as applicable. DHHS regulations [45 DFR 46102(f)] and VA regulations [38 CFR 16.102(f)] define a human subject as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual; or (2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (e.g. venipuncture) and manipulations of the participant or their environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and participant/subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the participant is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human participants.

A *clinical investigation* is defined by FDA regulations [21 CFR 56.102(c)] as any experiment that involves a *test article* and one or more *human subjects [participants]* and that either is subject to requirements for prior submission to the FDA, or is not subject to requirements for prior submission to the FDA under the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
Research submitted to the HIC Office will undergo a pre-review to first determine if the research involves human participants. Criteria for this review can be found on the HIC website, "What is Human Participant

Research?" Research that does not meet the criteria, will be returned to the researcher with a memo of explanation for the return, based on federal regulations.

Research

1. Under DHHS regulations, "research" means a systematic investigation, including development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
2. Under FDA regulations research 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 under section 505(i) or 520(g) of the Food, Drugs, and Cosmetics Act, or need not meet the requirements for prior submission to the FDA under these sections of the Food, Drug, and Cosmetics 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. For research involving drugs, an experiment is any use of a drug, except for the use of a marketed drug in the course of medical practice, and is defined as a systematic investigation designed to develop or contribute to generalizable knowledge.

Note: If the research activity does not quality under any of the above circumstances, then the activity would not need to be submitted and reviewed by the HIC. If a PI has questions about whether or not a research activity requires IRB review, consultation with the Human Investigation Committee (HIC) office is strongly recommended.

Risk – the probability of harm, injury, or loss (e.g. physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Risks can be classified in one of the following categories:

- Physical – risks that may arise from the use of test agents such as chemicals or therapeutic drugs, devices, physical agents (including radiation), and clinical procedures;
- Psychological – risks that may arise from the utilization of behavioral questionnaires or surveys, interview interactions, the collection of sensitive data, or the emotional stress of study participation;
- Social – risks that may arise from actual or potential breaches of confidentiality or anonymity such as harm to interpersonal relationships, damage to reputation or social standing, or exposure to legal sanctions; or
- Legal – risks that may lead to legal action against the participant such as investigation or arrest;
- Economic – risks that may affect an individual's financial status, employment status or employability, or insurability.

Systematic investigation - A systematic investigation may include research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

A ***Test article*** [56 CFR 21.102(i)] is defined as any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, drug, and Cosmetic Act.

Types of Review

The types of IRB review include: 1) exemption from review; 2) expedited review; and 3) full board review. In addition, IRB notification is required for the emergency single-time use of a non-approved investigational drug or biologic [21 CFR 312.34(b), 21 CFR 312.36], a non-approved investigational device [21 CFR 812.62] or a Humanitarian Use Device [21 CFR 814.124(a)]. (See HIC Policy/Procedure "Emergency and Single Time Use of a Test Article, Humanitarian Use Device")

- Exempt Review: Exempt review can be requested for research where the entire project falls within one or more of the six specific regulatory categories set forth in 45 CFR 46.101(b) and satisfies all Institutional policies and procedures. An investigator cannot exempt his/her research project from HIC review and concurrence. Instead, the HIC chairperson or his/her designee must determine that a project is eligible for exemption. (See HIC Policy/Procedure "Exempt Procedures".) Any study that the HIC chairperson or his/her designee believes is not exempt must be reviewed by either an *expedited* or *full board* review process. A research project meeting the criteria for exemption cannot start until after the HIC chairperson or his/her designee has given "concurrence" of exemption. Retroactive "concurrence" or review cannot occur. Approval of research under an exemption is given for an indefinite time period. Re-review is not required unless the investigator proposes changes to the exempt research project.
- Expedited Review: Expedited review can be requested for project activities that: (1) present no more than minimal risk to human participants; and (2) involve only procedures listed in one or more of the regulatory categories set forth in 45 CFR 46.110 and satisfies all Institutional policies and procedures. (See HIC Policy/Procedure "Expedited Review Procedures".)
- Full Board Review: A research proposal that does not meet the criteria for review by exempt or expedited process, must be reviewed by a WSU IRB. The HIC currently has five IRBs that review initial submissions. They include the following:
    - M1, which reviews adult medical protocols,
    - MP2 and MP4, which review adult and pediatric medical protocols,
    - B3, which reviews behavioral research only, and
    - PH1, which reviews adult and pediatric medical protocols

Criteria for initial IRB review and approval of research protocols are set forth by DHHS regulations at 45 CFR 46.111, 38 CFR 18.111, and FDA regulations at 21 CFR 56.111 and include: determining the level of risk to the participant, potential benefits, informed consent process and documentation, and safeguarding the participant's rights and welfare (i.e. safety monitoring, equitable selection, protection of privacy, and confidentiality and special protections for vulnerable populations). For research under ICH-GCP guidance (E6), the following criteria for evaluation are required: (1) Evaluation of the available clinical and nonclinical information on an investigational product is adequate to support the proposed clinical trial; and (2) the clinical trials are scientifically sound and described in a clear and detailed protocol.

Possible IRB Actions

After an in-depth review of the range of the research study, possible actions by the Institutional Review Board include:

- Approved;
- Specific minor reviews required
- Tabled; and
- Disapproved.

(See HIC Policy/Procedure "Outcome of Proposal Reviews by the IRB".)

Scientific Review

Before the HIC can review a protocol involving the use of human participants in research, the protocol must be reviewed for scientific merit by the Principal Investigator's (PI) department. The scientific review must address the following: (1) appropriate support will be provided for the research project including adequate facilities and staff, and (2) appropriate scientific and ethical oversight has been and will be provided, (3) the research uses procedures consistent with sound research design, (4) the research design is sound enough to yield the expected knowledge. Directions indicate that any comments or feedback related to this certification should be in writing and accompany the research proposal submission.

Various departments conduct this scientific review in different ways and the IRB will accept any of these methods as long as the Chair and/or his/her designee certifies by affixing his/her signature on the Protocol Summary Form that the scientific review has been completed and that the research has scientific merit and ensures that appropriate support and resources will be provided to conduct the study. Research initiated by an investigator without a designated department must obtain certification from a department with the expertise to determine the scientific merit of the study (see HIC Policy/Procedure "Investigator Initiated Research").

All research involving cancer and human participants must be reviewed and approved by the Protocol Review Committee of the Karmanos Cancer Institute (PRMC). The approval letter must accompany the protocol submission.

All research involving human participants at the John D. Dingell VA Medical Center (JDD VAMC), must be reviewed and approved by the JDD VAMC Clinical Investigation Committee (CIC) before the protocol can be reviewed by the HIC. If the VA research involves cancer, an approval from the PRMC (see above) should be obtained before submission for review by the CIC. The approval letter(s) must accompany the protocol submission.

All research involving human participants whose Principal Investigator is a faculty member in the Department of Psychiatry and Behavioral Neuroscience, must first be reviewed and approved by the Department Review Board. That approval must accompany the protocol submission.

While not a scientific review, the Detroit Medical Center (DMC) conducts a mandatory pre-review on all protocols to be conducted in their institutions. This process involves a review for liability and privacy issues.

This review can occur concurrently with the IRB review process. A study cannot start until both the HIC and DMC reviews have been completed and official approval notice of both have been received.

All research involving human participants at the Oakwood Healthcare System must be reviewed by the Clinical Trials Office. A Research Project Administrative Approval (RPAA) document must be included with all submissions to the HIC. Resident projects require a separate review from the Resident Research Review Committee and that approval must be included (in addition to the RPAA) with a protocol submission to the HIC.

HIC Procedures

The IRB must review research at intervals appropriate to the degree of risk, but not less than once per year. Upon careful review of the submitted material, the IRB Committee will determine if the research project requires review more often than annually [45 CFR 46.103(b)(4)(ii);21 CFR 56.108(a)(1); VHA 1200.5.7.d(2)]. (See HIC Policy/Procedure "Criteria for Determining Frequency of Review")

The IRB Chair will assign reviewers with appropriate scientific or scholarly expertise as appropriate to the risk level of the protocol. If the appropriate expertise is not available on the committee then a qualified alternate, or consultant will be obtained to review the protocol. (See HIC Policy/Procedure "Expectations of IRB Membership".)

Consultant(s)

If deemed necessary, an IRB chair, in consultation with the HIC Chair and/or Associate Vice President for Research, will determine if additional scientific expertise or experience dealing with vulnerable populations is needed to conduct a research review. If a consultant is used to review a protocol, the following criteria apply:

- The consultant must either attend the meeting in which the protocol discussion takes place or submit the review information in writing;
- Any written information provided by the consultant will be maintained in the protocol file;
- The minutes will document the key information provided by the consultant;
- The consultant must meet the HIC Conflict of Interest policy requirements and will not participate in the review of protocols in which they have a conflict of interest, except to provide information requested by the IRB; and
- The consultant may participate in the IRB committee discussion but may not vote or be present when the voting takes place.

IRB Review Criteria for Approving Research

Before approving research that involves human participants, the IRB must determine that the following criteria are met:

- Risks to participants are minimized.
- Risks to participants are reasonable in relation to anticipated benefits.

- Selection of participants is equitable or justified for the center aims.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
- Informed consent will be appropriately documented.
- When appropriate, there are adequate provisions to protect the privacy interests of participants (an individual's interests in being left alone and free of physical or psychological intrusions or intrusions on information).
- When appropriate, there are adequate provisions to protect and maintain the confidentiality or participant data.

The factors that are reviewed to determine if the above criteria have been met include but are not limited to the following:

- Whether the research meets the FDA and DHHS definition of human subject research (see definition above), or, when applicable, the DoD definition of Experimental Subject;
- Whether the research has scientific merit
- A determination of the level of risk to the participants which determines that:
    - Risks to participants are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose participants to risk
    - Risks to participants are minimized, when appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes
    - Risks to participants are reasonable in relation to the potential benefits, if any, to participants, and the importance of the knowledge that might be expected to result
- If research is conducted via the Environmental Protection Agency (EPA), review to ensure that all regulations have been met (see 40 CFR 26)
- If research is conducted in association with a Department of Defense component (DoD), review to ensure that all regulations have been met (see DoD Directive 3216.02, and HIC Policy "Department of Defense Requirements for Human Subject Research Protection."
- For research sponsored by the DoD, when appropriate, the research plan makes adequate provisions for monitoring the data, including:
    - The IRB has considered the need for appointment of a research monitor:
        - Required for greater than minimal risk, although the IRB can require this for a portion of the research or studies involving no more than minimal risk if appropriate.
        - The independent research monitor is appointed by name.
        - The research monitor has authority to:
            - Stop a research study in progress.
            - Remove individuals from study.
            - Take any steps necessary to protect the safety and well-being of participants until the IRB can assess the situation.
- If research is conducted under any other federal agency, review of the regulations must be reviewed to ensure compliance. Links to many of the federal agencies are available on the HIC website.
- If the research involves treatment or interventions, the research plan makes adequate provisions for monitoring the data to ensure the safety of participants;

- The purpose of the research;
- The setting in which the research will be conducted;
- Whether prospective participants are vulnerable to coercion or under influence;
- The inclusion/exclusion criteria;
- Participant recruitment and enrollment procedures;
- The influence of payments to participants; or
- For VA research, whether the record should be flagged to protect the safety of the participant.

Exempt/Expedited Review

When reviewing research under and expedited review procedure, the HIC Chair or designee receive and review a Medical Exempt Form or a Medical/Behavioral Protocol Submission Form, and all consent documents, notices/flyers, and advertisements. (See HIC Policy/Procedures, "Exempt Review Procedures," "Expedited Review Procedures".) The reviewer will first determine that the proposal meets federal requirements for exemption or for expedited review [45 CFR 46.110] and then will conduct an in-depth review of the following submitted materials to determine whether the research meets the criteria for approval (see above).

Submission Requirements for Exempt or Expedited Review

Materials for submission of a new protocol for Expedited Review to the HIC must include:

- A completed Medical Exempt Form or Medical/Behavioral Protocol Summary Form and required Appendices (as applicable);
- A full research protocol/grant proposal; and
- The following items, as applicable:
    - If accessing WSU medical records, a completed HIPAA Summary Form and, if applicable, a HIPAA Authorization Form;
    - Informed Consent/Assent/Information Sheet documents;
    - An Investigator's Drug Brochure;
    - Surveys, questionnaires, data collection instruments or other measurement tools;
    - Advertisements, notices, and flyers;
    - Recruitment Material;
    - Educational materials that will be distributed to participants;
    - Data and Safety Monitoring plan if applicable, or
    - If the research will be conducted outside of the local jurisdiction, the PI must submit verification of that jurisdiction's pertinent laws, regulations, requirements or definitions.

When needed, the HIC Chair or designee may request a consultant to provide additional expertise.

The Principal Investigator will be informed by the HIC Chair or his/her designee of the review results and will be informed of any specific requirements via e-mail or fax and also by mail (See HIC Policy/Procedure "Outcome of Proposal Reviews by IRB").

Full Board Review

The IRB Committee Chair evaluates each protocol to ensure that at least one IRB member knowledgeable about or experienced in working with vulnerable participants will be present at the meeting. The protocol will then be assigned to a primary and secondary reviewer based upon their expertise. If additional scientific or scholarly expertise or a reviewer knowledgeable about or experienced in working with prisoners or a vulnerable population is determined to be necessary by the IRB chair, then either an alternate reviewer or consultant will be part of the review process. The IRB Chair also has the option of deferring a protocol to another IRB meeting or to obtain consultation if there is not appropriate scientific or scholarly expertise at his/her IRB meeting.

For research sponsored by the Department of Education, when a research proposal funded by the National Institute on Disability and Rehabilitation Research, which purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research participants, the IRB must ensure that at least one person primarily concerned with the welfare of these research participants will be present at the meeting.

For research sponsored by the Department of Defense (DoD), should additional review for DoD sponsored survey research or survey research within the DoD is required, the following applies:

- Surveys typically require DoD Survey review and approval.
- When appropriate, the research protocol is reviewed and approved by the IRB prior to DoD approval.

The primary and secondary reviewer each receive the required documentation at least one week prior to the regularly scheduled IRB meeting. The primary reviewer is provided with all of the documents required for submission (see Submission Requirements below).

All IRB members receive a Medical/Behavioral Protocol Summary Form, a Narrative Summary, and all informed consent documents, notices/flyers, and advertisements. All information is available upon request, to any IRB member for use prior to or during the course of a discussion at a convened meeting. The additional information may be requested from the Research Compliance Administrator.

The IRB committee will conduct an in-depth review of the completed Medical/Behavioral Protocol Summary Form and all pertinent documents to determine whether the research meets the criteria for approval. The criteria that must be satisfied in order for the IRB to approve research include, among other things, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects (45 CFR 46.111). (See HIC Policy/Procedures “Expectations of IRB Membership”). Reviewers are provided direction to specific regulatory sites and/or HIC policy/procedure guidelines when appropriate (e.g., research funded by the DoD, EPA, etc.)

No official action can be taken at a meeting of an IRB in the absence of a quorum [a majority (e.g., membership of 13, quorum is 7; membership of 12, quorum is 7)]. Issues may be discussed, but an official vote cannot be taken until a quorum is present.

The Principal Investigator will be informed of the IRB Committee’s decision and any specific requirements via e-mail or fax and also by mail (first class or campus). (See HIC Policy/Procedure “Outcome of Proposal

Reviews by IRB") If a protocol is disapproved the PI has the opportunity to appeal that decision to the IRB Committee of record, either in person or in writing. The Committee will review the appeal at the next convened meeting, and inform the PI of their decision, in writing, within 30 days of the convened meeting.

All of the proceedings regarding review of the research protocol will be documented in the IRB minutes for the convened meeting. This includes full discussion of controversial issues and protocol specific examples to justify the decisions that are made.

The primary and secondary reviewers receive a copy of the Protocol Summary Form and all accompanying documents (listed below) as submitted by the PI approximately one week in advance of the IRB meeting. The IRB members at large will receive a copy of the Protocol Summary Form and accompanying documents. A copy of the full application is available, upon request, to any IRB member for use during the course of a discussion at a convened meeting. These documents may be requested from the Research Compliance Administrator.

Submission Requirements for Full Board Review

Materials for submission of a new protocol to the HIC must include:

- A Medical/Behavioral Protocol Summary Form and required Appendices (as applicable);
- A full research protocol/grant proposal; and
- The following items, as applicable:
    - If accessing WSU medical records, a completed HIPAA Summary Form and, if applicable, a HIPAA Authorization Form;
    - Informed Consent/Assent/Information Sheet documents;
    - An Investigator's Drug Brochure;
    - Surveys, questionnaires, data collection instruments or other measurement tools;
    - Advertisements, notices, and flyers;
    - Recruitment Material;
    - Educational materials that will be distributed to participants;
    - Data and Safety Monitoring plan if applicable, or
    - If the research will be conducted outside of the local jurisdiction, the PI must submit verification of that jurisdiction's pertinent laws, regulations, requirements or definitions.

Office Process

When a protocol submission is received, it is date stamped by HIC staff, checked for appropriate original signatures, logged into the Coeus database, and assigned an HIC Protocol tracking number. Deadlines and directions for submission are available on the applicable HIC form and can be found on the HIC website (www.hic.wayne.edu).