WRIGHT STATE UNIVERSITY

Policy	P6
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REVIEW OF HUMAN SUBJECTS RESEARCH BY THE INSTITUTIONAL REVIEW BOARD

POLICY

All research at the university involving human subjects shall be submitted to the IRB for review and must be reviewed at a convened meeting of a University IRB unless the IRB determines the research qualifies for expedited review or exempt status.

The role of the IRB is to protect participants in human subjects' research by assuring that the risks of research are proportionate to the value to the subjects involved in the research, that the research is ethical, and that it is conducted in accordance with the principles of the Belmont Report and federal, state, and local laws and regulations. See:

- http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
  (the Common rule governing federally funded research)
- http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm
  (the Belmont Report)
- http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  (FDA Regulations governing the protection of human subjects)
- http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  (FDA Regulations governing Institutional Review Boards)
- http://www.fda.gov/cdrh/devadvice/ide/index.shtml
  (FDA Regulations governing clinical trials and investigational devices)
- http://www.fda.gov/cder/guidance/index.htm
  (FDA Guidance Documents)

DEFINITIONS

The IRB shall use the following definitions to determine whether an activity shall qualify as human subjects' research requiring IRB review and approval. IRB staff will refer any questions about whether a proposed study qualifies as human subject research to the IRB chair, who will make a determination using the criteria listed below:

As used herein,

A human subject is an individual on whose specimen an investigational device is used.

Human Subjects Research shall include all activities which either:

1. Meet the Department of Health and Human Services' definition of 'research' as any 'systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge' and which involve person(s) who qualify as 'human subjects' within the meaning of relevant regulations (45 CFR 46.102.d) as any 'living individual about whom an investigator conducting research obtains

(i) data through intervention or interaction with the individual, or

(ii) identifiable private information, or data from which the identity of the subject is or may readily be ascertained by the investigator.' (45 CFR46.102(f)).

Thus, to meet the definition of research with human subjects, one or both of the following must be true:

a. The researcher is conducting a pilot study, a preliminary study, or other preliminary research.
b. The researcher has designed a study to collect information in a systematic way with the intention of contributing to a field of knowledge. (This does not mean that the study needs to be replicable, but rather that there is an intent to develop or contribute to a field of knowledge in a manner consistent with your discipline.)

And the researcher must be:

1. Interacting with living human beings in order to gather data about them, using methods such as interviews, focus groups, questionnaires, and participant observation, or
2. Conducting interventions with living human beings such as experiments and manipulations of subjects or subjects' environments, or
3. Observing or recording private behavior (behavior that individuals have a reasonable expectation will not be observed and recorded), or
4. Obtaining private identifiable information that has been collected about or provided by individuals, such as a school record or identifiable information collected by another researcher or organization.

Examples of Studies That May Not Meet the Definition

- Analysis of de-identified data
- Expert consultation

Key words in the definition of a human subject are "a living individual about whom" a researcher obtains information. Some interactions with people for the purpose of collecting information do not any collect

information about that person. For example, a researcher may contact a non-governmental organization to ask about its sources of funding.

- Program evaluations and quality improvement studies
  Not every study is designed to contribute to a field of knowledge. For example, if data are being collected to improve a program within an institution and will be used only for that purpose, the collection of that information would not constitute research with human subjects.
- Classroom research
  In classes teaching research methods such as fieldwork, statistical analysis, or interview techniques, students may be assigned to conduct interviews, distribute questionnaires, or engage in participant observation. If the purpose of these activities is solely pedagogical and they are not designed to contribute to a body of knowledge, the activities do not meet the definition of research with human subjects.

-OR-

2. Qualify under the Food and Drug Administration regulations as an "Investigational use" involving any use of an approved product in the context of a clinical study protocol (21 CFR 312.3(b)) and which involves one or more "human subjects" as defined in relevant regulations as individual(s) who are or become participant(s) in research, either as recipient(s) of a test article or as a control. A subject may be either a healthy human or a patient (21 CFR 56.102(e); 812.3(p)).

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and 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 reasonable expect will not be made public (for example, a medical record). Private information must b individually identifiable in order for obtaining the information to constitute research involving human subjects (i.e., the identify of the subject is or may readily be ascertained by the investigator.

Research activities subject to this policy shall include clinical investigations, defined as any experiment that involves a test article and one or more human participants and that is one of the following:

- o Subject to the requirements for prior submission to the FDA, or
- o Not subject to the requirements for prior submission to FDA, 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 marketing permit.

Clinical Investigations may be regulated by the Food and Drug Administration

under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, including any use of a drug, other than the use of an approved drug in the course of medical practice, and clinical investigations regulated by the Food and Drug Administration under section 520(g) of the Act, including any use of a medical device, other than the use of an approved medical device in the course of medical practice. For research being carried out at the VA, an investigational drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.

The decision chart from the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services attached to the end of this procedure can be helpful in determining whether a research proposal involves "human subjects" as defined in the HHS regulations (45 CFR 46_Common Rule). Protocols submitted to the IRB will be reviewed and the determination made if the proposed activity constitutes research involving human participants. If this is in the affirmative, the protocol will be reviewed and the results communicated to the investigator in the minutes of the IRB meeting. If the protocol is found to not constitute research involving human participants, the investigator will be notified by mail of this finding.

If the IRB receives a protocol for review after a human subjects research study has been completed, without prior IRB approval, the protocol will not be reviewed. The Investigator will be notified of the regulatory requirements requiring prospective IRB approval of human subjects research. The Investigator will be informed that the data may not be used for any publications, presentations, thesis, or dissertation requirements.

APPLICABILITY

1. This policy shall apply to all human subjects' research:

   a. Sponsored by the University (unless the research is conducted at another institution with which WSU has an "IRB Authorization Agreement" as specified in WSU's FWA and described below under "Cooperative Activities); or

   b. Conducted by or under the direction of any University employee or agent of the University in connection with his/her institutional responsibilities (unless the research is conducted at another institution with which WSU has an "IRB Authorization Agreement" as specified in WSU's FWA); or

   c. Conducted by or under the direction of any University employee or agent of the University using any University property or facility; or

   d. Involves the use of the University's non-public information to identify or contact human research subjects or prospective subjects.

2. Cooperative activities

    a. Cooperative activities relating to human subjects are those which involve Wright State University and another institution. Normally the research must be reviewed and approved by the IRBs at both institutions before it can be initiated. However, the IRB of one institution may rely on the IRB of the other institution under the following conditions:
        i. Both institutions have Federalwide Assurances (FWAs) approved by OHRP
        ii. Both institutions have entered into an Authorization Agreement (or equivalent document) that stipulates the responsibilities of both parties; and
        iii. The appropriate section of the FWA of the deferring institution designates the IRB of the approving institution.

    b. In the absence of these conditions, the PI must secure the approval of the IRB at each institution engaged in the research, and submit documentation of such approvals to the other IRBs. The IRB Coordinator will verify (via the OHRP website) that the other institution(s) has/have approved FWAs.

3. Material reviewed by the IRB

    a. New protocols

        i. A copy of the petition, summary of research, and all informed consent documents (including any advertisement/recruiting materials) are provided to all members of the IRB prior to each meeting for their review. Copies of all material submitted by the investigator are available to any IRB member upon requested. . For protocols submitted after March, 2009, all items are available to all members through WebCT.

        ii. Primary reviewers (3 per each new protocol) receive copies of all materials submitted. These include (as applicable):
            1. The Petition for Approval of Research
            2. The Study Protocol
            3. C.V. of the Primary Investigator (nonDCOP protocols)
            4. Sponsor's brochure (if applicable)
            5. The Grant Application (if applicable)
            6. Informed consent document(s)
            7. Study Materials for Subjects (i.e. questionnaires, surveys; if applicable)
            8. Advertising Copy (if applicable)
            9. DHHS-approved sample consent document (if applicable)
            10. DHHS-approved protocol (if applicable)

11. Previous reviewer's comments and investigator's responses (if applicable)
12. For VA studies, the VA addendum form documenting that all required VA requirements for human research have been met.

b. Modifications of previously approved protocols

i. All members of the committee are provided with a copy of the petition for amendment, supportive materials submitted explaining or justifying the amendment, and, if appropriate, the consent document with any revisions clearly indicated.
ii. Copies of all materials initially submitted for approval of the research are available to any committee member if requested. For protocols submitted after March, 2009, all items are available to all members through WebCT.

c. Continuing review of protocols

i. All members of the committee are provided with a completed continuing review questionnaire, a summary of previous protocol activities and future project plans, and copies of all Informed Consent documents, surveys and/or questionnaires currently being used.
ii. Copies of all material initially submitted for approval of the research are available to any committee member if requested. For protocols submitted after March, 2009, all items are available to all members through WebCT.

CRITERIA FOR APPROVAL BY THE IRB

In order to approve human subject's research covered by this policy, the IRB shall determine human research requirements are satisfied. For FDA-regulated research, FDA regulatory requirements must also be met. The IRB has the final authority to decide whether requirements have been met, to identify steps that must be taken to meet requirements, and to approve or disapprove the research. These requirements include:

1. Risks to participants are minimized:

a. By using procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk; and
b. Whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.
c. The PI must provide a plan for data safety monitoring in any situation in which participants might be at greater than minimal risk of harm, including when a drug or device is being tested for safety or effectiveness for marketing approval or in placebo-controlled trials or when marketed drugs are being tested for another indication or compared for safety or effectiveness. The level of detail in the plan

should be based on the degree of risk to research participants. Low risk studies, for example, may have simple plans. Multi-center trials generally have Data Safety Monitoring boards (DSMB). Safety Monitoring plans, including plans for DSMBs, should:

1. Describe how risks are minimized and how they are reasonable in relation to anticipated benefits to participants
2. Describe the data required to be reported and monitored
3. Describe how the data is to be reported, including a plan to assure reporting of adverse events and unanticipated problems involving risk to participants or others
4. List procedures for analysis and interpretation of data
5. Describe the frequency of monitoring. The IRB will evaluate the frequency of data review, whether after a specific length of time or after a specific number of participants are enrolled, based on the likelihood or magnitude of risks to participants
6. Describe how or by whom the data will be reviewed. The IRB will evaluate whether the method is appropriate based on the size and complexity of the research and magnitude of risk to participants. Most large multicenter trials have DSMBs. Smaller trials could have monitoring committees, an independent medical monitor or other investigator, or if there is no other monitoring individual or committee, the IRB can request periodic data or safety monitoring.
7. Describe any proposed actions to be taken for specific events that may be anticipated, i.e., unexpected toxicities of drugs or greater than anticipated side effects
8. Describe the data and safety information that will be provided to the IRB and the frequency with which it will be reported
9. Specify whether serious adverse events will be promptly reported to and evaluated by a data safety and monitoring process

2. Scientific or Scholarly Review by qualified individuals(s) has demonstrated that (a) the research uses procedures which are consistent with sound research design; (b) the research design is likely to answer the proposed scientific question, and (3) the importance of the knowledge expected to result justifies approval of the research. In addition, the IRB should determine if the investigator has sufficient time to conduct and complete the research and that the investigator has adequate staff and other resources, including facilities, to conduct the research.

3. Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its

responsibility.

4. Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly aware of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, and others, as designated by the IRB.

5. The investigator (or spouse or dependent children) or other person(s) responsible for the research do not have financial interests which may be a perceived or real conflict of interest. These include :

    a. A vested interest in any actual or potential commercial enterprise/business associated with any aspect of the protocol (other than patents)

    b. Equity interests in the sponsor of this study whose value, when aggregated for the immediate family, is greater than $10,000, **or** ownership, stock options or other financial interest related to the research of any value whose value can not be determined through reference to publicly available prices

    c. Payment by the sponsor greater than $10,000 to the investigator's performing organization(s) exclusive of the costs of conducting the study

    Ownership interest, stock options or other financial interest related to the research whose value, when aggregated for the immediate family, represents $\geq$5% interest in any single entity.

    d. Compensation related to the research whose amount is affected by the outcome of the research

    h. Board or executive relationship related to the research, regardless of compensation

    i. Direct payment by the sponsor to the investigator(s), their spouses or dependent children

    ii. Financial interest (other than patents) in nonsponsored research

6. Informed consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CRF 50.20, the law of the state where the research is conducted, and as required by University policy.

7. When investigators need to obtain consent from the legally authorized representative of an adult subject (i.e. to conduct essential research on problems that are unique to persons who are incompetent or who have an impaired decision-making capacity), such

consent will be obtained from one of the following:

a. A health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC) or similar document
b. A court-appointed guardian of the person

Such consent shall be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note. Should participants become competent during the duration of the study, their consent to continue in the research should be obtained when possible.

In the case of VA studies, consent by a legally authorized representative will be limited to situations where the prospective participant is incompetent or has impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note and:

a. Determination that a participant is incompetent or had an impaired decision-making capacity will be made by a legal determination or a determination by the practitioner, in consultation with the chief of service or Chief of Staff, after appropriate medical evaluation that the prospective participant lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
b. If the determination that the prospective participant lacks decision- making capacity is based on a diagnosis of mental illness, the investigator will obtain consultation with a psychiatrist or licensed psychologist.
c. The practitioner will explain the proposed research to the prospective participant when feasible.
d. Participants will not be forced or coerced to participate in a research study.

8. Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CRF 50.20, with the law of the state where the research is conducted, and in accordance with and to the extent required by University policy.

9. When appropriate, the protocol makes adequate provision for monitoring the data collected to ensure the safety of participants.

10. When appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data. This includes assuring that only private information essential to the research is collected; that the circumstances in which private information is collected are conducive to privacy; and that this information is maintained in a secure environment. When protected health information (PHI) is being collected, there must be documentation that authorization under the Health Insurance Portability Authorization Act (HIPAA) is to be obtained. If a waiver of this documentation is sought, the IRB must ascertain and document that the criteria for waiver have been met (see appendix)

11. When some or all of the participants are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. (see appendix)

12. Payments are appropriate as described below:

a. The amount of payment and the proposed method and timing of disbursement is neither coercive nor presents undue influence.
b. Credit for payment accruing as the study progresses is not contingent upon the participant completing the entire study.
c. Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study

For VA research:

- It is prohibited to pay participants to participate in research when the research is integrated with a patient's medical care and when there are no special demands on the patient beyond those of usual medical care.

However, participants may be paid when:

- The research is not directly intended to enhance the diagnosis or treatment of the medical condition for which the participant is being treated, and when the standard of practice in affiliated non-VA organizations is to pay participants in this situation;
- The research is a multi-institutional study and participants at collaborating non-VA organizations are paid for the same participation in the same study at the same rate proposed;
- In the opinion of the IRB, payment of participants is appropriate in other comparable situations; or the participant will incur transportation expenses that would not be incurred in the normal course of receiving treatment and are not reimbursed by another mechanism.

The following payments are prohibited

- Payments to professionals in exchange for referrals of potential participants ("finder's fees").
- Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") unless they are judged not to interfere with providing prospective participants with sufficient opportunity to consider whether to participate and do not increase the possibility of coercion or undue influence on investigators or

participants.

RESEARCH PERFORMED AT THE VETERANS AFFAIRS MEDICAL CENTER

Requirements for research involving human subjects that is to be carried out at the VA are described in the VHA Handbook 1200.05. The following is a brief summary concerning requirements for these studies:

1. All new protocols involving research at the VA will first be reviewed by the Coordinator for Research & Development. The C/R&D will review the submission to make sure that VA-specific requirements have been made, and will submit a copy summarizing this review with each protocol submitted.

2. Non-veterans will only be allowed to enter VA-approved research studies when there are insufficient veterans available to complete the study

3. The C/R&D will make a recommendation to the convened IRB specifying that the medical record should be flagged indicating the subject's participation in the research. Criteria for flagging the chart include participation in a drug study, other interventional trials, or research involving risk that other health care providers should be aware of. Criteria for not flagging the chart include retrospective chart reviews, one-time anonymous surveys, and studies that might be stigmatizing or place the subject at greater than minimal risk.. The IRB will notify the VA if they disagree with the recommendation of the R&D committee, with the recommendation open for discussion prior to the initiation of research.

4. The following categories of research are prohibited at the VA:

    - Projects involving fetuses, in utero or ex utero (including human fetal tissue)
    - Projects involving in vitro fertilization
    - Projects involving embryonic stem cells
    - Research that is "planned emergency research (e.g. the investigator is seeking a waiver of prospective informed consent)
    - Projects involving a recruitment strategy that requires "cold calls" to veterans and/or asking veterans for social security numbers during a phone call

5. The following categories of research require a CRADO (Chief Research and Development Officer) waiver or have other special requirements (see VHA Handbook 1200.5, Appendix D for specific requirements that must be met for each of these categories):

    - Research involving children
    - Research involving prisoners
    - International research
    - Research involving pregnant women

- Research involving participants with impaired decision-making capacity
- Research involving banking of human biological specimens (see www.research.va.gov/programs/tissue_banking-FAQ.pdf)

EXPIRATION OF APPROVAL

Approval for new research will be granted for a period of up to one year minus one day from the date on which the protocol was initially approved. A shorter time may be specified based on the recommendation of the IRB. Reasons for a shorter period for review may include, but are not limited to, high-risk protocols, projects involving unusual types of risk to participants, projects involving vulnerable populations, and projects conducted by a P.I. who has previously failed to comply with IRB requirements. If restrictions have been placed on a protocol which require response or action from an investigator, the date of approval remains that of the meeting at which the protocol was approved (with restrictions) and not the date that the restrictions were met.

CONTINUING REVIEW

The IRB will conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year. The degree of risk, the inclusion of any vulnerable populations, occurrence of problems with the research, and determination of noncompliance will all be taken into consideration when determining the length of the interval for continuing review. Individuals as specified for vulnerable populations will be in attendance at any meeting where research involves vulnerable participants. The process for Continuing Review is completely described in a separate procedure.

CONSULTANTS

When the IRB or the IRB chair determines that there is not at least one member with sufficient expertise among the membership to review a human subjects research protocol, the IRB chair must obtain an individual or individuals with appropriate expertise review and comment on the human subjects research. The consultation may be by telephone conference at a convened meeting, by written opinion, or by attendance at a meeting. If the consultant has been asked to review a full board protocol, the consultant may be asked to be available to answer questions at a convened meeting but will be excused from the meeting for vote on the human subjects' research. The consultant will not be counted for purposes of a quorum and may not vote on the human subject's research. For expedited research, a consultant will be asked to give a verbal or written report to the screening committee. The committee will take this report into consideration in making a recommendation regarding the protocol, including possible referral to a convened meeting of the IRB.

If the appropriate expert is not available among the faculty of the university, an individual with the required expertise will be identified in the community, or if no one is available, within another community or academic institution.

Consultants will be asked to comply with the Conflict of Interest Guidelines for IRB members.

CONTINGENT APPROVALS AND SUBSTANTIVE MODIFICATIONS

The IRB may approve the study dependent upon minor wording changes as specified by the IRB or standard language as previously approved by the IRB. The IRB will specify that the IRB Coordinator, Chair or other IRB member will review the changes submitted by the researcher. If the changes conform to the specification of the IRB as reported in the meeting minutes, the designated reviewer will authorize the release of the approval letter. The IRB will be informed of the approval. If the designated reviewer determines that the changes do not correspond exactly with the requirements of the IRB, the research will be reviewed again by the IRB to determine whether it will be approved.

When the convened IRB requests substantive modifications or clarifications that are directly relevant to the regulatory criteria for approval, the response must be returned to the convened IRB for review and approval.

FURTHER APPROVALS

Human subject research covered by this policy that has been approved by the IRB may be subject to further appropriate review and approval or disapproval by officials of the University. However, those officials may not approve the human subjects research if it has not been approved by an IRB.

VAMC research that has been approved by the IRB always requires further approval by the VA R&D committee before any research is initiated.

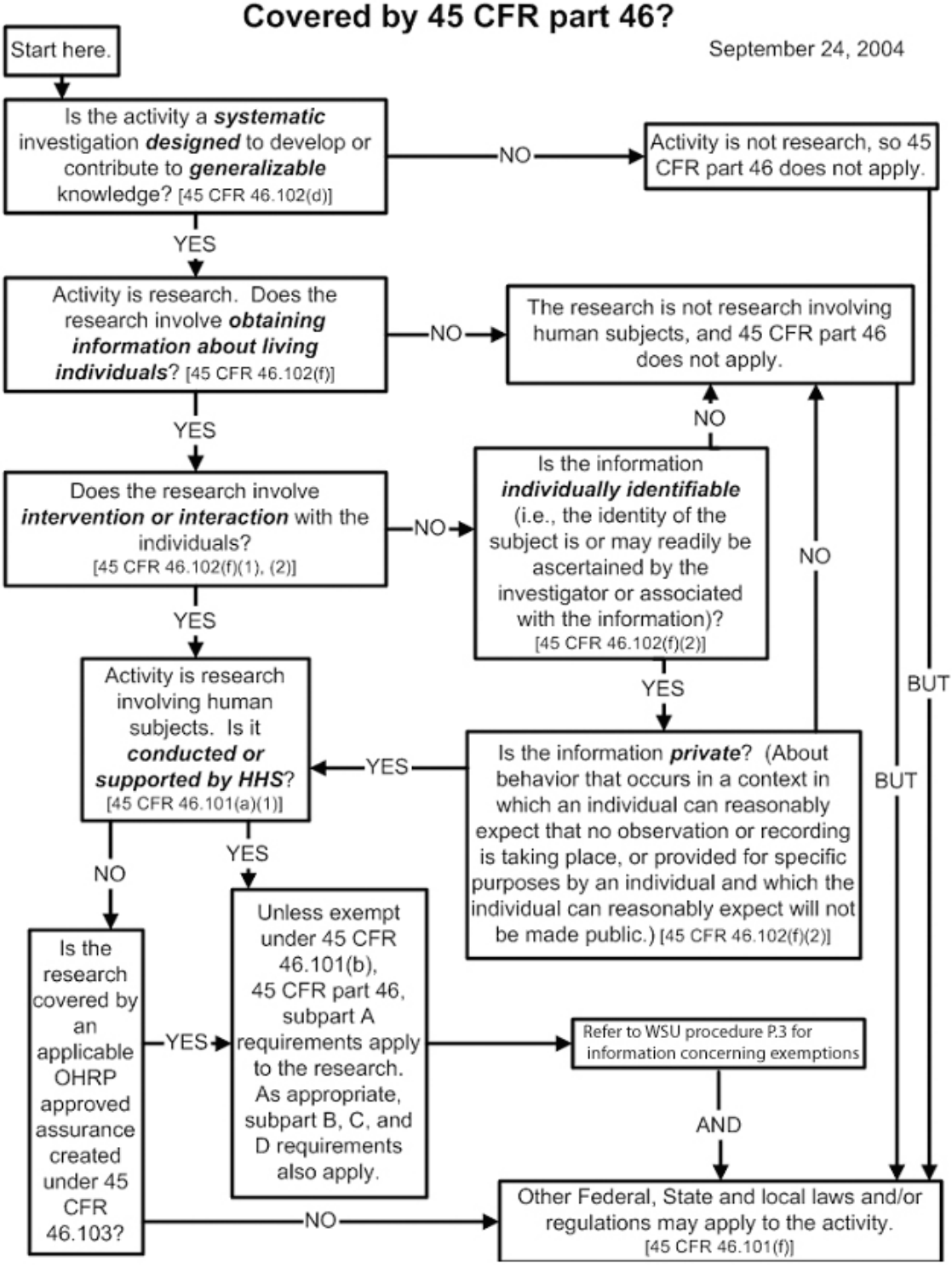
DOCUMENTATION

The minutes of the IRB meetings document separate deliberations, actions, and votes for each protocol under regular review. Within 21 days of the IRB meeting, the minutes of the meeting will be available for review. Minutes will be approved at a convened IRB meeting. The approved minutes will also be distributed to the WSU Institutional Official and the VA Research Office.

Applicable Regulations:
45 CFR 46.107-109
21 CFR 56.103, 107-109
45 CFR 46 et seq.
45 CFR 164.501
21 CFR 50.3(g)
21 CFR 56.102(e)
21 CFR 312.3(b)

21 C.F.R 812.3(p)

Chart 1: Is an Activity Research Involving Human Subjects Covered by 45 CFR part 46?



Note: examples of investigations which would NOT be considered to be subject to IRB review include:

1. Research involving deceased persons (e.g. autopsy studies)
2. Research involving insufficient data to provide generalizable knowledge. Examples:
    a. Patient case reports involving 3 or fewer cases
    b. Interviews with a single subject for an oral history, or with multiple subjects provided that the purpose of the histories is not to draw conclusions, inform policy, or generalize findings

When doubt exists about whether a proposed project meets the definition of human subject research, the Institutional Review Board (via Research and Sponsored Programs) should be consulted.

3. Appendix to IRB Procedure 6

Guidance for Chair of IRB when Conducting Meeting:

Questions to Ask with Each Protocol Reviewed:

1. Length of time recommended for next review?

2. Who will be required to review if revisions have been requested?

3. Are there any vulnerable populations to be enrolled?
   If yes, see below to answer required questions/ensure that criteria have been met.

4. Was any waiver of all or part of the elements of informed consent made (these questions must also be asked any time deception is used)? If yes, review the criteria for granting waiver to ensure that all have been met:
   a. The research involves no more than minimal risk to the participants;
   b. The waiver or alteration will not adversely affect the rights and welfare of the participants;
   c. The research could not practicably be carried out without the waiver or alteration;
   d. The research is not subject to FDA regulation.
   e. That if deception is used, the subjects will be debriefed after participation
   f. That for any person for whom consent has not been obtained, whenever appropriate, additional pertinent information will be provided after participation

   5. Has a waiver of informed consent <u>documentation</u> been requested? This can be waived only if the one of the following two criteria are met:

      a. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
      b. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

5. Has a waiver or request for alteration of the Privacy Rule been requested? This may be appropriate in certain cases (e.g. if a study involved the use of PHI pertaining to numerous individuals where contact information is unknown, and it would be impracticable to conduct the research). The IRB can waive or partially

waive the Authorization (e.g. HIPAA authorization) only if all the following criteria have been met (note: this must be documented in the minutes):

a. The PHI use or disclosure involves no more than minimal risk to the privacy of individuals based on at least the presence of (1) an adequate plan presented to the IRB to protect PHI identifiers from improper use and disclosure; (2) an adequate plan to destroy those identifiers at the earliest opportunity, consistent with the research, absent a health or research justification for retaining the identifiers or if retention is otherwise required by law; and (3) adequate written assurances that the PHI will not be reused or disclosed to any other person or entity except (a) as required by law, (b) for authorized oversight of the research study, or (c) for other research for which the use or disclosure of the PHI is permitted by the Privacy Rule
b. The research could not practicably be conducted without the requested waiver or alteration
c. The research could not practicably be conducted without access to an use of the PHI.

The IRB must specifically describe the PHI for which use or access has been determined to be necessary in connection with the specific research activity.

Questions to answer with reported Adverse Events

1. Was the event serious, unanticipated, or research related?
2. Are we satisfied with the description and reporting of the AE, and the action taken by the PI?
3. Are there additional risks that need to be included in the risk section of the consent form?
4. Is there a real or potential increase in risks indicating a need to halt enrollment, close the study, or modify the study design?
5. Do we need an outside expert to review or comment?
6. Is the study a VA study, where VA-specific reporting must occur (if the event was serious, unanticipated and research-related)

Questions to ask with any reported unanticipated problems

1. Does the problem involve noncompliance?

   Note*: Noncompliance* is defined as the failure to follow the federal regulations governing human subject protection requirements (e.g., 45 CFR 46, 21 CFR 50, 21 CFR 56) or the requirements and determinations of the IRB.

   Serious noncompliance is defined as one or more of the following:
   - Harm to research subjects
   - Exposure of research subjects to a significant risk of substantive

harm

- Compromised privacy and confidentiality of the subjects
- Damage caused to the scientific integrity of the data collected
- Willful or knowing misconduct on the part of the investigator
- An adverse impact on ethical principles

Continuing noncompliance is defined as willful, repeated noncompliance by an individual investigator either on a single protocol or multiple protocols.

Examples of noncompliant activities include:

- Conducting research without IRB approval (i.e., before approval obtained, after research expires, without IRB approval)
- Non-use or mis-use of consent forms (i.e., consent not obtained, wrong consent form used)
- Failure to follow approved protocol
- Changing protocol without IRB approval
- Failure to report unanticipated problems or serious adverse events
- Failure to maintain adequate records
- Inadequate training of investigators or research staff
- Other failure to follow university polices and federal regulations

2. Does the problem involve a risk to participants or others
3. Is the problem serious, or is it continuing in nature?
    a. If the answer to any of questions 1-3 is "yes" did the investigator take appropriate action?
    b. If not, what further action is required?

Questions to be asked with items submitted for information:

1. Do any of these items indicate that there is an increased risk to the subjects based on the information supplied?
2. If so, what action should be taken with respect to this information?

Questions to be asked with vulnerable populations:

1. Is the research to be carried out at the VAMC?

    a. Is the research allowable (see P_6 above)
    b. If allowable, have all the requirements in the VHA Handbook 1200.5, Appendix D, been met for the research?
    c. Has the Coordinator for Research & Development documented that all the requirements have been met?

2. For non-VAMC research, ensure that all the appropriate questions/requirements in the following sections have been answered/met.

3. Did a person experienced with the population review the protocol?

4. For research with incompetent individuals and individuals with impaired decision making capacity, were all the following conditions met?

a. The research can only be carried out by including subjects who are incompetent or with impaired decision-making capacity
b. The research entails no significant risks, tangible or intangible, or if risk is present, there is a greater possibility of direct benefit to the participant
c. There are procedures in place to ensure that the participants legally authorized representative are well informed about their role and obligations to protect the subject
    i. The representative will be given descriptions of both the research and their obligations to the subject
    ii. The representatives will be told that their obligation is to try and determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in he subject's best interest
d. An option to reconsent is give to any subject who becomes competent during the study
e. There is acknowledgement that if an incompetent subject resists participation, he/she cannot be forced or coerced to participate.
f. The following criteria must be met and documented in order to approve research involving adults unable to consent according to VA regulations:

    i. The determination of incompetence or impaired decision-making capacity was made in accordance with the following requirements:
        1. The practitioner, in consultation with the chief of service, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
        2. Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.
        3. Disclosures required by VA Handbook 1200.05 to be made to the subject, by the investigator, must be made to the subject's surrogate.
        4. If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

ii. Only incompetent persons or persons with impaired decision-making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research.
iii. The investigator has demonstrated to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as participants.
iv. Incompetent persons or persons with impaired decision-making capacity are not being proposed as participants simply because they are readily available
v. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
vi. Procedures have been devised to ensure that participant's representatives are well-informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision-making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

5. For research with minors:

§46.404 Research not involving greater than minimal risk.

Were adequate provisions made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408?.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Were **all** of the following criteria met?

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Were **all** of the following criteria met?

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Refer to regulations. It would be highly unusual for us to be involved in this sort of research.

§46.408 Requirements for permission by parents or guardians and for assent by children.

1. Are the children able to provide assent?
2. Were adequate provisions made for soliciting the assent of the children (if appropriate)
3. Will the permission of both parents or the guardian be sought? (note: one parent can give permission if the other parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the care and custody of the child
4. Have the conditions for how assent will be documented be described, and are these adequate?

Note: Research involving children must not be conducted by VA investigators while on official duty, or at VA or approved off-site facilities, unless a waiver has been granted by the Coordinator for Research & Development. If a waiver is granted, it must then be conducted in accordance with DHHS Subpart D: Additional DHHS Protections for Children Involved as Subjects in Research (source: 48 FR 9818, March 8, 1983; 56 FR 28032, June 18,1991)

6. For research with prisoners:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

> (i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
>
> (ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
>
> (iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or
>
> (iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into

Note: Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is supported by HHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a). The institution must send to OHRP a certification letter to this effect, which should also include the name and address of the institution and specifically identify the research protocol in question and any relevant HHS grant application or protocol. HHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to the institution on behalf of the Secretary under 45 CFR 46.306(a)(2).

Note: Research involving prisoners must not be conducted by VA investigators while on official duty, or at VA or approved off-site facilities, unless a waiver has been granted by the Coordinator for Research & Development. If a waiver is granted, then it must be conducted in accordance with DHHS Subpart C: Additional DHHS protections pertaining to biomedical and behavioral research involving prisoners as subjects

7. For research with pregnant women or fetuses (note, the VA does not allow research focusing solely on the fetus), have the following conditions been met?

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

(k) The researchers have supplied adequate study-specific information to ensure that adequate provision has been made to monitor the risks to the subject and the fetus

(l) The researchers have supplied adequate study-specific information to ensure that adequate consideration has been given to the manner in which potential subjects are going to be selected, and that adequate provision has been made to monitor the informed consent process.

(m) In order to approve VA research involving pregnant women ,the following provisions must be made to monitor the actual consent process by procedures such as:

- Overseeing the process by which the consent of individuals is obtained either by:
    - Approving enrollment of each individual
    - Verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed.
- Monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.
- Consent is obtained from the mother and father, except that the father's consent need not be secured if:
    - The purpose of the activity is to meet the health needs of the mother.
    - His identity or whereabouts cannot reasonably be ascertained.
    - He is not reasonably available.
    - The pregnancy resulted from rape.

8. For research with neonates:

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

(3) Individuals engaged in the research will have no part in determining the viability of a neonate.

(4) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those

individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.