

HUMAN RESEARCH PROTECTION PROGRAM DEPARTMENTAL POLICY AND PROCEDURE

6.2 IRB APPROVAL OF RESEARCH

RESPONSIBLE OFFICE: Human Research Protection Program Department (HRPPD)

EFFECTIVE DATE: November 5, 2021

I. POLICY STATEMENT

- A. This policy and procedure sets forth the human research approval criteria for the IRB and the procedures for the approval of research process.
- B. Review of research includes consideration of specific determinations required for approval (approval criteria) as defined in applicable federal, state and local regulations and further explained below.
- C. All UTSW IRBs may review any IRB related issues: new studies (initial review), re-approve active studies (continuation review), requests to modify previously approved research, reports of unanticipated problems involving risks to subjects or others, complaints that may indicate that a research subject's rights, safety or welfare may have been or were adversely affected, reports of possible serious or continuing noncompliance, or other issues.
- D. Approval criteria are used during initial and continuing review and as appropriate during review of modifications to previously approved research. In order to approve research, the IRB (the Full Board or Expedited Reviewer) shall determine that all required determinations of approval (45 CFR 46.111 and/or 21 CFR 56.111) are satisfied.
- E. The appropriate Full Board or Expedited Reviewer must consider deferral, disapproval (full board only), suspension (in part or in toto) or termination of research. These actions are considered (as appropriate) during initial and continuing review and during review of modifications to previously approved research (if necessary on an urgent basis) where evaluation of the above criteria results in unresolved controverted issues considered substantive for example but not limited to:
 1. Research not being conducted in accordance with the IRB's requirements.
 2. Research that has been associated with unexpected serious harm to participants.
- F. When study approval is suspended or terminated, the IRB or the person ordering the suspension will:
 1. Consider actions to protect the rights and welfare of currently enrolled participants.
 2. Consider whether procedures for withdrawal of enrolled participants take into account their rights and welfare (e.g., making arrangements for medical care off a research study, transfer to another investigator, and continuation in the research under independent monitoring).
 3. Consider requiring the investigator to inform current participants of the termination or suspension.

4. Consider requiring the investigator to report any adverse events or outcomes to the IRB.
- G. If IRB approval of a specific study expires, the IRB must decide whether investigators must stop all research activities involving human subjects or whether it is in the best interests of already enrolled subjects to continue to participate in the research. The IRB will consider the best interests of subjects either individually or as a group. If the IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities related to that study, including intervening or interacting with subjects, or obtaining or analyzing identifiable private health information about human subjects.

II. SCOPE

- A. This policy and procedure applies to the IRB, which will review all non-exempt human research activities and determine the appropriate action. The review of human research activities will occur only in the context of a duly constituted and operating convened IRB or under expedited procedure in the name of a duly constituted and operating IRB consistent with the applicable requirements of HRPP Policies and Procedures (2.1. INITIAL REVIEW OF RESEARCH, 2.2. CONTINUING REVIEW OF RESEARCH and 2.3 MODIFICATIONS TO RESEARCH). For the purpose of this policy, both the convened board and the expedited review procedure will be referred to as the “IRB”.

III. PROCEDURES FOR POLICY IMPLEMENTATION

- A. Procedures for review are incorporated into 2.1. INITIAL REVIEW OF RESEARCH, 2.2. CONTINUING REVIEW OF RESEARCH and 2.3 MODIFICATIONS TO RESEARCH.
- B. Criteria for approval
1. Criteria 1: Risks to subjects, that may result from the research, are minimized
 - a. Initial Review The IRB uses component analysis to evaluate each new submission for risks and determines whether the probability or magnitude of each risk is the least possible for addressing the research aims and do not unnecessarily expose participants to risk by considering multiple factors, including for example:
 - 1) Whether the risks listed in the submission adequately reflect the complete list of the risks that are reasonably expected to result from the research.
 - 2) Whether the study design is scientifically sound and likely to answer the research questions (purpose of the research).
 - 3) Whether an alternative research design would reduce the likelihood/magnitude of harm while still achieving the purpose of the study.
 - 4) Whether the rationale and details of research procedures are adequately described and acceptable.

- 5) Whether there is a clear differentiation between research-only procedures and standard of care / standard evaluation.
 - 6) Whether fewer procedures would reduce the likelihood/magnitude of harm while still achieving the purpose of the study.
 - 7) If the research procedures include those which may be performed for diagnostic or treatment (non-research) purposes, the IRB evaluates whether risks exist whose probability or magnitude can be reduced by using the non-research procedures rather than requiring the subjects to undergo the same procedures for both research and clinical purposes.
 - 8) Whether adequate preliminary data exists to justify the research.
 - 9) Whether sufficient justification exists for the research.
 - 10) Whether the rationale for the proposed study population is reasonable, and whether an alternative population would reduce the likelihood/magnitude of harm while still addressing the purpose of the study.
 - 11) Whether fewer participants could answer the scientific question(s).
 - 12) Whether plans for data analysis are defined and justified.
 - 13) Whether members of the research team are qualified to perform the research procedures.
 - 14) Whether adequate staff, facilities or other provisions are available to protect the rights and welfare of research subject and to deal with possible harmful sequelae. For example: If the investigator is not a clinician, when appropriate, the protocol must have provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties that may include, but not be limited to:
 - i. Reviewing the data, adverse events, and new study findings; and
 - ii. Making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject)
 - 15) Whether criteria for enrollment and withdrawal are appropriate in relation to the anticipated risks.
- b. Continuing Review -The IRB reviews each request for re-approval to identify information related to new risks or changes to previously identified risks. The IRB determines whether the probability or magnitude of each risk continues to be the least possible for addressing the research aims and does not unnecessarily expose participants to risk by considering multiple factors, including for example:
- 1) Detailed description of the reasons for withdrawal of subjects from the study since the last IRB review.

- 2) Previously reported and new (unreported) unanticipated problems involving risks to subjects or others (UPIRSOs).
 - 3) Information from an independent safety monitoring entity (e.g., medical monitor, Data Safety Monitoring Board, etc.) (if applicable).
 - 4) Information from the multi-center sponsor (if applicable).
 - 5) Information from the literature or other sources.
 - 6) Information contained in the summary of the progress of the study in the local progress report that may address risks or problems.
- c. Review of proposed modifications - The IRB evaluates whether a proposed modification includes new risks or changes to existing risks and determines whether the probability or magnitude of each risk is the least possible for addressing the research aims. Additionally, the modification shall not unnecessarily expose participants to risk by considering the factors used during Initial Review to determine that risks are minimized. In this case, the factors listed for Initial Review are used only as applicable to the changes contained in the modification.
- d. In addition, the IRB may include other aspects of the research that may minimize risks and don't fit into the criteria listed above.
2. Criteria 2: Risk Level
- a. The IRB evaluates all sources of risk that may result from the research and determines the appropriate risk level for the study as a whole. Depending on the research activity under review, the overall risk level may change over the course of time a study is conducted (further discussed in the Initial Review of Research Policy and Procedure). The overall risk level must be one of the following levels:
 - 1) minimal risk
 - 2) more than minimal risk or;
 - 3) minor increase over minimal risk (only when considering children in research)
3. Criteria 3: The risks to subjects that may result from the research are reasonable in relation to anticipated benefits to subjects (if any) and the importance of the knowledge that may reasonably be expected to result.
- a. Initial Review
 - 2) The IRB uses component analysis to evaluate each submission for benefits and determines whether the probability and magnitude of each benefit is the greatest possible, given the research aims (maximizes benefits).
 - 3) Components are divided into either:
 - i. those that offer the prospect of direct benefit to research participants, or

- ii. those designed solely to answer the research question(s).
- 4) The IRB confirms that each of the components that do not offer a direct benefit contributes to answering the research question(s). For each of these components, the IRB determines whether the risks are justified only by the potential benefit associated with the knowledge to be gained.
- 5) The IRB determines whether the direct benefits listed in the submission accurately reflect the complete list of anticipated benefits to the subject from the research, or by a monitoring procedure that is likely to contribute to the subject's well-being. For each of the components that do offer the prospect of direct benefit where that benefit does not justify the risk, the IRB determines whether the risks are justified by the potential benefit associated with the knowledge to be gained, and whether the components meet the criteria for research equipoise (general uncertainty whether the study procedures or accepted practice is preferred).
- b. Continuing Review - The IRB evaluates each request for re-approval (continuing review) for changes in the study components, risks or benefits and determines whether the changes affect the component analysis.
- c. Review of proposed modifications - The IRB uses component analysis in the same general manner as during initial review. In this case, the factors listed for initial review are used only as applicable to the changes contained in the modification.
- 4. Criteria 4: The selection of participants is equitable.
 - a. Initial Review - The IRB evaluates the following to determine whether selection criteria are equitable and recruitment practices promote voluntariness:
 - 1) The purposes of the research and setting in which the research will be conducted
 - 2) That the study objectives, not the vulnerabilities or privileges of participants, guide inclusion criteria and choice of targeted populations.
 - 3) That the inclusion/exclusion criteria impose fair and equitable burdens and benefits.
 - 4) Limited English Proficiency (LEP).
 - i. In accord with the Belmont Report the UTSW IRB will consider if an injustice would occur when some benefit to which a person is entitled would be denied without good reason or when some burden would be imposed unduly.
 - ii. Based on federal policies and ethical considerations, the IRB should not routinely allow investigators to exclude LEP persons from research studies without acceptable justification.
 - iii. Investigators are justified in excluding LEP persons only if there is:

- a) A sound scientific reason for excluding LEP persons,
 - b) A sound ethical reason for excluding LEP persons, or
 - c) If there are insufficient resources to include LEP persons and the proportion of LEP subjects is very low.
 - d) For example the IRB may decide to allow exclusion of LEP persons if the benefit exists outside the study (e.g., standard care is considered effective not generally declined due to toxicity and excluding LEP persons would not result in irreversible health problems or extreme suffering. Should excluding LEP persons have the potential for irreversible health problems or extreme suffering strong justification would be required to consider this to be a valid argument.)
- 6) Whether prospective participants may be vulnerable to coercion or undue influence (e.g., lack mental capacity or voluntariness) and, if so, a description of appropriate additional safeguards is included
 - 7) Whether additional actions, limitations or safeguards are appropriate to protect the safety and welfare of the subjects
 - 8) That participant recruitment and enrollment procedures and materials are fair and equitable
 - 9) Payments made to subjects (both the amount and schedule) should be structured to reduce any possible undue influence. The IRB will take into consideration the following when determining acceptable compensation:
 - i. the schedule of payment;
 - ii. the number of hours or visits completed;
 - iii. the number of procedures completed;
 - iv. the amount of discomfort, inconvenience and/or expenses to the subject that is anticipated as appropriate;
 - v. whether or not a bonus payment is offered for completing all procedures.
 - vi. The IRB may not allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.
- b. Continuing Review - New information provided is reviewed to determine whether the selection of subjects continues to be equitable, including for example:
 - 1) Any new information related to the actual subject recruitment information that indicates an issue with equitable selection of subjects
 - 2) Any new information related to issues of coercion or undue influence

- 3) Any new information relevant to protecting vulnerable populations (e.g., children, prisoners, pregnant women/fetuses, etc.)
 - c. Review of Proposed Modifications - The IRB evaluates whether a proposed modification includes changes that affect the equitable selection of subjects or vulnerable populations by considering the factors used during initial review. In this case, the factors are used only as applicable to the changes contained in the modification.
5. Criteria 5: Informed consent will be sought from each prospective subject or legally authorized representative (LAR).
- a. Initial Review and Review of Proposed Modifications
 - 1) The IRB evaluates whether the study plan meets the requirements for full informed consent and represents legally effective informed consent of the subject or the subject's legally authorized representative, unless:
 - i. the IRB finds and documents that informed consent can be waived (45 CFR 46.116(c) or (d)); or
 - ii. the IRB finds and documents that the research meets the requirements of the HHS Secretarial waiver under 45 CFR 46.101(i) that permits a waiver of the general requirements for obtaining informed consent in a limited class of research in emergency settings. When informed consent is required, it must be sought prospectively.
 - 2) The IRB evaluates whether the plan for obtaining consent could be improved to better ensure participant understanding and voluntary decision-making.
 - 3) The consent process must be presented in a manner that enables a person to voluntarily decide whether or not to participate as a research subject.
 - 4) The circumstances surrounding consent must provide sufficient opportunity for the subject or LAR to consider whether or not to participate.
 - 5) The circumstances surrounding consent must minimize the possibility of coercion or undue influence.
 - 6) Persons who conduct the consent interview, and/or obtain consent are acceptable, given the nature of the study.
 - 7) The information given to the subject/representative must be in language understandable to the subject/representative (may also be reviewed as part of Criteria 6 – consent documentation).
 - 8) The consent does not contain exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence. If the study sponsor has provisions for injury compensation, the consent

information provides this information (may also be reviewed as part of Criteria 6 – consent documentation).

- 9) Unless deemed not appropriate or waived/altered by the IRB, informed consent will provide the information described in the general requirements, basic elements, and additional elements of informed consent (45CFR46.116(a-c)) (may also be reviewed as part of Criteria 6 – consent documentation).
- 10) The assent of children, incompetent persons or those determined to have impaired decision-making capacity must be appropriate

b. Continuing Review - The IRB evaluates whether informed consent continues to meet the requirements for full informed consent and represents legally effective informed consent by determining the circumstances that might require repeating or supplementing the informed consent process. (For example, if the protocol design or risks have changed, or if a substantial period of time has elapsed between the time consent was obtained and the study began)

6. Criteria 6: Informed consent will be appropriately documented.

a. Initial Review and Review of Proposed Modifications (as appropriate) - The IRB reviews the written consent form(s) to be used to document informed consent (unless consent was waived). The form(s) are intended to provide a written representation of the information used in the informed consent process and are later available for the subjects' future reference.

1) Except as provided in the section on waiver of a signed consent form of this section, the consent form must be one of the following:

- i. A written consent document that embodies the elements of informed consent required by the IRB under Criteria 5; Informed Consent (above) is the preferred method of documenting consent.
- ii. IRB review of research includes the consent process to ensure that the person obtaining consent gives either the subject or the representative adequate opportunity to read it before it is signed, regardless of whether it had already been read to the subject.
- iii. While not the preferred method of documenting consent, a short form written consent process may be used to document consent as described in the 3.4 INFORMED CONSENT OF SUBJECTS WITH LIMITED ENGLISH PROFICIENCY.

2) Where waiver of the requirement to obtain a signed consent form is requested, the IRB must determine the following in order to approve the request:

- i. The IRB agrees that:
 - a) For non-FDA regulated studies, the only record linking the subject and the research and the principal risk would be the

potential harm resulting from a breach of confidentiality (the PI must include provision for asking each subject whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern),

- b) For non-FDA regulated studies, If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained, or
- c) The research procedure(s) for which the waiver is being requested presents no more than minimal risk and involves no procedures for which written consent is normally required outside the research context.

- ii. The IRB determines whether the waiver of consent documentation applies to some or all subjects.

- iii. The IRB determines whether the investigator must provide subjects with a written statement regarding the research.

b. Continuing Review - New information is reviewed to determine if the study continues to meet this requirement, for example:

- 1) New information in the progress report related to whether the consent document remains accurate, complete and up-to-date.
- 2) New information in the progress report related to whether the consent document attached to the progress report is the current approved consent.
- 3) Significant new findings in the progress report related to the subject's willingness to participate are added to the consent document process.
- 4) New information in the progress report related to any identified problems related to consent are adequately resolved.
- 5) New information in the progress report related to the consent process in general.

7. Criteria 7: The research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.

a. Initial Review and Review of Proposed Modifications (as appropriate)

- 1) The IRB determines whether Data and Safety Monitoring is required because:

- i. The study is more than minimal risk or;

- ii. Data and Safety Monitoring is required by NIH, FDA, or funding agency or;
 - iii. The IRB/IRB Expedited Reviewer decides that a plan to monitor collected data is required to ensure the safety of subjects.
 - 2) The IRB determines whether the local plan for collecting, monitoring, analyzing and reporting safety data is acceptable, given the nature of the study and the anticipated risks of the research.
 - 3) The IRB determines whether the local plan for reviewing the data to ensure accuracy is acceptable, given the nature of the study.
 - b. Continuing Review - The IRB reviews new information to determine if the study continues to meet this requirement, for example:
 - 1) Any new information that indicates the need to revise the local plan for continuously collecting and monitoring the safety data of subjects
 - 2) Any new information that indicates the need to revise the DSMP to reflect the required prompt reporting of UPIRSOs
 - 3) When a history of not following prompt reporting procedures is noted, any new information concerning why prompt reporting procedures were not followed
- 8. Criteria 8: There are adequate provisions to protect privacy and maintain confidentiality of data (if required).
 - a. Initial Review and Review of Proposed Modifications (as appropriate)
 - 1) Privacy
 - i. The recruitment plan and consent process address protections of the privacy of the individual.
 - ii. The IRB reviews plans to ensure subjects privacy rights are protected during visits and procedures.
 - iii. Examples for both considerations above include: self-determination of access to their person, whether they will be seen in a setting in which they will not be overheard particularly if the visit involves sensitive discussions and whether the subject will be comfortable in the setting in which the procedures are taking place.
 - 2) Confidentiality
 - i. The study procedures minimize the possibility of a breach of confidentiality.
 - ii. Whether the research data constitutes a significant risk if placed in the medical record.
 - iii. Whether the study is covered by a Certificate of Confidentiality (CoC) due to funding status or a CoC is appropriate given the study procedures

conducted (refer to the HRPP Guidance on Certificates of Confidentiality for more information).

- b. Continuing Review, new information is reviewed to determine if the study meets this requirement, for example, any new information that indicates the need to revise the plan to protect privacy and assure confidentiality
9. Criteria 9: Other criteria as determined by the IRB
- a. The IRB shall ensure additional appropriate protections are in place for subjects determined to be vulnerable as applicable (see 2.6 RESEARCH INVOLVING INDIVIDUALS WITH DIMINISHED AUTONOMOUS DECISION-MAKING CAPACITY).
 - b. During Initial and Continuing Review, or Review of Proposed Modifications, the IRB must determine whether the research should be reviewed by a consultant to supplement the IRB expertise.
- C. After appropriate review, results are reported in accordance with the 8.2 REPORTING POLICY AND PROCEDURE.

IV. DEFINITIONS

SEE GLOSSARY OF HUMAN RESEARCH TERMS

V. REFERENCES

Resource
21 CFR 50 – PROTECTION OF HUMAN SUBJECTS
45 CFR 46 – PROTECTION OF HUMAN SUBJECTS
45 CFR 164 – SECURITY AND PRIVACY (HIPAA PRIVACY RULE)
21 CFR 56 – INSTITUTIONAL REVIEW BOARDS

VI. REVISION AND REVIEW HISTORY

Revision Date	Author	Description
November 2021	HRPP	Included reference to Certificate of Confidentiality guidance document
June 2021	HRPP	Separated policy from P&P manual. Updated references to AVPHRA and IRB Director. Minor administrative edits.
January 2019	HRPP	Revision to reference 2019 common rule
August 2017	HRPP	New Policy Development
March 2012	IRB Office	IRB Written Procedures