IRB Policies

Human Research Protection Program

Contents

APPLYING FOR VIRTUA HEALTH IRB APPROVAL

Any person who requests to carry out research at a Virtua Health facility must have approval of the Virtua Health IRB. Non-employed researchers must name a Virtua Health employee, with sufficient knowledge to oversee the study.

A. How to apply for Virtua Health IRB approval: In order to apply for full board review, the following documents must be submitted to the Virtua Health IRB at least 21 days before the Virtua Health IRB meeting:

1. One copy of the study protocol in its unabridged form
2. One copy of the consent form to be used (If applicable)
3. A completed Virtua Health IRB Application
4. A completed "Conflict of Interest Statement" for all investigator(s) and study personnel
5. An Investigator's Brochure (if applicable)
6. Any other relevant materials, including recruitment materials
7. CVs for investigators
8. Proof of human subjects protection training for all investigators and study personnel; this training must be renewed every 36 months

To apply for expedited review, the above-listed documents must be submitted.

B. Information Provided to the Virtua Health IRB. The information the investigator provides to the Virtua Health IRB for all initial studies must include the following:

1. Title and summary of the study protocol
2. Benefits, discomforts and risks of participation
3. Sponsor of study
4. Local Principal Investigator, Co-Investigators, and any study personnel
5. Professional qualifications to do the research
6. Description and approval of necessary support services and facilities
7. Alternatives of participation
8. The proposed informed consent document (If applicable)
9. Justification for waiver of consent, waiver for documentation of consent, or a HIPAA waiver (if applicable)
10. Design and purpose of study
11. Results of previous related research
12. Subject selection and exclusion criteria
13. Justification for the use of any special/vulnerable subject populations
14. Provisions for protecting the privacy and security of health information that may identify subjects per HIPAA regulations
15. Description of procedures to be performed
16. Provisions for managing Adverse Drug Reactions (ADR)
17. Procedures for documentation of informed consent
18. Compensation to subjects for their participation
19. Any compensation for injured subjects or a statement that no compensation is offered in case of injury
20. Participation voluntary
21. Right to withdraw at any time
22. Extra costs to subjects for their participation in the study
23. Duration of the study
24. Estimated count of study population at Virtua or count of local enrollment goal

C. Studies approved by the Virtua Health IRB

1. submit a continuation/progress report at intervals as determined by the Virtua Health IRB

2. submit a modification if any revisions are made to the study prior to initiating those revisions
3. any protocol deviations and/or violations must be reported to the Virtua Health IRB. Please refer to the Protocol Deviation/Violation policy.
4. any events that meet the criteria of an unanticipated problem must be reported to the Virtua Health IRB. Please refer to the Complaints, Allegations, Unanticipated Problems policy.

AUTHORITY, REPORTING STRUCTURE, RELATIONSHIPS

Authority of the Virtua Health IRB

The Virtua Health IRB is charged by the Virtua Board with the responsibility of reviewing, modifying, approving, or denying of all research studies (e.g. drug therapies, procedures, treatments, and the use of devices classified by the FDA as investigational devices, etc.) conducted in any Virtua Facility.

All research involving human subjects conducted in or through a Virtua Facility shall only be done with the approval of the Virtua Health IRB in order to ensure the research is being conducted in a manner which safeguards the rights, health and welfare of patients subjected to research protocols. The Virtua Health IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with Virtua Health IRB requirements or that has been associated with unexpected serious harm to subjects.

The Virtua Health IRB maintains responsibility for ensuring the initial and ongoing qualifications of investigators and maintaining compliance with federal regulations, state, local and institutional requirements. As part of ensuring safe and appropriate performance of the research, the Virtua Health IRB has the authority to observe any aspect of the research study including observing the consent process.

Reporting Structure

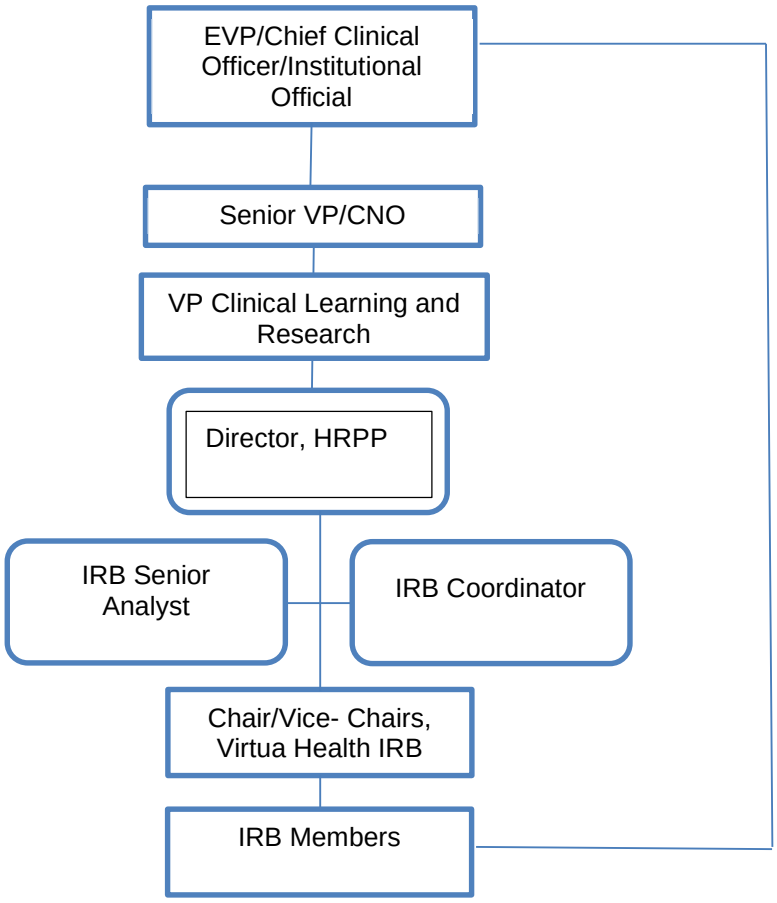
The Virtua Health IRB is administered by the Director, Human Research Protection Program who reports through chain of command to the Virtua CEO, and ultimately to the Virtua Board of Trustees.

Relationships

The Virtua Health IRB interfaces with the following entities:

- Institutional Official
- The Virtua Board of Trustees
- All clinical researchers
- Outside cooperative groups (e.g. RTOG, ECOG)
- Outside institutions, e.g., Penn Medicine Cancer Center at Virtua Memorial is affiliated with Penn Medicine Cancer Center/Philadelphia.
- Regulatory bodies (e.g. FDA/NCI/OHRP). The Virtua Health IRB and its documents will be audited regularly by the agencies that regulate clinical research.

Virtua Human Research Protection Program Reporting Structure



INFORMED CONSENT, WAIVER/ ALTERATION OF CONSENT

1. **Documentation of Consent.** Subject to certain limited exceptions, no investigator may involve a human being in research involving a drug, biological product or medical device without first obtaining the informed consent of the subject or that subject's legally authorized representative. The informed consent must be documented by the written consent form approved by the Virtua Health IRB and signed by the subject or the subject's legally authorized representative and a member of the study team. A copy of the signed consent must be given to the subject or their legally authorized representative prior to the commencement of that person's participation in the study.

2. **Minimizing Coercion.** The consent must be sought only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.

3. **Consent Process.** The consent process is as important to the protection of human subjects as is the consent form. Potential subjects must be provided with an explanation of the study and be given an opportunity to ask questions and seek additional information during the consent process.

4. **Plain Language.** The language used in the consent procedure (including printed consent forms) must be understandable to the subject or the legally authorized representative and minimize the use of scientific language. When possible, the target grade level should be written in the subject's native language at a 6th to 8th grade reading level.

5. **Non-English Speaking Persons.** In the event a non-English speaking person wishes to participate in a research study, a certified translation of the approved consent form will be given to the participant. A translator will be provided to orally explain the protocol and to answer any questions the participant may have.

6. **Key Information.** The informed consent, as a whole, must present information in sufficient detail organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding the reasons why one might or might not want to participate in the research. The informed consent must begin with a concise and focused presentation of the key information relating to the research that will facilitate comprehension.

   The first page of the consent must contain a "key information" section. This key information must include the following: (1) that the consent is for research; (2) purpose of the research, expected duration of participation and procedures to be followed; (3) reasonably foreseeable risks/discomforts; (4) benefits that may reasonably be expected; (5) appropriate alternatives and procedures.

7. **Exculpatory Language.** No informed consent may include exculpatory language through which the subject or the legally authorized 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.

8. **Required Elements of Informed Consent**: The following information must be provided to each subject or the legally authorized representative:

   a) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of subject's participation, a description of the procedures to be followed and identification of any procedures that are experimental or investigative.

   b) A description of any reasonably foreseeable risks or discomforts to the subject.

   c) The approximate number of subjects involved in the study.

d) A description of any potential benefits to the subject or to others which may reasonably be expected from the research. The consent must also be clear if no direct benefit is expected.

e) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject or affect the subject's willingness to participate in the research.

f) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, including the possibility that representatives of the institution (such as the Virtua Health IRB) or external, such as OHRP, FDA or the sponsor may inspect the records for auditing purposes.

g) For research involving more than minimal risk, an explanation as to whether any compensation or any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

h) An explanation of whom to contact for answers to pertinent questions about the research and subject's rights and whom to contact in the event of a research-related injury to the subjects.

i) A statement that participation is voluntary and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

j) For research involving the collection of identifiable private information or identifiable biospecimens, one of the following statements must be included:

    a. that the identifiers might be removed and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or legally authorized representative
    b. that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research

9. **Additional Elements of Informed Consent**.

a. a statement that the particular treatment or procedure may involve unforeseeable risks to the subject (or the embryo/fetus, if the subject is or may become pregnant).

b. anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or legally authorized representative's consent.

c. any additional cost to the subject that may result from participation in the research study.

d. the consequences of the subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

e. a statement that significant new findings developed during the course of the research, which may affect the subject's willingness to continue to participate will be provided to the subject.

f. a statement that the subject's biospecimens (even if the identifiers are removed) may be used for commercial profit and whether the subject will or will not share in the commercial profit.

g. a statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.

h. a statement as to whether the biospecimens collected include whole genome sequencing.

i. a description of any reasonably foreseeable risks or discomforts to the subject;

j. a description of any benefits to the subject or to others that may reasonably be expected from the research.

k. a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

l. a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

m. a general description of the types of research that may be conducted with the identifiable private information/biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted

n. a description of the identifiable private information/biospecimens that might be used in research, whether sharing of identifiable private information/biospecimens might occur and the types of institutions or researchers that might conduct research with the identifiable private information/biospecimens

o. a description of the period of time that the identifiable private information/biospecimens may be stored and maintained as well as the period of time which it may be used for research purposes (both of which could be indefinite)

p. unless they will be provided details about specific research studies, a statement that the subject/legally authorized representative will not be informed of the details about specific research that might use the subject's identifiable private information/biospecimens, including the purpose of the research and that they might have chosen not to consent to some of those specific research studies.

q. a statement that clinically relevant research results, including individual results, may not be disclosed to the subject

r. contact information for who will answer questions about the subject's rights and about storage and use of the subject's identifiable private information/biospecimens and whom to contact in the event of research-related harm

The following statements should be added, if appropriate:

a) a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.

b) For research involving biospecimens, whether the research will or might include whole genome sequencing

11. **Short Form Consent**. A "short form" written consent document stating that the required elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there must be a witness to the consent process. Only the short form itself is to be signed by the subject or the representative as well as the witness. The person obtaining "short form" consent must be the PI or a co-investigator for the study, who shall also sign. A signed copy of the form must be provided to the subject or the legally authorized representative.

    For non-FDA regulated research studies, the short form written informed consent form must state that the key information required by 45 CFR 46.116(a)(5)(i) (described above) was presented first to the subject, before any other information was provided.

12. **Waiver of Documentation of Consent (45 CFR 46.117 & 21 CFR 56.109)**: The Virtua Health IRB may waive the requirement for the investigator to obtain a signed informed consent for some or all subjects if it finds any of the following:

    a) that the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality;

    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; or

    c) if the subject or legally authorized representative is a member 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.

In cases in which the documentation requirement is waived, the Virtua Health IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

13. Waiver/**Alteration of Consent (45 CFR 46.116):** The Virtua Health IRB may waive the requirement to obtain informed consent or alter some or all of the elements of informed consent provided the following requirements are satisfied and documented:

    a) the research involves no more than minimal risk to the subjects;

    b) the research could not practicably be carried out without the requested waiver or alteration;

    c) if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format

    d) the waiver or alteration will not adversely affect the rights and welfare of the subjects; and

    e) whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

14. **Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials.** In order to waive or alter these consents, the IRB must find and document that the research or demonstration project could not practicably be carried out without the waiver or alteration. Additionally, that the research is designed to study public benefit or service programs; procedures for obtaining benefits or services under those programs; changes or alternatives to those programs; or possible changes in methods or levels of payment for benefits or services under those programs.

15. **Frequency of Review.** The consent form will be reviewed for appropriateness by the Virtua Health IRB at initial submission and annually, for continuing review; and more frequently, if indicated.

16. **Approved Consents.** A consent form, bearing the Virtua Health IRB approval stamp evidencing the date of approval, must be signed and dated at the time of consent (including in an electronic format) and a copy provided to the person signing the form; the original will be maintained by the investigator. The case history (source document) for each individual shall document that informed consent was obtained prior to participation in the study.

17. **Standard Language.** The Virtua Health IRB has adopted standard language and format to be used in portions of all consent documents unless special circumstances make it inappropriate. It is the investigator's responsibility to ensure that

his/her consent conforms to the standard language and format, where appropriate, prior to submitting for the Virtua Health IRB review.

18. **Amendments to Consent.** Any amendments to consent forms must undergo the same Virtua Health IRB review and approval process prior to being given to the subject. Existing subjects should sign new consent forms to assure their understanding of the new information and to provide them an opportunity to reconsider their participation.

19. **ClinicalTrials.gov** Pursuant to 21 CFR 50.25(c), the following statement must be reproduced word-for-word in informed consents documents for applicable clinical trials. Applicable clinical trials generally include controlled interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the United States, involves a drug, biologic or device that is manufactured in the United States (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE). Trial sponsors and investigators have the responsibility of determining whether or not a trial is an "applicable clinical trial." Definitions vary for applicable device and drug trials including biologics.

    "A description of this clinical trial will be available on *http://www.ClinicalTrials.gov* as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

21. **Posting of clinical trial consent form.** For federally funded clinical trials, one Virtua Health IRB-approved consent form must be posted on a publicly available web site, e.g. ClinicalTrials.gov. The informed consent must be posted after the clinical trial is closed to enrollment but no later than 60 days after the last study visit by any subject.

DETERMINATION OF IND/IDE REQUIREMENT; AND EXPANDED ACCESS FOR INDIVIDUAL PATIENTS

1. Definitions

Humanitarian Use Device (HUD): A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

Humanitarian Device Exemption (HDE): A marketing application for a HUD

Investigational New Drug Application (IND): is a request for authorization from the FDA to administer an investigational drug or biological product to humans.

Investigational Device Exemption (IDE): allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.

Investigational New Drug (IND): a new drug or biologic used in a clinical investigation or diagnostic purposes.

Medical Device:

> An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is recognized in the official National Formulary, or the United States Pharmacopeia and intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body and which does not achieve any of its primary intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Significant Risk Device (SR): A SR device presents a potential for serious risk to the health, safety, or welfare of a participant: SR devices may include implants, devices that support or sustain human life and devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health.

Non-Significant Risk Device (NSR): a device that does not meet the definition for an SR device study. If the Virtua Health IRB determines that the study involves a SR device and disagrees with the assessment of the sponsor, the Virtua Health IRB notifies the investigator and the sponsor of this decision. The sponsor notifies the FDA that an SR determination has been made and submits an IDE application to the FDA. The FDA, however, has the ultimate decision in determining if a device is SR or NSR. If determined to be SR, the study cannot begin until the FDA approves the IDE and the Virtua Health IRB approves the study. The investigator/sponsor must provide the documentation from the FDA to the Virtua Health IRB.

If the Virtua Health IRB determines that the device is classified as NSR (concurs with the assessment of the sponsor) and approves the study, the clinical research may begin without the submission of an IDE application to the Virtua Health FDA.

Once the SR/NSR decision has been reached and proper documentation provided, the Virtua Health IRB considers whether the study should be approved or not. Full Virtua Health IRB review is required for all studies involving investigational devices. The criteria for approving the clinical research study are the same as for all other studies. Minutes of Virtua Health IRB meetings document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

Emergency Use Exception to IRB Review for FDA-Regulated Studies

Under 21 CFR 56.104**, for FDA-regulated research**, one emergency use of an investigational test article (drug or device or biologic) may be done only in a life threatening (which includes severely debilitating) situation in which (1) no standard acceptable treatment is available, and (2) there is not sufficient time to obtain Virtua Health IRB approval. This is an exception to Virtua Health IRB review, not an exception to informed consent; informed consent must be obtained unless the criteria for waiver of informed consent are met.

An IND or an IDE should be sought prior to the emergency use. The investigator must contact the sponsor, or the FDA, regarding an IND or IDE. If time does not allow, the Virtua Health IRB must be notified of the emergency use as soon as possible. The investigator must document as feasible: an independent assessment by a physician not involved in the research, informed consent from the patient or his/her legal representative, notice to the institution and the Virtua Health IRB.

Any emergency use must be reported to the Virtua Health IRB within five business days. Any subsequent use of the test article at the institution is subject to Virtua Health IRB review. Investigator follow-up with the IDE/IND holder or the FDA must be provided following emergency use, indicating the conditions constituting the emergency, subject protection measures and the outcome.

2. **Humanitarian Use Devices:**-Federal regulations allow the use of a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals in the United States per year. The FDA issues a Humanitarian Use Device Exemption (HDE) to use a HUD in clinical treatment or as the subject of a clinical investigation. The statute and the implementing regulation (see 21 CFR 814.124(a)) require IRB review and approval before a HUD is used. The PI must submit an application to the Virtua Health IRB for review at a convened meeting. In addition, the PI must include the following information:

    - Generic and trade name of the device
    - The FDA HDE number
    - a letter from the Sponsor or FDA, if applicable, to verify HDE number and permission for use
    - The date of HUD designation
    - The indications for use of the device
    - A description of the device
    - Contradictions, warnings and precautions for use of the device
    - Adverse effects of the device on health
    - Alternative practices and procedures
    - The HUD brochure
    - Marketing history; and
    - A summary of studies using the device

If patient information packets are available, the Virtua Health IRB will require documentation that these have been given to patients. In addition, the Virtua Health IRB may require documentation of informed consent.

The Virtua Health IRB is responsible for initial as well as continuing review of the HUD. For initial review of a HUD, the Virtua Health IRB is required to perform a full board review. For continuing review, however, the Virtua Health IRB may use the expedited review procedures (section 56.110) unless the Virtua Health IRB determines that full board review should be performed. The Virtua Health IRB approval must verify that the use of the HUD, as proposed, is congruent with current labeling of the device and does not exceed the scope of the FDA approved indication.

If, however, a physician in an emergency situation determines that approval from the Virtua Health IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval. In such an emergency, the PI must notify the Virtua Health IRB within (7) seven days after the use of the device. Such written notification must include the identification of the patient involved, the date on which the device was used, reason for the use and outcome of the subject.

3. **Treatment Use of Investigational Drugs/Devices.** Treatment IND studies require prospective Virtua Health IRB review and informed consent. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human

subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

4. **Expanded Access for individual patients**. Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor or treat a patient's disease or condition rather than to obtain the kind of information about the drug than is generally derived from clinical trials. Except in cases of emergency expanded access, an investigator is responsible for obtaining Virtua Health IRB review and approval before treatment can begin. The investigator must submit an Virtua Health IRB application and the informed consent, if any, and the reason for the intended treatment. The FDA deems it appropriate, in cases of individual patient expanded access, for the investigator to waive the full board review, but the Virtua Health IRB Chair, or her/his designee, must review the documents before treatment may begin.

   In the case of emergency expanded access use, FDA authorization is still required but it is not necessary to wait for Virtua Health IRB approval to begin treatment. However, the Virtua Health IRB must be notified of the use within seven working days.

INVESTIGATOR AND STUDY PERSONNEL RESPONSIBILITIES
Definitions

Principal Investigator- is an individual who has full responsibility and authority for the project

Co/Sub Investigator- is an individual who makes significant contributions, but does not have overall responsibility and authority for the project

Study Personnel - are appropriately qualified research staff engaged in human subjects research performing research related tasks delegated by the PI. Individuals are considered engaged in human research if they will interact with participants or access their personally identifiable data of human subjects

Ethical Obligations

- risks to research participants are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose the subjects to risk;
- selection of human subjects for research participation is equitable;
- informed consent of research participants, or their legally authorized representative, will be obtained in advance of research participation and appropriately documented pursuant to 45 CFR 46 and as stipulated by the Virtua Health IRB;
- where appropriate, there is routine monitoring of the data collected to ensure the safety of research participants;
- the privacy of research participants is protected and the confidentiality of data is maintained;
- appropriate additional safeguards are included in the study to protect the rights and welfare of research participants who are likely to be vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons);
- all investigators and study personnel have (i) been trained to conduct the study in accordance with the approved protocol; (ii) completed mandatory human subjects protection training as required by the Virtua IRB; and (iii) completed all financial disclosures required by Virtua;
- ensure all research team members act in accordance with the approved protocol, maintain privacy of participants and confidentiality of data, and protect the rights and welfare of research participants;
- abstaining from enrolling any individual in a research study (i) until such study is approved in writing by the IRB; (ii) during any period when study activities are suspended; or (iii) following termination of the study, for any reason;
- in the event a research participant experiences a significant adverse event, every reasonable effort is made to provide the subject with adequate care to correct or alleviate the consequences of the event to the extent possible;
- that the investigator will abide by all determinations of the IRB and will accept the final authority and decisions of the IRB, including but not limited to directives to terminate participation in designated research activities
- that the investigator will comply with all other applicable federal, state and local laws, regulations and policies that may provide additional protection for human subjects participating in research conducted under this agreement
- that adequate resources and facilities are available to carry out the proposed research study
- that he/she is primarily responsible for safeguarding the rights and welfare of each research subject and that the subject's rights and welfare must take precedence over the goals and requirements of the research

Documentation and Communication

- prompt response to all requests for information or materials solicited by the Virtua Health IRB Office, including the timely submission of the research study for Virtua Health IRB renewal;
- prompt reporting of any change in the principal investigator, co-investigators, or study personnel, change in the consent or protocol;
- reporting any mortality or morbidity (which is unanticipated or statistically higher than outlined in the protocol) associated with the investigation within seven days of the occurrence;
- prompt reporting to the Virtua Health IRB of any internal or external adverse event that is considered to be (i) unexpected; (ii) serious; and (iii) related to the study; Please reference Policy: complaints_allegations_unanticipated_adverseevents.
- prompt reporting of any significant changes in the risk/benefit of study participation;
- prompt reporting of any protocol deviation/violation or investigator misconduct

AUDIT OF HUMAN SUBJECT RESEARCH ACTIVITIES

Virtua Health IRB Human Research Protection Program (HRPP) investigates concerns, allegations, complaints on non-compliance, and will conduct random audits of human subject research activities to ensure compliance with Virtua policies, state and federal regulations.

Studies to be audited will be selected at random from Virtua Health IRB Office.

Once a study is selected for audit, notification is sent to the principal investigator and the study team to arrange a date and time. The audit review may include:

- observing the consenting process
- comparing the participants' signed consents to the current Virtua Health IRB approved consent
- reviewing the entire study to confirm that unapproved changes have not been initiated

A report of the findings will be submitted to the Virtua Health IRB Committee for review at their next meeting. If any inconsistencies or instances of non-compliance are found, the Virtua Health IRB may take the following actions:

- No action;
- Suspension: Suspend enrollment and/or all research procedures for the specific research study in question;
- Termination of Virtua Health IRB approval of the research;
- Termination of the research;
- Require a response from the Investigator with a plan for corrective action and proposed timeline within 10 days;
- Require an action plan from the investigator and conduct a follow-up audit to ensure that the action plan has been properly implemented;
- Initiate audits of all or part of the Investigator's active protocols;
- Modification of the research protocol;
- Modification of the information disclosed during the consent process;
- Additional information provided to past participants;
- Modification of the continuing review schedule;
- Obtain more information pending final decision;
- Conference with other IRB's involved with the research;
- Requirement that current participants re-consent to participation;
- Provide information to current participants whenever such information might relate to the participant's willingness to participate to continue to participate in research;
- Monitoring of the research;
- Monitoring of the consent process;
- Re-audit of the study at a later date

The Virtua Health IRB's determinations will be documented in the meeting minutes and the principal investigator will be notified, in writing of the results of the investigations and any remedial actions required by the Virtua Health IRB.

IRB MEETING PROCEDURES

Meeting Frequency. The IRB will meet on a regular basis throughout the year. A schedule of IRB meetings is established by the Director, HRPP in consultation with the IRB Chair.

Meeting Packet Distribution. One week prior to the scheduled meeting the following material is distributed to all members:

1. Meeting Agenda, including time and location of the meeting
2. Previous meeting minutes
3. Educational Items
4. IRB Protocol, Research Protocol and consent forms to be reviewed
5. Other relevant materials, as indicated
6. List of protocols granted approval using the exempt/expedited procedures

IRB Member Requirements:

1. At least one IRB member or consultant is responsible for scientific/scholarly review of research.
2. Protocols are reviewed by IRB members and consultants with sufficient expertise.
3. When IRB members review research that involves vulnerable subjects, at least one individual who is knowledgeable about or experienced in working with such subjects will be present at the meeting.
4. IRB members are provided sufficient information so that each member can provide an opinion on whether the regulatory criteria for approval are met.
5. Alternate IRB members serve the same function as other IRB members, both the IRB Member and Alternate IRB Member vote. When an Alternate IRB Member is substituting for an IRB member present only one member may vote.

IRB Chair Procedures:

1. Call the meeting to order.
2. Ask IRB members whether anyone has a Conflicting Interest in any item on the agenda and note the responses

Voting Requirements:

1. The PI and anyone who will participate in the implementation of the protocol are not permitted to vote and will be asked to leave the room meeting before a vote is taken on the study.

2. The IRB shall consist of a minimum of 5 members. To meet quorum requirements, a simple majority of eligible members (1/2 of total membership plus one) listed on the official IRB roster must be in attendance. If the membership roster is an odd number, the number of members necessary to reach quorum will be rounded up to the next whole number. Quorum must include at least one member whose primary area of interest is non-scientific. A simple majority of the voting members present is required to approve a study. The Chair, with the assistance of the IRB Team member, will confirm that quorum is present before calling a meeting to order. The IRB Team member will keep track of members leaving the meeting and notify the Chair if quorum is lost. If quorum is lost, the meeting shall be adjourned or suspended until the required conditions can be restored. This information is documented in the minutes.

3. Voting can only occur when quorum is established. Members may vote for or against or abstain from voting. Abstaining members continue to count toward quorum. Members who are investigators on a study must recuse themselves from voting on that study and, for purposes of that particular vote, are not counted toward quorum.

If an IRB member is unable to attend a meeting, his or her designee may attend in their place. Proxies are not allowed and members may only vote after participating in the discussion of the study.

4. Any member with a conflicting interest may not participate in the deliberation and must abstain from voting.

5. The Virtua Board has the right to disapprove studies that have been approved by the IRB, but cannot approve studies that have been disapproved by the IRB.

Meetings held via virtual meeting or teleconference. Every effort will be made to convene meetings at which all members are present using virtual meeting technology. Members participating remotely call may vote, as they have the opportunity to review all the materials..

If necessary, IRB meetings may be conducted via telephone conference call, only if the following conditions are met:

1. Each participating IRB member must have received all pertinent material prior to the meeting.
2. Each participating IRB member must be able to actively and equally participate in the discussion of all protocols reviewed during the teleconference.
3. Minutes of meetings conducted via teleconference must clearly document that the above two conditions have been satisfied in addition to the usual regulatory requirements.

Decision Type and Notification. The IRB shall notify the PI in writing of its decision. The IRB should take one of the following actions with regard to each protocol reviewed:

Approved

- The IRB deems the proposed research activity, as submitted, meets all the criteria for approval as defined by regulation.

Approved with Conditions

- To secure approval, the IRB requires specific changes to newly proposed research, modifications to existing IRB-approved research, or other action(s) to be taken by the investigator. The IRB will include in its written notification a statement of the reasons for the decision and recommendations on what study elements must be changed or modified in order to secure IRB approval.

Approved with Stipulations

- The IRB approves the proposed research as submitted, however, there are stipulations limiting the conduct or initiation of some research activities until additional information or documentation is provided to the IRB for approval. (e.g., such as a site approval, limited data set use agreement, etc.).

Tabled/Deferred

- An IRB may table/defer review of proposed research for a variety of reasons (e.g., insufficient meeting time to conduct a thorough review of the proposed research, loss of quorum, insufficient detail provided in the application to make a determination, etc.) The investigator may not initiate proposed research activities or implement proposed changes to previously approved research until the IRB completes its review and approves the research.

Disapproved

- The IRB has determined that the research activity, as submitted, does not meet the criteria for approval as required by regulation and/or the IRB requires substantial revisions in order to approve the research. The IRB will explain the reasons for disapproval and the investigator has the opportunity to request a meeting with the IRB or submit revisions to the study.

IRB Meeting Minutes

1. Minutes are to comply with regulatory and guidance requirements.
2. Minutes are to record separate deliberations for each action.
3. Minutes are officially approved by majority vote on behalf of the IRB by the IRB chair, or IRB Director.

4. The IRB staff composes minutes and make them available for review at a minimum of 7 business days before the next meeting date.
5. IRB members may make corrections to minutes at the convened meeting before approval by the Committee.
6. Minutes are made available to the Institutional Official (IO) or designee.
7. Any proposed changes to approved minutes must be returned to the convened IRB for approval.
8. Indicate whether members present by telephone or videoconferencing received all pertinent material before the meeting and were able to actively and equally participate in all discussions.
9. Record the meeting start time.
10. Record a summary of each business item that was discussed.
11. For each protocol reviewed record:
    a. Type(s) of review: Initial review, continuing review, review of modifications to previously approved research, or review of Unanticipated Problem Involving Risks to Subjects or Others, Serious Non-Compliance, Continuing Non-Compliance, Suspension of IRB Approval, Closure of IRB Approval
    b. Protocol Title
    c. Investigator name
    d. IRB identification number
    e. Funding Agency
    f. Grant Title
    g. Grant ID
    h. IND or IDE
    i. Documents reviewed
    j. Study summary
    k. Consultant report
    l. Controverted issues and their resolution. Summarize the issues where IRB members expressed a difference of opinion.
    m. Motion: Approved, Approved with Conditions, Approved with Stipulations, Tabled/Deferred, or Deferred.
    n. Period of approval (annual, semi-annual, etc)
    o. Vote: Record as the number of members for, against, abstaining, absent, or recused. List the names of IRB members who were absent or recused. Do not count votes of consultants. If both a regular IRB member and the alternate IRB member are present at the meeting record the vote of just one.
        i. For: Voting for the motion
        ii. Against: Voting against the motion
        iii. Abstain: Present for the vote, but not voting "For" or "Against"
        iv. Absent: Listed under "Members Present" but not present for the discussion and vote on this protocol for reasons other than a Conflicting Interest. List the names of absent members in the vote. For example: "For: 7 Against: 3 Abstain: 2 Absent: 2 (Alice Baker, Charlie Delta) Recused: 0
        v. Recused: Listed under "Members Present" but not present for the discussion and vote on this protocol for because of a Conflicting Interest. List the names of recused members in the vote. For example: "For: 7 Against: 3 Abstain: 2 Absent: 0 Recused: 2 (Evelyn Foxtrot, George India) Substitutions: 0"
        vi. Substitutions: Listed under "Members Present" When regular members and their alternate(s) are listed under "Members Present" and an alternate member substitutes for the regulator member, identify the name of the alternate to indicate which individual is serving as the voting member for this vote. May be deleted if there are no substitutions. For example: "For: 7 Against: 3 Abstain: 2 Absent: 0 Recused: 0 Substitutions: 1 (Evelyn Foxtrot substituted for George India)"
        vii. Level of risk determined by the convened IRB.
        viii. Determinations and findings that require documentation: (i.e., if the research involves waiver or alteration of consent, waiver of written documentation of consent, children, pregnant women, neonates, Prisoners, or cognitively impaired adults)

ix. Rationale for a significant/non-significant device determination: Describe the rationale for the determination.
x. Modifications required to secure approval: If this is the motion, document the required changes and corresponding reasons.
xi. Deferral/disapproval reasons and recommended changes: If this is the motion, document the recommendations and corresponding reasons.
xii. Suspension/termination reasons and recommended changes:
xiii. Tabled reason: If the protocol was tabled, provide the reasons.

p. Record the meeting end time.
q. Within 2 business days revise minutes for accuracy and provide them to the HRPP Director for review and approval.
r. Once approved by the HRPP Director, make them available to:
    i. IO or designee
    ii. IRB members
    iii. Authorized representatives of Federal Departments or Agencies

VIRTUA HEALTH IRB MEMBER CONFLICT OF INTEREST

The Virtua Institutional Review Board (IRB) is charged with ensuring that research studies conducted at its facilities safeguard the rights, health and welfare of patients who participate in research protocols. Part of these safeguards is to identify potential conflicts of interest in research studies. A conflict of interest may arise when an investigator of an Virtua Health IRB study is able to influence the study in ways that could lead directly or indirectly to financial gain for the investigator or his or her family. Virtua Health IRB members are also investigators and are required to disclose any potential conflicts of interest in reviewing submissions. Virtua Health IRB members are required to disclose any potential conflicts, whether financial or other personal interests and the obligation to abide by principles of the ethical conduct of research prior to reviewing submissions.

Conflicts of interest training and disclosure is required prior to an Virtua Health IRB member reviewing an Virtua Health IRB submission.

It is desirable to avoid conflicts of interest whenever possible. If a potential conflict cannot be eliminated, the Virtua Health IRB will attempt to determine if the conflict can be reduced or managed (e.g., include financial disclosure in the patient's consent form). To prevent, reduce or manage the risk of potential conflicts of interest from improperly biasing a study or compromising the protection of human subjects the Virtua Health IRB requires investigators to disclose any financial interest gained by the investigator, his or her spouse, domestic partner, children, parent or siblings from the sponsor of the study. Financial interests that must be disclosed include the following:

1. Service as an officer, director or in any other fiduciary role for a financially interested company, whether or not remuneration is received for such service. Any compensation paid to the investigator, directly or indirectly, per participant, or for meeting study accrual goals, or for any other purposes where such payment might affect the investigator's study recruitment, willingness to report adverse reactions or his/her analysis and interpretation of study data.

2. A proprietary interest in the tested product, including but not limited to, a patent, trademark, copyright, licensing agreement or other commercial enterprise.

3. Any equity interest in any sponsor of the covered clinical study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. This requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

4. Any equity interest in any sponsor of the covered study if the sponsor is a publicly held company and the interest, when aggregated, exceeds $5,000 in value. This requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study.

Membership and Management

A. Chairperson. The Virtua Health IRB will be chaired by a physician of active status with Virtua. The Chairperson is responsible for the following:

1. Preside over meetings of the Virtua Health IRB. The Chair will direct the proceedings and discussion of the meeting. The Chair should review all protocols presented to the full committee.
2. Appoint and/or attend subcommittees of Virtua Health IRB.
3. Complete review assignments.
4. Call special meetings when necessary.
5. The Chair should represent the Virtua Health IRB in discussions of Virtua Health IRB decisions with researchers.
6. Recruit and recommend committee members for appointment to the Virtua Health IRB.
7. Make decisions in direct consultation with HRPP Director (or designee) in emergency situations to protect subjects and remain in compliance with regulations.
8. Inform the HRPP Director (or designee) and University Officials of developing concerns.
9. Relate concerns of IRB staff and members to HRPP Director (or designee) and University Officials regarding issues (including non-compliance) in human research review.
10. Play a leadership role in establishing and implementing Virtua Health IRB policy.
11. Represent the IRB in discussions with other representatives of the organization.
12. Represent the organization in discussions with federal authorities.
13. Attend regular continuing education events periodically, including, to the degree permitted by their research and academic obligations, regional or national conferences, the costs of which shall be reimbursed by the Office of Research.

The Chairperson may be removed by the Institutional Official in consultation with the HRPP Director.

B. Membership Composition and Responsibilities. Federal Regulations, 45 CFR 46.107, indicate all requirements regarding Virtua Health IRB membership. The Virtua Health IRB shall have at least five (5) members with varying backgrounds to promote complete and adequate review of research activities conducted at the Facilities. The HRPP Director shall appoint the Virtua Health IRB members, upon consultation with the Institutional Official (IO) or based upon an investigator, faculty or staff who express interest in joining the Virtua Health IRB. The Virtua Health IRB shall consist of members whose professional and personal backgrounds provide diversity including consideration of race, gender, cultural background, and sensitivity to local community attitudes. In addition to possessing the professional competence necessary to review the specific research activities, the Virtua Health IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. Virtua Health IRB Member duties shall include:

1. Attend at least 50% of the Virtua Health IRB meetings per calendar year
2. Review and be familiar with consent forms being reviewed at the convened Virtua Health IRB meeting
3. Objectively evaluate all protocols presented to the IRB to ensure adequate protection of human subjects
4. Participate fully in the reviews of protocols and discussions at IRB meetings
5. Review and inform the IRB Team of corrections or additions to meeting minutes
6. Sign a conflict of interest statement annually
7. Meet education and certification requirements as follows: Complete on-line human subjects protection training deemed appropriate by Virtua. This training must be completed every three years and the completion is verified by the IRB Office or a completion certificate is submitted to the Virtua Health IRB Office.
8. Maintain knowledge of the federal, state and institutional policies governing human subjects research
9. Hold all matters pertaining to IRB activities in confidence

The Virtua Health IRB shall include at least one member whose primary professional experience is not scientific in nature. Non-scientific members are defined as members who have little or no scientific medical training and who do not currently hold positions which involve scientific research or clinical practice. Scientific members are defined as members who are physicians or who hold PhD, PharmD or other post-graduate degrees in the social, behavioral or biological sciences and disciplines. It may also include at least one member who is not affiliated with Virtua. The Virtua Health IRB membership shall also include at least one registered nurse.

All members will serve on the Virtua Health IRB until such time as they resign from the committee or are removed by the Institutional Official or designee with consultation from the HRPP Director. Virtua Health IRB members can be removed for cause (such as breach of confidentiality, non-compliance, etc).

C. Conflict-of-Interest. The Virtua Health IRB members shall exclude themselves from all discussions of their own investigations, except to provide information requested by the Virtua Health IRB. They shall abstain from voting on their own studies. Additionally, all members will be polled at the beginning of each meeting to determine if any conflict of interest exists with the studies on that meeting's agenda.

D. Outside Experts. The Virtua Health IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available in the Virtua Health IRB. These individuals may not vote.

E. **New Member Orientation/Continuing Education.** New members shall be provided with the following items:

1. Belmont Report
2. FDA Regulations
3. 45 CFR 46 (Common Rule)
4. HIPAA regulations
5. Updated education on a monthly basis
6. CITI Virtua Office of Research Administration Program

F. **Reference Materials.** All members will have access to reference materials in the Virtua Health IRB Manual and to the following documents in the office of the Virtua Health IRB. These documents will also be available electronically.

1. Minutes of previous meetings
2. Any studies/consents previously approved by the Virtua Health IRB and currently open for accrual and/or follow-up.
3. 21 CFR 50, 21 CFR 56, and 45 CFR 46
4. FDA Information Sheets for Institutional Review Boards and Clinical Investigators
5. Belmont Report

G. **Agent Status.** The Virtua Health IRB members will be considered agents of Virtua for indemnification and insurance coverage purposes.

H. Alternate Members. Alternate members may be appointed. Each primary member can suggest an alternate. These suggestions shall be reviewed by the HRPP Director in consultation with the Virtua Health IRB Chair and, if acceptable, shall be approved. The alternate member will complete the same training requirements and provide the same information as a primary member. The alternate will also sign a conflict of interest statement. The alternate's qualifications should be comparable to the primary member to be replaced. The Virtua Health IRB minutes will document when an alternate member replaces a primary member. The alternate member may vote.

I. HRPP Office: These responsibilities may be assigned to a single individual or divided into two positions as long as all responsibilities are covered.

- Developing, managing and evaluating policies and procedures that ensure compliance with all Virtua policies, state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection.
- Ensuring FWAs are submitted, approved, implemented and maintained through the Department of Health and Human Services Office of Human Research Protection (OHRP). Any revisions to the roster are submitted within 90 days after changes are implemented.
- Managing the finances of the Virtua IRBs.
- Serves at the contact person for OHRP and FDA
- Provides support and training to investigators and IRB members
- Send timely meeting notices and materials to all members
- Notify the Principal Investigators (PI) of the scheduled Virtua Health IRB meetings
- Maintain Virtua Health IRB documentation and files
- Function as the primary contact for PIs
- Monitor quorum during meetings
- Record and distribute minutes
- Maintain the attendance and voting records
- Retain the protocols, consents, Virtua Health IRB checklists and forms and periodic reports for each approved protocol for a minimum of three (3) years after completion of study.
- Maintain the Protocol Database
- Notify the Principal Investigator when a continuing review report is required

OPERATIONS OF THE VIRTUA HEALTH IRB

A. Virtua Health IRB Record Requirements: The Virtua Health IRB shall prepare and maintain adequate documentation of its activities for a period of at least three years, including:

1. The minutes of the Virtua Health IRB will be recorded and kept on file in the Virtua Health HRPP Office. Minutes must contain the following information: date of meeting; attendance, written summary of actions and discussion including controverted issues and their resolution; vote on actions taken, include the number of members voting for, against, and abstaining; the basis for requiring changes or disapproving research; details on discussions regarding additional safeguards needed for studies involving vulnerable populations; any corrections to previous minutes; items reviewed and approved through an expedited process; unanticipated problems, protocol deviations/violations and study closures/suspensions.

2. Membership roster listing of all Virtua Health IRB members identified by name, credentials, representative capacity, and voting status will be maintained and revised as new Virtua Health IRB members are added or removed.

3. Copies of all protocols reviewed, reviewers sheets, consent documents, progress reports, adverse event reports, advertising materials, Virtua Health IRB forms, correspondence and investigator brochures. Copies of all CTSU certifications, HHS 310 Forms and Virtua Health IRB approval letters.

4. Copies of all correspondence between the Virtua Health IRB and the investigators and cooperative groups or sponsors.

5. Written policy and procedures of the Virtua Health IRB.

6. An Excel spreadsheet listing details of all studies

All study documents will be made available for review by authorized representatives of regulatory agencies.

B. The Virtua Health IRB Policy and Procedures: The policies and procedures of the Virtua Health IRB will be reviewed every three years by the HRPP Director and legal counsel, if applicable. Revisions to any policy will be shared with the Virtua Health IRB members at a full board meeting where they will be given an opportunity to provide feedback. Any Virtua Health IRB member who becomes aware that an Virtua Health IRB policy is not being followed should report the deviation to the HRPP Director. Appropriate measures for correction or revision will be put in place.

C. Application and Processing Fee: The Virtua Health IRB shall be authorized to charge a fee of $2,000.00 for full board review of each new research protocol involving human subjects for industry funded studies; studies qualifying for expedited review will be billed at the rate of $1,500.00. This fee shall compensate the Virtua Health IRB for initial review and preparation of regulatory documents as well as on-going reviews for amendments, adverse events and annual reapprovals. Studies requiring local context review will be billed at $1,000.00. Studies requiring review to determine qualification for exempt status will be billed at $500.00. The Virtua Health IRB, at its discretion, shall designate some studies, e.g., cooperative group studies, single patient use, emergency use and internally funded protocols, as fee-exempt.

PROTOCOL DEVIATION/VIOLATION

Deviation: a variance from the approved study protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s)

Deviations can be major or minor and can be the result of actions by the participant or the investigator or his/her study team.

Except when necessary to eliminate apparent immediate hazards to the research participant [45 CFR 46.103(b)(4)(iii) and 21 CFR 56.108(a)(4)], federal regulations require Virtua Health IRB approval of modifications to Virtua Health IRB approved protocols prior to initiating a change to the Virtua Health IRB approved protocol.

A major protocol deviation is one that affects subject safety, rights, welfare, or data integrity. Examples of major protocol deviations include:

- Failure to obtain informed consent
- Enrolling subject who does not meet inclusion/exclusion criteria
- Error in dispensing or dosing of drug/study medication; committed by subject or study team
- Enrollment of subjects after expiration of Virtua Health IRB approval

A minor protocol deviation is one that does not affect subject safety, rights, welfare or data integrity. Examples of minor protocol deviations include:

- Study procedure conducted out of sequence
- Failure to perform a required lab test
- Study visit conducted outside of required timeframe
- Failure of subject to return study medication

It is the responsibility of the PI to determine if a deviation is major or minor. Major protocol deviations must be reported to the IRB within ten working days of discovery. Minor protocol deviations may be reported at continuing review. Reports of protocol deviations must include:

- A detailed description of the incident;
- Indication as to whether the deviation placed the subject at risk;
- Information regarding changes implemented by the study team to ensure that such deviations will not occur in the future.

Violations: a variance from the approved study protocol that:

- Has harmed or increased harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, state or local laws, or institutional human subject protection regulations, policies or procedures.

Protocol Violations must be reported within 10 days of the investigator becoming aware.

Reports of protocol violations must include:

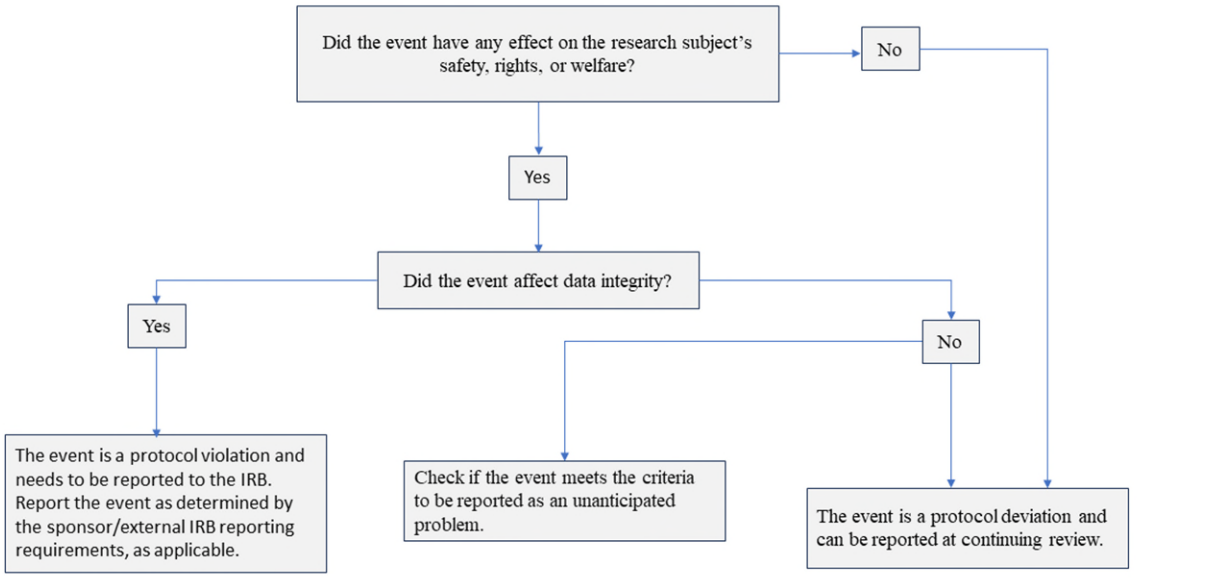
- A detailed description of the incident;
- Information regarding changes implemented by the study team to ensure that such deviations will not occur in the future.

- Corrective action plan

Reports of protocol deviations/violations will be reviewed by the Virtua Health IRB chair/designee. The reviewer may initiate further inquiry or review, depending on the severity of the deviation/violation. If a deviation/violation proves to be serious, the reviewer may bring it to the full Virtua Health IRB meeting for review and choose to suspend or terminate the protocol. Deviations/Violations that do not represent a change to the risk/benefit profile of the study can be processed following an expedited procedure and reported to the board as information.

Investigators will be informed in writing of all Virtua Health IRB inquiries and determinations. If determinations of serious noncompliance, continuing noncompliance or an unanticipated problem are made, the incident will be reported appropriately to external agencies and the Signatory Official will take appropriate corrective action.

Protocol Deviation vs. Protocol Violation



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Purpose and Mission

The mission of the Virtua Health Institutional Review Board (IRB) is the protection of human subjects involved in research. The Virtua Health IRB review and monitors all human subject studies conducted at any of the locations listed above.

Under Office for Human Research Protections (OHRP) and Food and Drug Administration (FDA) regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

The IRBs are responsible to ensure compliance with FDA, Department of Health and Human Services (HHS) and the Office for Human Research Protections (OHRP), regulations pertaining to research involving human subjects.

Ethical Principles

Virtua is committed to conducting research with the highest regard for the welfare of human subjects. It upholds and adheres to the principles of The Belmont Report: *Ethical Principles and Guidelines* for the Protection of Human Subjects in Research by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

- **Respect for Persons**, which is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- **Beneficence**, which is assured by ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
- **Justice**, the equitable selection of subjects.

Regulatory Compliance

Virtua is responsible for ensuring compliance with federal regulations, state laws and institutional policies. Virtua operates its Virtua Health IRB under the authority of its Federal Wide Assurance (FWA00002656).

RESEARCH INVOLVING VULNERABLE POPUALTIONS

Not every person is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

Potentially vulnerable groups may include:

- Prisoners
- Pregnant Women
- Children
- Individuals with impaired decision-making capacity
- Others (e.g., Non-English speaking subjects, employees, medical students, residents, fellows, economically or educationally disadvantaged persons, etc)

This policy describes the requirements concerning review of research that involves groups that could be potentially vulnerable to coercion in regard to autonomy, and present conditions that may affect risk/benefit determinations or bearing unequal burden in research.

Prisoners

Virtua-Health IRB is not constituted to meet regulatory requirements that would permit participation of prisoners as research participants. Therefore, Virtua does not permit research that targets a prisoner population.

Prisoners – an individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statues or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Investigators must promptly contact the Virtua-Health IRB Office should an active research subject become a prisoner (according to the OHRP definition) in the course of their participation in the study. When this scenario presents, every effort to safely discontinue the individual's participation from the research will be made.

If the investigator wishes to have a prisoner continue to participate in the research, Virtua will outsource Virtua-Health IRB review to a duly constituted Virtua-Health IRB. If there are fees associated with this review, the principal investigator will cover this charge. Virtua will notify OHRP and wait for a letter of authorization. Otherwise, the prisoner participant must stop participating in the research, except in situations in which the investigator asserts that it is in the best interest of the participant to remain in the research study while incarcerated. In this case, the Virtua-Health IRB Chair may determine that the prisoner participant may continue to participate in the research until the requirements of subpart C are satisfied by a duly constituted Virtua-Health IRB.
Additional regulations may apply, depending upon sponsor status. The Virtua-Health IRB will consult with the Office of General Counsel as needed for research protocols involving prisoners.

Children

To safeguard their interests and to protect them from harm, ethical and regulatory considerations are in place for reviewing research involving children.

Children – as person(s) who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted. As a result, permission of the child's parent(s) or guardian(s) must be obtained prior to participation of the child in research.

The following exceptions to the general rule apply, where a person under the age of 18 does not meet the federal definition of 'child' and may provide legally effective consent to participate in research if either:

The research involves the provision of medical care/treatment. (Including care or treatment deemed to be experimental) AND the person:

- Has graduated from high school, or
- Is married, or
- Is or has been pregnant.

Any of these scenarios must be documented in the research records (i.e., EMR).

- The person is an emancipated minor. If an emancipated minor provides consent for themselves, the court order must be copied and included in the research record (i.e., EMR) with the signed consent document.

All individuals defined as "children" will be afforded the protections under Subpart D, 45 CFR 46.401-409 and 21 CFR 50.50-54.

- Subpart D Protections are not applicable for minors who do not meet the definition of children. The Virtua-Health IRB may consider these participants potentially vulnerable and may choose to apply additional protections.
- When a research protocol involves minors who do not meet the definition of children, the Virtua-Health IRB will carefully balance the potential risks and benefits of the proposed research.
- If the research includes enrollment of participants in other states or countries, the principal investigator is responsible for providing the Virtua-Health IRB with sufficient information to verify the age at which participants in such jurisdictions have the ability to consent to participate in research, including any medical treatments or procedures, if applicable.
- The Virtua-Health IRB may, if it appears advisable, require the submission of an opinion rendered by an attorney from any applicable jurisdiction on age at which an individual can consent to participate in research.

Guardian – an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

Determinations of Risk: Federal regulations require Virtua-Health IRBs to classify research involving children into one of four categories and to document their discussions of the risks and benefits of the research study.

The four categories of research involving children based on degree of risk and benefit to individual research participants are as follows:

- Research not involving greater than minimal risk. (45 CFR 46.404, 21 CFR 50.51)
- Research involving greater than minimal risk but presenting the prospect of direct benefit to an individual research participant (45 CFR 45.405, 21 CFR 50.52)
- Research involving greater than minimal risk with no prospect of direct benefit to individual research participants, but likely to yield generalizable knowledge about the research participant's disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR 46.407, 21 CFR 50.54)
- Research that is not approvable under any of the previous mentioned categories, may be conducted or funded by DHHS provided that the Virtua-Health IRB, and the Secretary, after consultation with a panel of experts, finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles. (45 CFR 46.408, 21 CFR 50.55)

Parental Consent

Children may be participants of research only if informed consent is obtained from the parent(s) or legal guardian. The Virtua Health IRB will determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered not reasonably available.

- The regulations provide that the Virtua-Health IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 (minimal risk research) or 45 CFR 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to individual research participants) [45 CFR 46.408(b)].
- Where research is covered by 45 CFR 46.406 and 45 CFR 46.407, and permission is to be obtained from parents, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child [45 CFR 46.408 (b)].
- Where parental permission is to be obtained, the Virtua-Health IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under 21 CFR 50.51 or 50.52.
- Where clinical investigations are covered by 21 CFR 50.53 or 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law. Permission by parents or guardians must be documented in accordance with and to the extent required by 21 CFR 50.27. Participation of children in clinical investigations who are wards of the state is governed by 21 CFR 50.53, 50.54 and 50.56.

Assent of Children

Assent – a participant's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

The Virtua-Health IRB must determine that adequate provisions are made for soliciting the assent of the child(ren) when in the judgment of the Virtua-Health IRB the child(ren) can provide assent. In determining whether the child(ren) can provide assent, the Virtua-Health IRB must consider the age, maturity, and psychological state of the child(ren) involved. This judgement may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the Virtua-Health IRB deems appropriate. When the Virtua-Health IRB determines that assent is required, it must also determine whether and how assent must be documented. The Virtua-Health IRB may also waive assent.

In determining whether participants are capable of assenting, the Virtua-Health IRB shall consider the age, maturity, and psychological state of the participants involved. This judgement may be made at the time of (initial) review for all participants to be involved in research under a particular protocol, or for each participant, as the Virtua-Health IRB deems appropriate,

If the Virtua-Health IRB determines that the capability of some or all of the participants is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the participant and is available only in the context of the research, the assent of the child(ren) is not a necessary condition for proceeding with the research.

Documentation of Assent

When the Virtua-Health IRB determines that assent is required for a child(ren) of seven or older, the child(ren) shall sign the assent signature page by either personally signing it or making a mark. If the child(ren) verbally assents but refuses to sign the form or is unable to, then this must be documented on the assent form. The assent process must be documented in the child(ren)'s medical/research record.

Waiving Assent for Research Involving Children

The Virtua-Health IRB may waive requirements for obtaining or documenting assent if the Virtua-Health IRB determines:

Capability of the child(ren) with impaired decision-making capacity is limited such that they cannot be reasonably consulted;
The child(ren) with impaired decision-making capacity are not capable of providing assent based on the age, maturity or psychological state; or
The research intervention or procedure(s) involved hold out a prospect of direct benefit that is important to the health or well-being of the child(ren) with impaired decision-making capacity; Or
When the following criteria is satisfied:

- The research involves no more than minimal risk to the child(ren); and
- The waiver will not adversely affect the rights and welfare of the child(ren); and
- The research could not practicably be carried out if assent was required; and
- When appropriate, pertinent information is provided after participation.

Pregnant Women and Fetuses

The Virtua-Health IRB may approve only research that satisfies all the conditions of Subpart B as follows:

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;

- 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.
- Any risk is the least possible for achieving the objectives of the research.
- 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 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 accordance with the informed consent provisions of subpart A of this part;
- If the research holds out the prospect of direct benefit to the pregnant women, 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 the 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 accordance with the informed consent provisions of subpart A of this part;
- 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 accordance 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 if the pregnancy resulted from rape or incest;
- Each individual providing consent as stated above, is fully informed regarding the reasonable foreseeable impact of the research on the fetus or neonate;
- For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accordance with the provisions of subpart D of 45 CFR 46,
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy,
- Individuals engaged in research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy, and
- Individuals engaged in the research will have no part in determining the viability of a neonate.

Research Involving Neonates

After delivery, neonates may be involved in research if all the following conditions are met:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;

- The individual(s) providing consent under the applicable regulations is/are fully informed regarding the reasonably foreseeable impact of the research on the neonate; and
- The regulatory requirements have been met as applicable.

Neonates of uncertain viability

After delivery, and until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by federal regulations unless the Virtua-Health IRB has determined the following additional conditions are met in addition to those noted below:

- 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 the objectives of the research;
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means, and there will be no risk to the neonate resulting from the research; and
- 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 LAR is obtained in accord with 45 CFR 45 subpart A, unless altered or waived in accord with 45 CFR 46.101(i) or 45 CFR 46.116 (c) or (d).

Nonviable Neonates

After delivery, a nonviable neonate may not be involved in research covered by federal regulations unless all of the following conditions are met in addition to those in part A of 45 CFR 46:

- Vital functions of the neonate will not be artificially maintained;
- The research will not terminate the heartbeat or respiration of the neonate;
- There will be no risk to the neonate resulting from the research;
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
- The legally effective informed consent of both parents of the neonate is obtained in accord with 45 CFR 46 Subpart A, except that the waiver and alteration provisions of 45 CFR 46.116(c) and (d) do not apply. However, if one parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of the other parent will suffice to meet the requirements, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of an LAR of a nonviable neonate will not suffice to meet the requirements of the regulations.

Individuals with Impaired Decision-Making Capacity

Investigator Responsibilities

Adults with impaired decision-making capacity or institutionalized participants (e.g., psychiatric hospitals) must not be selected for research studies solely due to such a person's availability, compromised position or ease of recruitment.

When applying to the Virtua-Health IRB for research that directly targets adults with impaired decision-making capacity, the investigator must:

- Explain why it is necessary to involve adults with impaired decision-making capacity as targeted participants for this research,
- Provide sufficient justification for the use of that population,
- Explain why the research pertains to aspects of institutionalization, if applicable,
- Explain why non-institutionalized participants are not appropriate for the research and why they may not be reasonably available, if applicable,

- Explain the procedures proposed for evaluating the mental status of prospective participants to determine whether they are capable of consenting,
- Explain how the Principal Investigator will identify persons authorized to give legally valid consent on behalf of any individual(s) judged incapable of consenting on their own behalf, and whether assent from such individuals will be sought,
- Describe if the patient's physician or another health care provider will be consulted before any individual is invited to participate in research,
- Describe if it is reasonable to expect that during the course of the study, participants may lose or regain their capacity to consent or their ability to withdraw (e.g., research involving administration of or withdrawal from psychotropic agents), and
- Describe if the research is likely to interfere with ongoing therapy or regimens.
- The investigator must determine that the prospective research subject does not have the capacity to make or communicate decisions about proposed responsibilities and this must be documented in the medical record.

Virtua Health IRB Responsibilities

At the time of initial review, the Virtua-Health IRB will follow the below procedures if it is determined that individuals with impaired decision-making capacity can enroll.

The Virtua-Health IRB will determine which of the following three categories best describes the proposed research:

1. The research involves no greater than minimal risk;
2. The research involves an intervention or procedure that presents an increase over minimal risk to involved participants, but which offers the potential for direct individual benefit to the subject and is available only in the context of the research study; or
3. The research involves an intervention or procedure that presents an increase over minimal risk and no potential for direct individual benefit, but likely to yield generalizable knowledge for understanding or eventually alleviating the subject's disorder or condition.

The Virtua Health IRB will apply the following required findings for each of the above listed categories as follows:

1. The research involves no greater than minimal risk;
    a. Adequate provisions are made for soliciting consent of a capable subject or assent of an incapable subject and consent of the subject's representative.
2. The research involves an intervention or procedure that presents an increase over minimal risk to involved participants, but which offers the potential for direct individual benefit to the subject and is available only in the context of the research study;
    a. The risk is justified by the anticipated benefit to the participants; and
    b. The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches; and
    c. Adequate provisions are made for soliciting consent for a capable subject or assent of an incapable subject and consent of the subject's representative.
3. The research involves an intervention or procedure that presents an increase over minimal risk and no potential for direct individual benefit, but likely to yield generalizable knowledge for understanding or eventually alleviating the subject's disorder or condition.
    a. The risk represents a minor increase over minimal risk;
    b. The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; and
    c. The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for understanding/amelioration of (such) disorder or condition; and
    d. Adequate provisions are made for soliciting consent of a capable subject or assent of an incapable subject and consent of the subject's representative.

4. The Virtua-Health IRB may apply the following additional considerations:

a. An Virtua-Health IRB member who is independent of the research and the investigator(s), and who is knowledgeable about the experience with adults with impaired decision-making capacity is present at the Virtua-Health IRB meeting.
b. There are adequate procedures for evaluating the mental status of prospective participants to determine if they are capable of giving informed consent.
c. There are adequate procedures for identifying persons authorized to give legally valid consent on behalf of any individuals assessed to be incapable of consenting on their own behalf.
d. If the research proposes to involve institutionalized participants with decisional impairment, sufficient justification has been provided for using this population.
e. The following additional safeguards may be required to protect the rights and welfare of these participants:
    1. Use of an independent party (not associated with the research, but with appropriate expertise) to assess the capacity of a potential subject;
    2. Use of an independent monitor to observe the recruitment, assessment, and/or the informed consent process;
    3. Use of informational or educational techniques to assess and enhance comprehension at each stage of the research;
    4. Use of a waiting period to provide additional time for participants to consider participating in the research; and/or
    5. Other considerations that are decided by Virtua-Health IRB leadership.

5. Informed Consent: Generally, adult individuals with impaired decision-making capacity who are competent to understand the issues of being a research participant should be allowed to either refuse to assent to participate in a research study, even if such persons lack capacity to provide consent to participate in a research study even if such persons lack capacity to provide consent to participate in research on their own behalf. Impaired decision-making capacity alone should not disqualify a person from providing consent; rather, the investigator shall present specific evidence of impaired decision-making capacity to a degree that shows that the person lacks the ability to make or communicate decisions about proposed research activities.

The Virtua-Health IRB shall respect and observe the objection or refusal of an individual with impaired decision-making capacity to participate in a research study, even if the intervention is expected to provide a direct health benefit to the participant and the intervention is available only in the context of the research. This is in keeping with the National Commission's recommendation that "despite the fact that consent may be obtained from an LAR or guardian, the feelings and expressed wishes of a 'cognitively impaired' person should still be respected'.

Studies involving participants with impaired decision-making capacity may take place over extended periods. The Virtua Health IRB shall consider whether periodic assessment of individuals is required to reassess whether a participant's continued involvement is voluntary. The Virtua-Health IRB may require that investigators consent participants after considering the study's anticipated length and the condition of the individuals to be included (e.g., participants with progressive disease).

The Virtua-Health IRB will require a LAR signature line in the informed consent document if all of the above are met.

Legally Authorized Representatives by State

For adults who are unable to consent to participate in a research study, surrogate consent may only be provided by an LAR in accordance with applicable law. An LAR is an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the research.

The laws of the jurisdiction where the research is to be conducted determine who may serve as the LAR. Some states have laws that specify who can provide surrogate consent for research studies, but most states only have laws that define who can provide surrogate consent for medical procedures or treatment.

The Virtua-Health IRB and the investigator shall seek guidance from the Office of General Counsel to determine who may provide surrogate consent in other jurisdictions, as needed.

TYPES OF VIRTUA HEALTH IRB REVIEW

Virtua Health IRB Pre-Review

Applications submitted are triaged by the HRPP Office team who ensure completeness of the submission. Complete submissions are processed for Virtua Health IRB review (convened board or expedited review).

A. **Full Board Review.** The Virtua Health IRB uses a primary reviewer system. For initial review of a study, one or more Virtua Health IRB members will be designated based upon their level of expertise by the IRB Team, with the approval of the Virtua Health IRB chair, to review the complete study documentation. The reviewer(s) are to complete the designated reviewer sheet(s) and present their review to the committee at the Virtua Health IRB meeting. The reviewer(s) will also make a recommendation **(**Approved, Approved with Conditions, Approved with Stipulations, Tabled, Disapproved) The remainder of the Virtua Health IRB members will also receive the complete study documentation for review. A non-scientific member may be appointed as an additional reviewer of the informed consent to ensure that the readability of the consent conforms to applicable regulations. The principal investigator (PI) may be asked to attend the Virtua Health IRB meeting to provide clarification and/or to answer questions raised by members. The PI will be asked, by the Chairperson, to leave the room during the deliberations and voting.

Criteria for Approval of Research

(45 CFR 46.111, 21 CFR 56.111)

A study will be approved only if the following requirements are satisfied:

1. Risks to research participants are minimized:
    a. By using procedures that are consistent with sound research design and which do not unnecessarily expose research participants to risk, and
    b. Whenever appropriate, by using procedures already being performed on the research participants for diagnostic or treatment purposes.
2. Risks to research participants are reasonable in relation to anticipated benefits, if any, to research participants, and the importance of the knowledge that may be expected to result.
    a. In evaluating risks and benefits, the Virtua Health IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that research participants would receive even if not participating in the research). The Virtua Health IRB will 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.
3. Selection of research participants is equitable.
    a. In making this assessment the Virtua Health IRB will consider:
        i. purposes of the research
        ii. Setting in which the research will be conducted
        iii. Categories of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
4. Provisions are made for appropriately obtaining and documenting informed consent
    a. Informed consent will be sought from each prospective research participants or the research participant's legally authorized representative, in accordance with and to the extent required by appropriate local, state and federal regulations.
    b. Informed consent will be appropriately documented or appropriately waived as required by local, state and federal regulations.
5. Appropriate measures are in place for data management and data analysis
    a. Research plan makes adequate provisions for monitoring the data collected to ensure the safety of research participants.
6. Appropriate measures are in place to protect the privacy of subjects and maintain the confidentiality of data
    a. Research plan makes adequate provisions to protect the privacy of research participants and to maintain the confidentiality of the research data.

Additional Review Considerations

To approve research, the Virtua Health IRB will determine that studies have the resources necessary to protect participants:

- Adequate time for the researchers to conduct and complete the research.
- Adequate number of qualified staff
- Adequate facilities
- Access to a population that will allow recruitment of the necessary number of participants.
- Availability of medical or psychosocial resources that participants might need as a consequence of participation in the research.

The Virtua Health IRB will ensure that studies are reviewed at periods appropriate to the degree of risk research participants are exposed to due to their participation in the study, but at least annually. Generally, those protocols that are high risk, where informed consent process is particularly complex or where there is a history of investigator noncompliance may be reviewed more frequently than annually.

The Virtua Health IRB may require verification of information submitted by a Principal Investigator, the need to verify any information will be determined by the Virtua Health IRB at a convened meeting. The purpose of the verification will be to provide necessary protection to research participants when deemed appropriate by the Virtua Health IRB.

The criteria used to determine whether third-party verification is required may include:

- Investigators that conduct studies that involve a potential high risk to research participants,
- Studies that involve vulnerable populations,
- Investigators that conduct studies that involve large numbers of research participants, and
- Investigators selected at the discretion of the Virtua Health IRB.

B. **Continuing Review**

The Virtua Health IRB conducts continuing review of non-exempt human subject research occurring within its jurisdiction at intervals appropriate to the degree of risk, but not less than once per year. During continuing review, the Virtua Health IRB determines that all regulatory requirements and institutional requirements are met. In addition, during continuing review the Virtua Health IRB determines which projects require verification from sources other than the investigator to ensure that no material changes in the research have occurred since the previous Virtua Health IRB review.

The Virtua Health IRB is responsible for continuing review of ongoing research to ensure that the rights and welfare of human subjects are protected. The Virtua Health IRB must conduct continuing review of protocols for purposes of renewal of the IRB approval period, at intervals appropriate to the degree of risk, but not less than once per year. "Not less than once per year' means that the research must be reviewed on or before the one-year anniversary of the previous Virtua Health IRB approval date, even though the research activity may not have begun until sometime after Virtua Health IRB granted its approval. Risk level is determined at the initial review and may be revised at the time of continuing review. Periodic review for individual studies may be required more frequently, at the discretion of the Virtua Health IRB. Studies which involve new modalities or in which the side effects of agents are unknown will most likely be reviewed more often.

Principal Investigators are required to complete and submit a Continuing Review Form prior to the expiration of the study or as specified by the Virtua Health IRB.

Expiration of Virtua Health IRB Approval. There is no grace period extending the conduct of the research beyond the expiration date of Virtua Health IRB Approval. If Continuing Review and Virtua Health IRB approval has not occurred as scheduled and Virtua Health IRB approval expires, the investigator must stop all research interactions and interventions. The continuation of research after the expiration of the Virtua Health IRB approval is not permitted. If the Virtua Health IRB has not reviewed and approved a research study by the study's current expiration date, (i.e. the Virtua Health IRB approval has expired) all research activities related to the study must stop. No new subjects can be enrolled in the study. However, if the Principal Investigator believes that stopping research related interventions or interactions would adversely affect the safety of

currently enrolled participants, the PI must immediately contact HRPP Leadership to discuss the specific safety concerns. The Virtua Health IRB Chair/Vice Chair will determine whether it is in the best interest of the individual participants to continue to receive research related interventions. During the lapse of Virtua Health IRB approval, new participants cannot be enrolled, prospective data cannot be collected, and no procedures that are only being performed for the protocol may be conducted until the continuing review process has been completed.

Criteria for Renewal:

Continuing review must be substantive and meaningful. The criteria for approval of research are detailed at 45 CFR 46.111 and 21 CFR 56.111, as well as all applicable regulatory subparts will be followed.

To determine the status of the study, the following will be revisited:

- Consent document
    - The Virtua Health IRB shall review the currently approved consent document and ensure that the information is still accurate and complete.
- Protocol document
    - The Virtua Health IRB shall review the currently approved protocol document and ensure that the information is still accurate and complete. Amendments to the protocol since initial review are submitted to the Virtua Health IRB for review and approval in real-time without waiting until the time of continuing review.

Continuing Review
All Virtua Health IRB members shall receive a completed Continuing Review Form prepared and signed by the Principal Investigator which includes:

- The number of participants accrued
- The number of participants who have withdrawn
- The reason(s) for withdrawal
- A summary since the last continuing review (or initial review if a continuing review hasn't occurred) of:
- Complaints about the research
- Any relevant recent literature
- Any interim findings
- Any relevant multi-center trial reports
- The current risk-potential benefit assessment based upon study results
- Audit summaries
- ClinicalTrials.gov reporting and/or updates

Possible Outcomes of Continuing Review

As an outcome of continuing review, the Virtua Health IRB may require that the research be modified or suspended altogether. The Virtua Health IRB may need to impose special precautions or relax special requirements it had previously imposed on the research protocol, such as shortening the approval time frame.

Status Report

Criteria for the renewal of Virtua Health IRB approved non-exempt human research that does not require a regulatorily mandated Virtua Health IRB continuing review.

Unless the Virtua Health IRB determines otherwise, a progress report (in lieu of a continuing review submission) is required in the following circumstances:

- When research is eligible for expedited review
- When research has progressed to the point that a study is in data analysis only

This is not an option for FDA-regulated studies.

A progress report will undergo the same requirements for Virtua Health IRB review as a Continuing Review.

B. **Study Changes.** The Virtua Health IRB is to review, and approval all proposed changes in Virtua Health IRB-approved research prior to initiation of any changes. Approval of all study changes to IRB approved research is contingent upon the protocol meeting the regulatory requirements of 45 CFR 46.111 or 21 CFR 56.111 and all applicable regulatory subparts. Minor amendments may be processed by the expedited review procedure whenever appropriate. Changes in research activity that are, in the opinion of the investigator, necessary to eliminate apparent immediate hazards to a research participant may be undertaken without prior Virtua Health IRB approval. In such cases, the investigator must promptly inform the Virtua Health IRB of the implemented change.

Study Updates

1 Minimal Risk Studies

Studies that are initially approved by expedited procedures at Virtua Health IRB, all changes may be reviewed expedited, if the added procedures involve no more than minimal risk to participants and do not alter the initial risk determination(s).

Examples of Minor Changes may include, but are not limited to, the following:

- The changes proposed do not affect the study's risk determination(s);
- The changes do not substantially change the specific aims or design of the study, if greater than minimal risk; or
- Added procedures involve no more than minimal risk to participants including procedures that fall not categories (1-7) of research that can be reviewed using the expedited procedures;
- The addition of research activities that would be considered exempt or expedited if considered independent from the main research protocol;
- An increase or decrease in proposed human research participant's enrollment;
- Alterations in the dosage form (e.g., tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration remain constant;
- Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement;
- The addition or deletion of qualified investigators;
- The addition or deletion of study materials, such as but not limited to pill diaries, questionnaires, and/or translated documents

2 Greater than Minimal Risk Studies

Some changes may be approved by expedited procedures if the changes are minor and do not pose additional risk to participants. When a proposed change in a research study is not minor, then the Virtua Health IRB must review and approve changes at a convened meeting before changes can be implemented.

Examples of Major Changes may include, but are not limited to, the following:

- Broadening or narrowing the range of inclusion criteria;
- Alterations in the dosage or route of administration of an administered drug;
- Extending substantially the duration of exposure to the test material or intervention;
- The deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations;
- The addition of serious unexpected adverse events or other significant risks to the Informed Consent Document; or

- Changes, which, in the opinion of the Virtua Health IRB Chair or the Virtua Health IRB Chair's designee, do not meet the criteria or intent of a minor amendment.

Re-Consent/Notification of Participants

The investigator must determine if the proposed change to the research requires a modification to the informed consent and describe which participants will be re-consented.

The Virtua Health IRB will review the investigator's assessment and may determine that the proposed changes to the research activities require a change in the informed consent document and may warrant re-consenting of currently enrolled participants or notification of participants who have completed research interventions. The Virtua Health IRB will make the final determination on how participants are re-consented.

Modifications to the informed consent documents for research that is closed to accrual may not be required if the sponsor, investigator and/or the Virtua Health IRB determines that the participants will not need to be re-consented, i.e., all participants are off study.

Notification(s) to Investigator

All Virtua Health IRB determinations will be reported in writing to the investigator.

Changes Made Without Virtua Health IRB Approval to Eliminate an Immediate Hazard

Changes made to eliminate hazards to research participants may be undertaken without prior Virtua Health IRB review. Changes in approved research that are initiated without Virtua Health IRB approval to eliminate apparent hazards to participants:

- Must be reported as a deviation and the investigator must report such changes with a detailed explanation as to why the change was necessary.
- Are reviewed by the Virtua Health IRB to determine whether the change was consistent with ensuring the participant's continued welfare.

C. **Facilitated review** is a procedure through which certain kinds of research may be reviewed and approved without convening a meeting of the Virtua Health IRB. If no issues are found, the investigator may continue the study and the central Virtua Health IRB that initially approved the study will remain the Virtua Health IRB of record.

D. **IRB of Record**: For those studies where Virtua Health IRB will be the IRB of Record or elects to cede IRB review to another entity a Reliance Agreement will be executed. A reliance agreement will be utilized when (a) Virtua is the IRB of record for non-exempt human subjects research being conducted by employees or agents of another institution; or (b) rely on another entity to be the IRB of record for non-exempt human subjects research being conducted by the employees or agents of our institution. Virtua's Institutional Official (IO) or designee, retains final authority to determine whether Virtua will enter into a RA.

The Office for Human Research Protections (OHRP) requires single IRB review for non-exempt human subjects multi-center domestic protocols that meet the following requirements:

- The study or a portion of the study is federally funded or supported
- Approved on or after January 20, 2020

For federally funded research, the reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance by the Federal department or agency supporting the research.

The policy from the NIH stipulates that at the time of new and re-competing applications/proposals for funding, the primary Principal Investigator must indicate that single IRB (sIRB) will be applicable.

Federal wide Assurance (FWA): A written document signed by an institution (not an IRB) outlining the institution's commitment to the Department of Health and Human Services (DHHS) that the institution will abide by 45 CFR 46, as well as the Terms of Assurance, when the institution becomes engaged in non-exempt human subjects research that is covered by the institution's FWA.

IRB Reliance Agreement (RA): A written agreement that is entered into between an engaged institution and an institution operating an IRB when an engaged institution relies upon an IRB that is operated by another institution or organization for review of research covered by the engaged institution's FWA. The RA outlines the IRB review relationship and includes a commitment that the IRB will adhere to the requirements of the engaged institution's FWA. The RA must be kept on file at both institutions/organizations and made available to ORHP or any U.S. federal department or agency conducting or supporting research covered by the FWA upon request.

IRB of Record: The IRB responsible for the review and oversight of non-exempt human subjects research.

E. **Expedited review** is a procedure through which certain kinds of research may be reviewed and approved without convening a meeting of the Virtua Health IRB. Under the expedited review procedure, review of research may be carried out by the Virtua Health IRB Chairperson or by one or more experienced members of the Virtua Health IRB as designated by the Chairperson. The reviewer(s) may exercise all the authorities of the Virtua Health IRB, with the exception of disapproval. Studies can only be disapproved following the review of the full Virtua Health IRB committee. When an expedited review procedure is used, the Virtua Health IRB must be advised of the studies approved under this procedure at the next scheduled meeting. The expedited reviewer will evaluate the research study to ensure that the rights and welfare of human subjects are protected and that all criteria for Virtua Health IRB approval have been met. The Expedited Review Checklist, ReviewerSheet_Non-Committee Review623, will be completed for each submission to document the reviewer's comments, concerns and recommendations. The checklists will be kept in the Virtua Health IRB file.

   Research activities involving no more than minimal risk and in which the only involvement of human subjects that meets one of the categories may be reviewed through the expedited procedure.

   Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review procedure may not be used for classified research involving human subjects. Classified research is research, knowledge of the procedures and results of which, that is restricted to individuals with United States Government security clearances.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review utilized by the Virtua Health IRB.

F. **Exempt from Review.** Certain low-risk research is exempt from the requirements in the Federal regulations concerning the IRB review and approval. The PI will not make the final determination of exemption.

Exemption Request Procedures: The principal investigator must submit the full protocol along with the request for exemption. Only the Chair, or a designate, can determine the exempt status of a research proposal. Reviewers will use the Checklist for Exempt Protocol Determination, ReviewerSheet_Non-Committee Review623, to determine and document whether the protocol meets the exemption criteria.

Research determined to be exempt from IRB review will be exempt from continuing review unless changes made to the protocol remove it from the exempt category and requiring full board or expedited review.

A letter confirming the exempt status of the research will be issued to the investigator.

G. Emergency exemption from prospective Virtua Health IRB approval. Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. The emergency use provision in the FDA regulations is an exemption from prior review and approval by the IRB. The exemption allows for one emergency use of a test article without prospective IRB review. Any subsequent use of the investigational product must have prospective Virtua Health IRB review and approval. Each of the following conditions must exist to justify emergency use:

1) the patient is in a life-threatening condition that needs immediate treatment and there is no comparable or satisfactory alternative therapy;
2) the potential benefit justifies the potential risk and those risks are not unreasonable
3) providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval

After an unapproved device is used in an emergency, the physician should:

1) report to the Virtua Health IRB within 7 business days and otherwise comply with Virtua Health IRB regulations;
2) evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain Virtua Health IRB approval and an approved IDE for the device's subsequent use; and
3) if an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Any subsequent use of the investigational product must have prior Virtua Health IRB review and approval.

Even for an emergency use, the PI is required to obtain informed consent of the subject or the subject's legally authorized representative, unless the PI and a physician who is not otherwise participating the clinical investigation certify in writing all of the following: 1) the subject is confronted by a life-threatening situation necessitating the use of the test article; 2) informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject; 3) time is not sufficient to obtain consent from the subject's legal representative; 4) no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

H. Advertising. When advertising to recruit subjects for investigational studies is proposed, the Virtua Health IRB must review the information contained in the advertisement and the mode of communication to determine that the procedure for recruiting subjects affords adequate protection. This includes printed advertisements and radio or television broadcasts. The Virtua Health IRB review is necessary to ensure that the information is not misleading to subjects and that appropriate safeguards exist to protect the rights and welfare of research subjects.

1. The final copy of printed advertisements, as well as audio and/or video tapes, shall be submitted to the IRB prior to public use.

a) The Virtua Health IRB must review the wording of an advertisement prior to taping to reduce the need for re-taping.
b) The review of a taped message prepared from the Virtua Health IRB-approved text may be accomplished through expedited procedures.

2. In reviewing advertisements, the Virtua Health IRB shall consider the following issues:
   a) Information that is presented in a way that is misleading to potential subjects.
   b) The procedure for recruiting subjects may not be coercive.
   c) The advertisement may not state or imply a certainty of favorable outcome or other benefits beyond what is described in the approved consent form and protocol.
   d) No claim may be stated or implied that a drug, biologic, or device is safe or effective for the purposes under investigation or that the test article is known to be equivalent or superior to any other drug, biologic, or device.

3. Any advertisement to recruit subjects should be limited to:
   a) The name, address and phone number of the PI
   b) The purpose of the research and, in summary form, the eligibility criteria that will be used for prospective subjects into the study
   c) A straightforward and truthful description of the benefits to the subject for participation in the study
   d) The location of the research and the person to contact for further information

I. Appeal of the Virtua Health IRB decisions: Investigators have thirty (30) days to respond in writing to the Virtua Health IRB Chairperson if they wish the Virtua Health IRB to reconsider its decision. The Virtua Health IRB holds the ultimate authority to disapprove the research. The Chairperson will report the final decision of the Virtua Health IRB to the investigator in writing.

J. Termination of a Study:

1. The Virtua Health IRB must be notified when a study closes to accrual, when no patients are currently being treated on the study, and when no patients remain in long-term follow-up. A final closure report must be submitted when these conditions are met.

2. The Virtua Health IRB may withdraw approval for a study if any of the following occur:

   a. Updates, study/consent modifications and/or toxicity reports are not submitted as required;
   b. The investigator materially fails to comply with the Virtua Health IRB requirements;
   c. The committee comes to believe that the risks of the study outweigh the potential benefits for the participants; or
   d. The disqualification of the principal investigator by OHRP, FDA or the study sponsor.

UNANTICIPATED PROBLEMS, ADVERSE EVENTS

A. Federal Regulations

Federal regulations require prompt reporting to the Institutional Review Board (IRB), appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head of unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study at any Virtua location. (45 CFR 46.108(a)(4)(i) and 21 CFR 56.108(b)(1)).

B. Definitions

Unanticipated problems involving risk to participants or others refer to any incident, experience, outcome, or new information that:

1. Is unexpected
2. Is related or possibly related to participation in the research, and
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

1. Unanticipated: The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given:

(a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and
(b) the characteristics of the subject population being studied.

2. Related: There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

3. Adverse Event: Any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

C. Reporting

Investigators must promptly report the following problems to the IRB:

1. Adverse events involving direct harm to participants which in the opinion of the principal investigator meet the criteria for an unanticipated problem involving risk to subjects or others.

2. An unanticipated event related to the research that exposes participants to potential risk but that does not involve direct harm to participants.

3. An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk

4. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.

5. New information that indicates a change to the risks or potential benefits of the research. For example:
    a. An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.

6. A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.

7. A breach of confidentiality

8. Incarceration of a participant in a protocol not approved to enroll prisoners.

9. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial

10. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to the research participant

11. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team

12. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm

13. Sponsor imposed suspension, change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol

14. Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

D. Submission of Reports

Investigators must report unanticipated problems to the IRB promptly. Timeframe for reporting:

- REPORT WITHIN 24 HOURS OF DISCOVERY a death in an interventional study whether or not considered study-related

- REPORT WITHIN (7) SEVEN BUSINESS DAYS an unanticipated problem which is a serious adverse event

- REPORT WITHIN (10) TEN BUSINESS DAYS all other unanticipated problems

Investigators must report possible unanticipated problems to the IRB Office in writing using the IRB Reportable Form. The written report must contain the following:

- Detailed information about the possible unanticipated problems, including relevant dates

- Any corrective action, planned or already taken, to ensure that the possible unanticipated problems is corrected and will not occur again

- An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences

- Any other relevant information

- Any other information requested by the IRB Office

A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded by the IRB Office to the IRB Chair/Vice-Chair(s) if the IRB Office believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of the report of a possible unanticipated problem from someone other than the investigator or study staff, the HRPP Director will notify the PI on the study when appropriate.

E Subsequent Actions by the IRB Chair/Designee and the convened IRB to determine if the problem or event meets the definition of an unanticipated problem involving risks to subjects or others (UPIRTSO), defined as:

Any incident, experience, or outcome that meets both of the following criteria:

a unanticipated (defined above)

b indicates that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Any such incident, experience or outcome generally will warrant consideration of a quality improvement (corrective) action, such as a change in the research protocol and/or consent document, in order to protect the safety, rights and welfare of research subjects.

1 The IRB Chair/Designee reviews the report and determines whether it represents a UPIRTSO

The IRB Chair/Designee determination is based on whether the problem is both:

a unanticipated (defined above), and

b indicates that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

2 If the IRB Chair/Designeer determines that the problem is not a UPIRTSO

No further action is taken under this policy and procedure.

3 If the IRB Chair/Designee determines that the problem is an unanticipated problem involving minimal risk to subjects or others

The IRB Chair/Designee can require minor modifications to the research (as defined in procedures for review using the expedited procedure) or follow the procedure for unanticipated problems involving more than minimal risk to subjects or others.

4 If the IRB Chair/Designee determines that the problem is an unanticipated problem involving more than minimal risk to subjects or others

a The IRB Office places the matter on the agenda at the next IRB meeting.

b The IRB Office provides all members with a copy of the report, the IRB application, the currently approved IRB protocol summary, and the currently approved consent documents. All IRB members are expected to review these materials. The primary reviewer is additionally provided a copy of the investigator brochure and any previous reports of unanticipated problems involving risks to subjects or others related to the protocol.

c The convened IRB considers the following actions:

- Suspension of the study
- Termination of the study
- Modification of the protocol
  - Coordination of care planning with clinical staff
  - Revised plan for research staff competencies, roles and/or responsibilities

- Referral to institutional safety officer for root cause analysis and quality improvement plan
- Other appropriate quality improvement action plan

- Modification of the information disclosed during the consent process
- Providing additional information for current or past subjects
- Re-consent of current subjects taking part in the study.

d The Institutional Official is notified.

F Actions of the Institutional Official

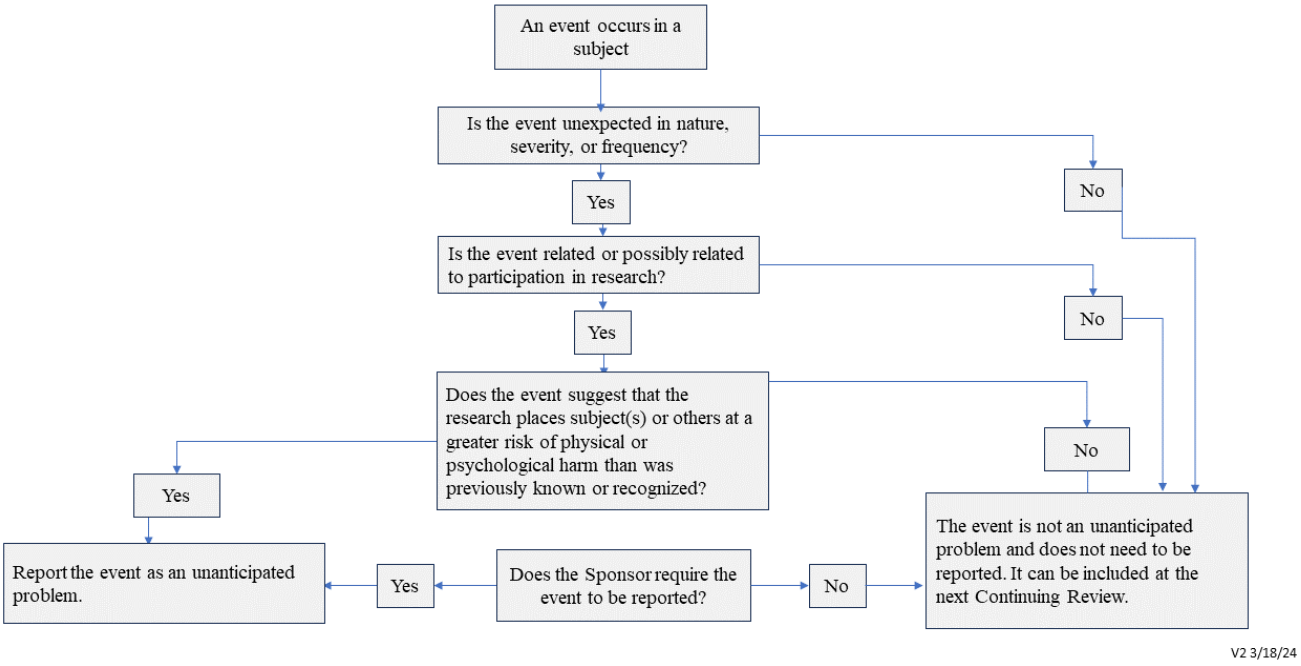
The Institutional Official(s) or their designees, with assistance from the IRB Chair, will report the institution's determination and findings to all appropriate entities within Virtua and to relevant regulatory agencies.

G Non-Reportable Events

The IRB recognizes that sponsors may require that the PI report all serious adverse events and IND safety reports to the IRB. The IRB complies with this request in an efficient manner to acknowledge receipt of these reports.

The PI's may report adverse events and IND safety reports that do not meet the above reporting requirements in summary form at the time of continuing review.

Reporting Unanticipated Problems



USE OF AN EXTERNAL OR CENTRAL IRB

Virtua Health IRB may approve the use of an External or Central IRB to review a study to be conducted by a Virtua investigator at a Virtua facility. The primary function of the External or Central IRB is to perform initial and continuing review of the study. The primary function of Virtua Health IRB is the consideration of local context and oversight of local performance. Virtua Health IRB will determine on a study-by-study basis whether to accept the review of the External or Central IRB or conduct its own review of the study.

A. **Scope:**

The following conditions must be met in order for an investigator to utilize an External or a Central IRB review:

- Multicenter industry-sponsored study already approved by an External or a Central IRB
- Virtua Health IRB may take action locally, if needed, to reduce risks to subjects and others

B. **Selection/Approval of External or Central IRB**

The External or Central IRB must be registered with OHRP and have a currently approved Federal Wide Assurance.

- The External or Central IRB must abide and meet the criteria as specified by 45 CFR 46 and 21 CFR 56.
- The External or Central IRB must be willing to provide their membership roster detailing the expertise of its members and a copy of their Standard Operating Procedures (SOP), upon request.
- The External or Central IRB must be independent of the sponsor of the research.
- The External or Central IRB must have a reliance agreement with Virtua.

Any approved External or Central IRB that receives any warnings from OHRP, FDA or the sponsor must notify Virtua IRB as soon as possible.

In those instances where Virtua authorizes the use of an External or Central IRB, the External or Central IRB will be the IRB of Record, not Virtua Health IRB.

C. **Process**

A request must be submitted to the Virtua Health IRB to utilize the External or Central IRB. If approved, further instruction will be provided dependent on the agreement between Virtua and the External or Central IRB. Virtua Health IRB will consider factors impacting the conduct of the study at Virtua. These may include ethnicity, education level, religious affiliations and community attitudes towards research. The investigator will be notified of the Virtua Health IRB determination. If applicable, any recommended changes to consent based on Virtua IRB review must be submitted to the External or Central IRB for approval. The investigator will provide a copy of the External or Central IRB approval letter to the Virtua Health IRB. After External or Central IRB approval letter is sent to the Virtua Health IRB, an acknowledgement letter is provided to the Principal Investigator.

D. **On-Going Requirements**

The Investigator will notify Virtua Health IRB of any or all of the following information:

- Notification in writing of local protocol violations/deviations, serious adverse events and unanticipated problems within 7 business days of the event. Notification of the death of a local participant must be with 48 hours of the occurrence. Reference policies: Protocol Deviations_Violations; complaints_allegations_unanticipated_adverseevents.
- Approval letters for amendments and continuing review along with a copy of any other items in the amendment and continuation submission
- Notification of study closure
- Suspension or termination of IRB approval.

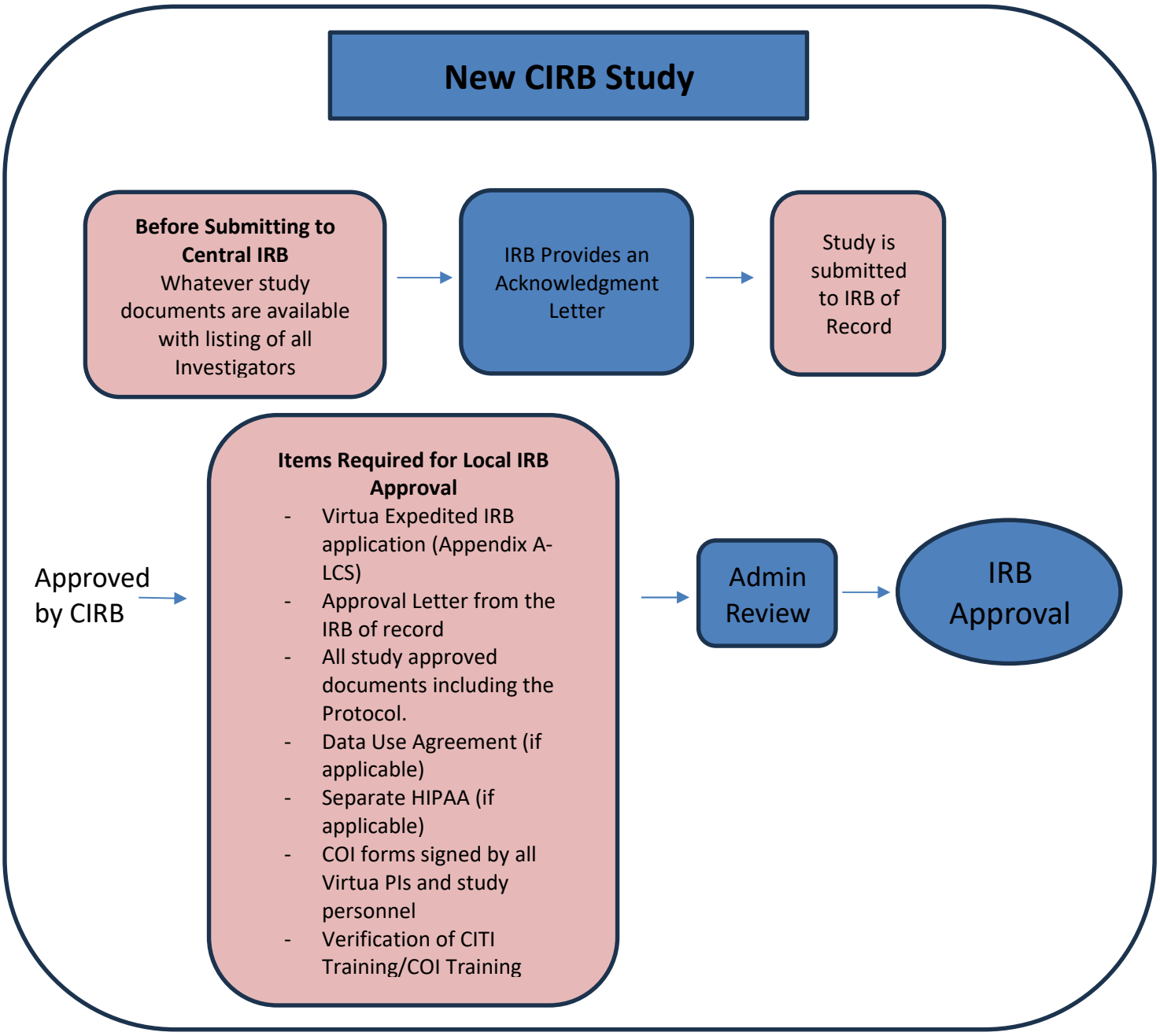
- Investigators will maintain compliance with Virtua's research policies, specifically Conflict of Interest and human subjects protection training

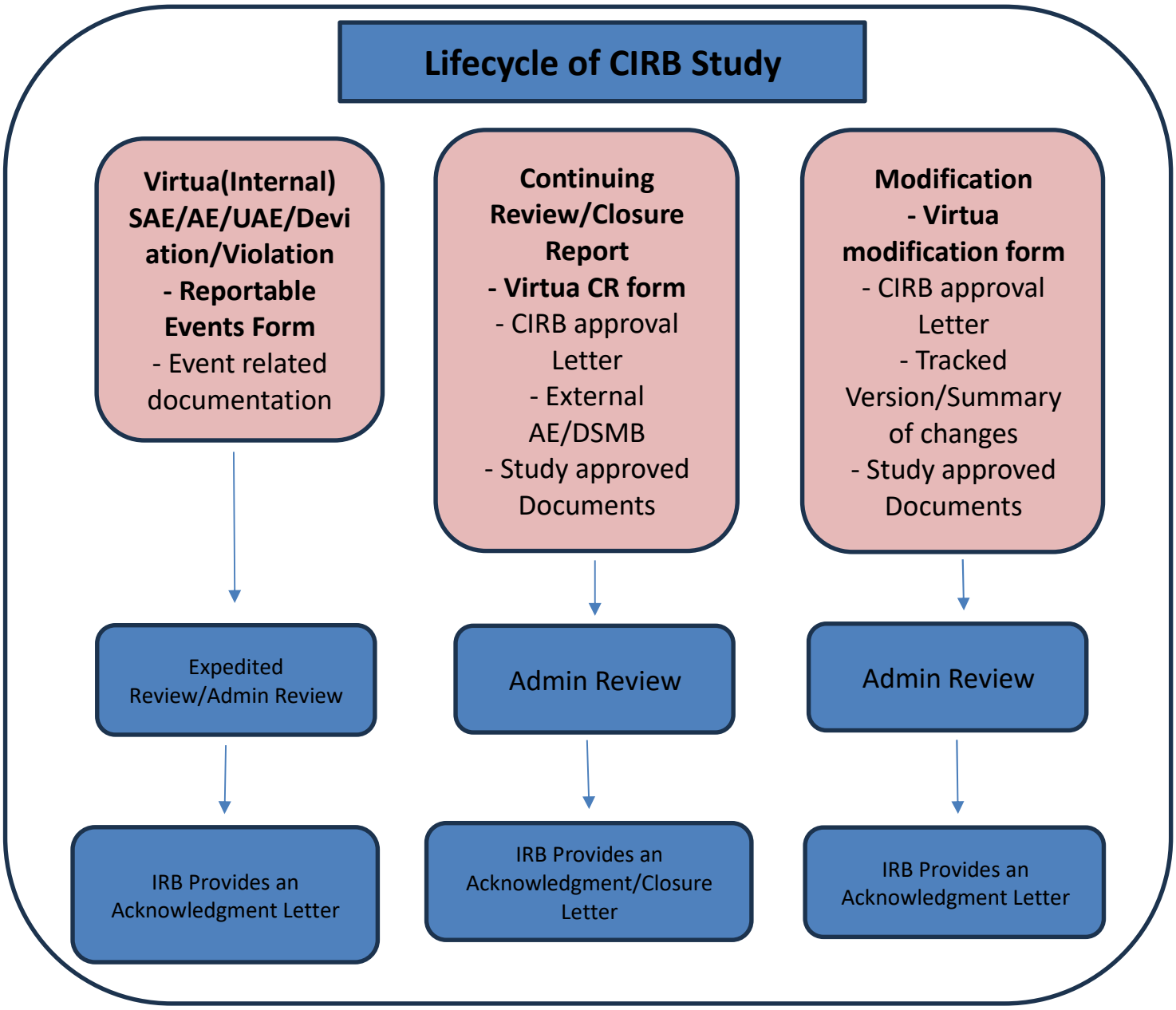
E. **Cooperative Group Research:** Cooperative research that is federally funded will be approved by a single IRB identified by the federal department or agency supporting or conducting the research. The Virtua Health IRB will rely on this reviewing IRB and this reliance will be documented.

F. **Reciprocity Agreements:** At the discretion of the HRPP Director, the Virtua Health IRB may designate an IRB at another institution as the IRB of record for a particular study or studies. A reciprocity agreement will be entered into between the institution providing the IRB review and the Virtua Health IRB.

G. **Post Approval Activity:** When an External or Central IRB is the IRB of record for a study, federal regulations require that the local IRB retain authority regarding local considerations (i.e., adverse events, protocol deviations/violations and unanticipated problems). Throughout the continuation of the study, Virtua Health IRB will review all decisions made by an External or Independent IRB for such local considerations and may take additional actions when necessary, including but not limited to additions or changes to the informed consent and/or assent documents, suspensions pending inquiry, and even disapproval.

   Virtua Health IRB will maintain all records of local review in accordance with applicable maintaining compliance with federal regulations, state, local and institutional requirements.


New CIRB Study
Before Submitting to Central IRB
Whatever study documents are available with listing of all Investigators
IRB Provides an Acknowledgment Letter
Study is submitted to IRB of Record
Approved by CIRB
Items Required for Local IRB Approval
- Virtua Expedited IRB application (Appendix A-LCS)
- Approval Letter from the IRB of record
- All study approved documents including the Protocol.
- Data Use Agreement (if applicable)
- Separate HIPAA (if applicable)
- COI forms signed by all Virtua PIs and study personnel
- Verification of CITI Training/COI Training
Admin Review
IRB Approval


Lifecycle of CIRB Study
Virtua(Internal) SAE/AE/UAE/Deviation/Violation - Reportable Events Form - Event related documentation
Continuing Review/Closure Report - Virtua CR form - CIRB approval Letter - External AE/DSMB - Study approved Documents
Modification - Virtua modification form - CIRB approval Letter - Tracked Version/Summary of changes - Study approved Documents
Expedited Review/Admin Review
Admin Review
Admin Review
IRB Provides an Acknowledgment Letter
IRB Provides an Acknowledgment/Closure Letter
IRB Provides an Acknowledgment Letter

USE AND DISCLOSURE OF PHI FOR HUMAN SUBJECTS RESEARCH
Policy

It is the policy of Virtua Health (Virtua) to recognize that the Use or Disclosure of Protected Health Information (PHI) for human subject research purposes must be handled in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH) privacy regulations and other applicable federal and/or state laws.

Purpose:

This policy outlines the procedures for Virtua's, Virtua Health Institutional Review Board (IRB) use or disclosure of PHI in human subject research.

Definitions:

Authorization is a patient's written permission to allow Virtua to Use or Disclose specified PHI. Different type of activities, such as research, have specific authorization requirements.

Disclosure means the release, transfer, provision of access to, or divulging in any manner of information outside the entity holding the information.

Protected Health Information or (PHI) is any information that is created, maintained, received, or transmitted by Virtua and relates to the past, present, or future physical or mental health or condition of a patient; the provision of health care to a patient; or the past, present, or future payment for the provision of health care to a patient; and that identifies the patient or there is a reasonable basis to believe that the information can be used to identify the patient. PHI includes information of persons living or deceased. PHI does not include employment records that a covered entity maintains in its capacity as an employer and education and certain other records subject to the Family Rights and Privacy Act (20 U.S.C. $1232g).

Research is a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes: basic research studies, clinical trials, or studies involving human subjects.

Use, with respect to PHI, means the sharing, employment, application, utilization, examination, or analysis of such information within an entity that maintains such information.

Waiver or Alteration of Authorization is the decision of a qualified Virtua Health IRB or Privacy Board, as evidenced by proper documentation, that states the Virtua Health IRB or Privacy Board has waived or altered the HIPAA requirement for patient Authorization and permits Virtua to Use or Disclose the patient's PHI for Research purposes.

Procedure

Permitted Uses and Disclosures for Research

Virtua may Use and Disclose PHI for research purposes, regardless of the source of funding of the research, under any of the following circumstances:

1. Authorization. A research subject, or their legal representative, generally must complete and sign a HIPAA-compliant Research Authorization Form (Authorization) giving permission for the Use and Disclosure of PHI for the specific research project. The Authorization must be study specific and provide a detailed description of what PHI will be used and how it will be used. A template for this Authorization is available from the Virtua Health IRB Office. PHI may not be Used or Disclosed in connection with any research purpose until the appropriate Authorization(s) and Virtua Health IRB approvals

are obtained.

i. Revocation of Authorization: Research subjects may revoke their Authorization at any time. If a research subject elects to revoke their Authorization, they must provide the Principal Investigator (PI) of the research study with a signed written revocation form. The template for the revocation form is available from the Virtua Health IRB Office.

2. Alteration or Waiver of Authorization: In limited instances, the Virtua Health IRB or Privacy Board with oversight responsibility for the research study may waive or alter the Authorization requirement. In order to be eligible for a waiver, a study must meet all of the criteria listed below:
   a) the Use or the Disclosure of the PHI involves no more than a minimal risk to the privacy of the research subject, based on, at least, the presence of the following three elements:
      i. an adequate plan to protect PHI from improper use and disclosure;
      ii. an adequate plan to destroy the PHI at the earliest opportunity consistent with the conduct of the research, unless there is a strong health or research justification for retaining; and
      iii. adequate written assurances from the researcher that the PHI will not be reused or disclosed to any other person or entity except as required by law or for authorized oversight of the research project.
   b) The research could not practicably be conducted without the Virtua Health IRB waiver or alteration.
   c) The research could not practicably be conducted without access to and use of the PHI.

   If the Waiver or Alteration of Authorization has been approved by the Virtua Health IRB or Privacy Board, Virtua may Use or Disclose PHI for research purposes pursuant to the Alteration or Waiver provided it has obtained documentation of the following:
   a) Identification of the Virtua Health IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved;
   b) A statement that the Virtua Health IRB or Privacy Board has determined the Alteration or Waiver of Authorization, in whole or part, satisfies the three-part test above;
   c) A brief description of the PHI for which Use or access has been determined to be necessary by the Virtua Health IRB or Privacy Board;
   d) A statement that the Alteration or Waiver of Authorization has been reviewed and approved under either normal or expedited review procedures; and
   e) The signature of the chair or other member, as designated by the chair, of the Virtua Health IRB or the Privacy Board, as applicable.

3. Limited Data Sets with a Data Use Agreement and De-identified Data: Authorization or a Waiver or Alteration of Authorization is not required, but Virtua Health IRB or Privacy Board approval and permission is required for the following research situations:
   a) If the PHI to be used is part of a Limited Data Set subject to a data use agreement; or
   b) If only de-identified data is to be used or disclosed in accordance with HIPAA and Virtua's *Disclosures of De-Identified Information* Policy.

4. Preparatory to Research: For activities preparatory to research by a Virtua workforce member, in additional to approval and permission from the Virtua Health IRB or Privacy Board, representations must be obtained from the researcher, in writing, that:
   a) the Use or Disclosure of the PHI is solely to prepare a research protocol or for similar purposes preparatory to research;
   b) the researcher will not remove any PHI from the covered entity; and
   c) the PHI for which access is sought is necessary for the research purpose.

5. Decedents: For research involving the PHI of decedents, in additional to approval and permission from the Virtua Health IRB or Privacy Board, representations must be obtained from the researcher, in writing, that:

a) the Use or Disclosure of the PHI is solely for research on the PHI of decedents;
b) the PHI sought is necessary for the research; and
c) at Virtua's request, documentation of the death of the individuals whose PHI is being sought.
d) the proposed research will not identify any living individual