UH HRPP
Investigator Manual

Investigators are required to conduct research in accordance with the procedures as laid out in this document. The guidance in this document is considered to be UH IRB Policy.

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Chapter 1- Purpose and Scope

Purpose of this Manual

This Investigator Manual is designed to guide you through policies and procedures related to the conduct of human subject research that are specific to the University Hospitals Cleveland Medical Center Institutional Review Board (UHCMC IRB). Investigators are required to abide by procedures as described in this manual.

General information regarding human subject research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see *Chapter 2- Required Training*.

The Human Research Protection Program

The mission of the University Hospitals Cleveland Medical Center (UHCMC) Human Research Protection Program (HRPP) is to promote growth in clinical and translational research programs for the continued advancement of public health through academic medicine and to protect the rights, dignity, welfare and privacy of human research participants.

The UHCMC research program is guided by the ethical principles regarding research involving human participants as set forth in the Belmont Report. UHCMC assures that all of its research involving human participants will comply with the Terms of Assurance for Protection of Human Subjects for Institutions within the United States (http://www.hhs.gov/ohrp/assurances/index.html). Research conducted outside of the jurisdiction in which UHCMC resides is also subject to the same ethical and regulatory requirements, in addition to country/region specific requirements. This fundamental commitment to the protection of human participants applies to all UHCMC research involving human participants, regardless of the funding source and regardless of the location of the research.

The Institutional Review Board at University Hospitals

The IRB is an independent committee established by the UH Clinical Council and reports only to the UH Board of Directors.

The UHCMC HRPP has under its jurisdiction three (3) IRB committees that are responsible for reviewing research involving human subjects conducted on UH property, using UH patients or UH data, and by staff or faculty of UH and Case Western Reserve University School of Medicine (as established by affiliation agreements). Each committee is constituted appropriately according to the Federal Regulations to review research with the sole purpose of protecting the rights and welfare of human subjects recruited to participate in research activities conducted under the auspices of the institution.

The UH IRB will not provide or publish the names of the members of the IRB except to federal regulatory agencies requiring specific disclosure. Others, such as industry sponsors, may request a list of IRB members identified by initials and area of specialization.

The responsibilities of the Institutional Review Board are:

- To protect human subjects from undue risk and deprivation of human rights and dignity.
- To disapprove studies which are unethical or of no scientific merit (Belmont Report – Respect of Persons).
- To ensure that participation by subjects is voluntary, as indicated by a voluntary and fully informed consent.
- To ensure equitable selection of subjects (Belmont Report – Justice).
- To maintain an equitable balance between potential benefits of the research to the subjects and/or society and the risks assumed by the subject (Belmont Report – Beneficence).
- To determine that the research design and study methods of a protocol are appropriate to the objectives of the research and the field of study.
- To assist the investigator by providing peer review and institutional approval.
- To ensure compliance of protocols with the regulations of the FDA, DHHS, and other funding agencies when appropriate.

Key Information

IMPORTANT: The IRB does not have the authority to grant retroactive approval should a research study be initiated without prior IRB review.

No institutional official at UHHS or Case can reverse IRB decisions that involve disapproval, deferral, suspension, or termination of a research study. However, a UHHS Institutional Official can disapprove an IRB approved protocol for activation or continuation at UHHS.

UHCMC prohibits officials, investigators, employees, and sponsors from attempting to or using undue influence with the UH IRB, any of its members or staff, or any other member of the research team to obtain a particular result, decision, or action. “Undue influence” means attempting to interfere with the normal functioning and decision making of the UH IRB or to influence IRB members or staff, or any other member of the research team outside of established processes or normal and accepted methods, in order to obtain a particular result, decision, or IRB action.

If a UH IRB Committee member, IRB staff, principal investigator, research participant, or other individual feels that he/she has been unduly influenced (e.g., coerced to participate, approve a study, or conduct a study), a report should be made to the UH Compliance Officer through the Compliance Hotline (1-800-227-6934) or UH Research Compliance. The person or office receiving the report will investigate the allegation and when appropriate, take corrective actions. Appeals related to IRB policies and procedures (including investigator concerns or suggestions regarding the review process) may be reviewed and forwarded to the Clinical Council if necessary.

Who should submit to the University Hospitals IRB

All UH employees are eligible to submit to the UH IRB. All research that involves UH patients, PHI, or data must be submitted to the UH IRB. Studies where UH involvement is limited to procedures carried out on UH premises, or using the services of any University Hospitals Health System facility should be submitted to the UH IRB but exceptions will be considered on a case-by-case basis.

With rare exceptions, any study submitted to the UH IRB should have a UH Principal Investigator listed in the SpartaIRB system, even if the UH IRB is not acting as the IRB of record. If the PI is a trainee (student, resident, fellow), then a UH faculty advisor is required to be listed and provided PI proxy privileges. Trainees may not be PI of clinical trials at UH. See Chapter 5- Research Staff Responsibilities for more information on PI requirements.

How do I get additional information and answers to questions?

This document and additional information regarding the Human Subjects Research Protection Program are available on the IRB Web Site.

If you have any questions or concerns about the Human Subjects Research Protection Program, contact the IRB Administration Office at 216-844-1529, by email at UHIRB@UHhospitals.org, or in writing at:

Malia Fink, CIP
Human Research Protection Program
University Hospitals Cleveland Medical Center
11100 Euclid Avenue
Lakeside 1400
Cleveland, OH 44106
Email: malia.fink@UHhospitals.org

If you have questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Subjects Research Protection Program that cannot be addressed by contacting the IRB Administration Office, you may contact the Vice President of Research, Research Compliance, or Hospital Compliance.

Chapter 2- Decisions made by the IRB

This chapter includes decisions and determinations made by the IRB and the process of appealing such determinations

Human Subjects Research: A Definition

The UHCMC IRB has the sole authority to determine whether an activity meets the definition of "Human Subject Research." When activities are conducted that might represent "Human Subject Research," the activities must be submitted to the IRB for a determination. An Investigator may request a determination that an activity is "Non-Human Subject Research," but the final determination will be made by the IRB.

The IRB will make a determination whether an activity is "Human Subject Research" by considering whether the activity either:

- Meets the DHHS definition of "research" and involve "human subjects" as defined by DHHS **OR**
- Meets the FDA definition of "research" and involve "human subjects" as defined by FDA. The definition of research and human subjects must consistently reference the ***same set of regulations*** (i.e., DHHS or FDA) and cannot reference the definition of research from one set of regulations, and the definition of a human subject from the other.

The "HUMAN SUBJECTS RESEARCH PROTECTION PROGRAM PLAN (HRP-101)" defines the activities that this institution considers to be "human subjects research." An algorithm for determining whether an activity is human subjects research can be found in the "WORKSHEET: human subjects research (HRP-310)," located in the SpartaIRB Library.

Non-Research

Activities are not research if they do not involve a systematic approach involving a predetermined method for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing theory. Examples of systematic investigations include, but are not limited to observational studies, interviews (including those that are open-ended) or survey studies, group comparison studies, test development; or program evaluation. Examples of activities that would not normally be considered systematic investigations include, but are not limited to training activities (e.g., human subjects being trained to perform a certain technique or therapy such as art therapy, psychoanalysis, oral history techniques) and classroom exercises involving human participants or human participant data where the objective of the activity is to teach proficiency in performing certain tasks or using specific tools or methods.

Activities are not research if they do not contribute to generalizable knowledge or if the results (or conclusions) of an activity are not intended to be extended beyond a single individual or an internal program (e.g., publications or presentations). Examples of activities that are typically not generalizable include: biographies and service or course evaluations, unless they can be generalized to other individuals; services, courses, or concepts where it is not the intention to share them beyond the UHCMC community; classroom exercises solely to fulfill course requirements or to train students in the use of particular methods or devices; and quality assurance activities designed to continuously improve the quality or performance of a department or program where it is not the intention to share them beyond the

UHCMC community. Thesis or dissertation projects conducted to meet the requirements of a graduate degree are usually considered generalizable and therefore, require IRB review and approval.

Non-Human Subject

Activities do not involve humans as participants if they do not involve the process of obtaining specimens or data through intervention or interaction with individual participants or identifiable private information. Information is considered "not identifiable" if it includes none of the following:

1. Name;
2. Any geographic subdivisions smaller than a state, including street address, city, country, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code;
3. All elements of dates (except year) directly related to an individual (e.g., date of birth, admission);
4. Telephone numbers;
5. Fax numbers;
6. Electronic mail addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web Universal Resource Locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including finger and voiceprints;
17. Full-face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code.

Specimens/data that are received by the Investigator as de-identified stripped of all HIPAA identifiers as noted above. When the Investigator receives the private information or specimens with no code or link that would allow an Investigator to establish identity, this would not involve human subjects. For example, a publicly available, unidentifiable, non-linked cell line qualifies as not involving human subjects. The Investigator may receive coded private information or specimens and qualify for non-human subject if the following conditions are met:

1. The code is not derived or related to the HIPAA identifiers that must be stripped from the PHI (e.g. patient medical record # + last 4 digits of individuals Social Security Number);
2. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
3. The Investigator cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain, because:

    a. The key to decipher the code is destroyed before the research begins;
    b. The Investigator and the holder of the key enter into an agreement prohibiting the release

of the key to the Investigator under any circumstances, until the individuals are deceased; c. The private information is received from an IRB-approved repository or data management center that includes written operating procedures that prohibit the release of the key to the Investigator under any circumstances, until the individuals are deceased; or d. There are other legal requirements prohibiting the release of the key to the Investigator until the individuals are deceased.

A cadaver is not considered to be a human subject. Projects involving cadavers should be submitted to the UH IRB on a "Not Human Subjects Research Protocol (HRP-503NHR) Template". The IRB will determine if there are other considerations that should be addressed, such as HIPAA, genetic information, communicable diseases, etc.

Any change that might disqualify the activity from a "Non-Human Subject" or "Non-Research" status must be reported to the IRB for review and verification prior to implementation.

All "Non-Human Subject Research" is subject to all applicable institutional policies and procedures. When activities are conducted that might represent "Human Subject Research", the activities must be submitted to the IRB for a determination. The Chairperson or his/her Designee will determine whether an activity meets the definition of "Human Subject Research."

The IRB staff/ Chairperson or his/her Designee will document the determination and its justification. If the request is determined to meet criteria for Human Subjects Research, the IRB staff will determine the appropriate level of review, communicate this to the Investigator, and guide the Investigator with the re-submission. If the request is determined to be Not Human Subjects Research, the IRB staff will send a letter documenting the determination.

IRB Decisions

The IRB may approve research, require modifications to the research to secure approval, defer research, or disapprove research:

- Approval: Made when all criteria for approval are met. See "WORKSHEET: Criteria for Approval (HRP-314)." The human subject research may commence once all other institutional approvals have been met. IRB approval is for a period of time which is noted in the approval letter. If no expiration date is noted, a periodic check-in may still be required
- Modifications Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be finalized. If the IRB requires modifications to secure approval the study team must make the requested modifications and submit them to the IRB. If the IRB determines that all requested modifications have been addressed, final approval will be issued. Research cannot commence until this final approval is received. If you do not accept the modifications, submit a response through the system justifying your disagreement with the request. Any substantive modification made outside of requested changes will void the determination and the study will again be reviewed as a whole.

- Deferred: Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB. If the IRB defers the human subjects research, a statement of the reasons for deferral and suggestions to make the study approvable will be provided. The study team may address the issues and resubmit. In most cases if the IRB's reasons for the deferral are addressed the human subjects research can be approved.
- Disapproval: Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision. Any further proposals would have to be part of a new submission.

The criteria for IRB approval can be found in the "WORKSHEET: Exemption (HRP-312)" for exempt human subjects research and the "WORKSHEET: Criteria for Approval (HRP-314)" for non-exempt human subjects research. The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found in the SpartaIRB library.

These checklists are used for initial review, continuing review, and review of modifications to previously approved human subjects research. You are encouraged to use the checklists to write your Investigator Protocol in a way that addresses the criteria for approval.

Appealing an IRB determination

A UHCMC Institutional Review Board (IRB) may determine that some or all of a proposed research activity cannot be approved, or the IRB may require the researcher to make changes to the research in order to obtain IRB approval. Per federal regulation, these IRB decisions may not be reversed by any official or agency, including another IRB. However, a researcher may appeal to the IRB to do a formal re-review of a decision if, after repeated interactions with the IRB, the researcher believes that the IRB's decision is due to inadequate or inaccurate information, a misunderstanding, or IRB non-compliance with UHCMC policy, state law, or federal regulation.

If the research has already been conducted no appeal can be made as the IRB does not have the authority to grant approval for a project conducted without prior review and approval.

The investigator will submit an IRB Appeal Form outlining the decision(s) being appealed and providing information supporting his or her position. The form will be reviewed by the Manager, Human Research Protection Program and referred to the Appeals Committee.

The Vice President of Research (or designee) will serve as Chair for the Appeals Committee. The Appeals Committee will be comprised of the following voting members: Chairs/Vice Chairs from the Boards, member(s) from one of the IRB Boards not involved with the review under appeal, the Manager, Human Research Protection Program, members of the Policy Oversight Committee with relevant expertise, and invited guests. Consultants (as approved by the Chair of the Appeals Committee) may be invited to present relevant information, background, or precedent in regard to the issue(s). A minimum of 6 voting individuals must be present at the meeting. The Institutional Official (IO), Chief Scientific Officer, or Vice

President of Research may be present at the meeting and may provide information relevant to the appeal, but are not voting members.

At the meeting, the committee will focus on the unresolved issue(s), but will review the issue(s) in the context of the entire project. The IRB Chair will present the protocol and issue(s) at hand. The Chair/Vice Chair and/or Board reviewers will present relevant information from the Board's prior discussions and decisions.

During the meeting, The Appeal Committee may hold a closed session without the researcher and colleagues, prior to the appeal portion of the meeting, to establish the key issues and questions to consider. The researcher is invited to present information and rationale to the Appeal Committee. There is a question-and-answer session between the Committee members and the researcher. The researcher and any guests/colleagues leave the meeting room. After hearing the information and reviewing the documents, consultants and those not a part of the Appeals Committee will be excused for the discussion and voting by the Committee.

The Appeals Committee will reach a final decision by majority vote to either agree or disagree with the IRB decision regarding the procedure, wording, or plan as proposed by the investigator. The following decisions may be rendered by the Appeals Committee:

- If the Appeals Committee disagrees with the decision of the IRB Board, the protocol will be transferred to another UH IRB Board for full review after appropriate revisions.
- If the Appeals Committee is in agreement, the decision of the IRB of record will stand. For example, if the original decision involved disapproval of the entire protocol, and the Appeals Committee is in agreement with the original decision, the protocol will continue to be disapproved by the IRB.
- Defer the appeal and obtain additional information or consultation in order to make a final decision.

In all cases, the findings of the Appeals Committee will be provided to the investigator and IRB(s) in writing. The Institutional Official and investigator's Chairperson will be copied on the written communication. The minutes and the letter will become part of the IRB file.

After final disposition of a case prompting an Appeals Process, the Clinical Research Executive Committee will review the case and its findings in light of current policies and procedures to determine whether clarifications, changes in practice, new guidelines or SOPs are needed.

Appeal Form

Request to Appeal a UHCMC IRB Board Determination

Date: _____

Investigator: _____

Investigator email: _____

Investigator phone number: _____

IRB protocol number: _____

Does this appeal involve the entire protocol or element(s) of the protocol?

☐ Entire Protocol

☐ Elements of the protocol

Please answer the following questions (attach pages to this form):
1. Specifically list the decision(s) that is being appealed. Remember that the Appeals Committee will only address/vote on these items. Include the version (date) of the protocol/synopsis or document(s) that are involved.

2. Provide background, and supporting documents to be reviewed by the Appeals Committee.

Chapter 3- Regulatory Classifications

This chapter includes information about regulatory classifications for research including quality improvement, case reports, expanded access/compassionate use, and emergency use

Submitted activities may fall under one of the following four regulatory classifications:

- Not human subject research: Activities that do not meet the institutional definition of human subjects research do not fall under IRB oversight. Projects may be submitted to the UH IRB for an official "NHR (Not Human subjects Research) determination". The UH IRB will make its own determination rather than accepting another institution's determination of NHR.
- Exempt: Certain categories of human subjects research may be exempt from regulation but require IRB review. It is the responsibility of the IRB Office, not the investigator, to determine whether human subjects research is exempt from IRB review. Review the IRB Office's "WORKSHEET: Exemption (HRP-312)" for reference on the categories of research that may be exempt.
- Review Using the Non-Committee (Expedited) Procedure: Certain categories of non-exempt human subjects research may qualify for review using the non-committee procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the IRB Office's "WORKSHEET: Eligibility for Review Using the Expedited Procedure (HRP-313)" for reference on the categories of research that may be reviewed using the non-committee procedure.
- Review by the Convened IRB: Non-Exempt human subjects research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

Quality Improvement Activities

Institutions may engage in "quality improvement" projects or activities which are designed to evaluate outcomes and determine appropriate institutional clinical, practical or administrative practices. In many cases, these activities do not qualify as "human subject research" that would require IRB review and approval under the Federal Regulations. However, many investigator-initiated "quality improvement" protocols include elements of research, for example, patient or provider surveys, measurement of novel outcomes, or new devices or approaches. In these situations, prospective IRB approval is needed prior to engagement in the activity. Investigators CANNOT assume that their protocol is "quality improvement" simply because the ultimate goal of their protocol is to improve the quality of specific aspects of patient care. If an investigator conducts a project that they self-determine to be quality improvement, and then requests an IRB determination, the IRB does not "rubber stamp" this effort: the IRB is required by federal regulations to make its own determination, which could include research non-compliance if the protocol either is research or has elements of research.

It is often difficult to tell research from quality improvement, and as noted the principal investigator is strongly encouraged to submit their protocol to the IRB for a determination regarding whether the project is solely quality improvement (which is NHR – not human subjects research) or has elements of research

also (which would not be determined to be NHR) before beginning the work. Quality improvement (QI) involves an evidence-based intervention or intervention bundle – this generally means that the investigator can cite published peer-reviewed guidance or literature in support of the specific intervention (or intervention bundle) - and the specific intervention is administered to all eligible patients in a local setting. In QI, there is no randomization, and there are no differing treatment or intervention arms – these are elements of research. In general, the main outcome for a QI project relates to successful implementation of the intervention since it is already known to be beneficial.

Quality improvement activities are intended to apply to those patients who are being treated within the QI initiative and are not intended to be generalized to those beyond the protocol. However, the intent not to publish or share results beyond the institution does not automatically make a project "quality improvement." Institutions can collaborate in performance of QI, but at each site the stated purpose is to improve local care, not generate new knowledge. Almost all Sponsor-funded projects and those involving devices or medications that are either new or being used in a new way, are research, not QI. In general, educational research is also not QI, and should be submitted for an Exempt determination – please consult the IRB for assistance if unfamiliar.

Case Reports

If an investigator develops a case report that he/she wishes to present, publish, or use to fulfill the requirement for scholarly activity outside this institution and associated departments at Case Western Reserve University (Case), this case report must be submitted to the UHCMC IRB for review prior to dissemination (publication, presentation, etc). Please utilize the HRP-503 NHR template.

A case report that includes information from three or fewer patients generally does not meet the definition of a "systematic investigation leading to generalizable knowledge" and therefore does not meet the definition of "research" (45 CFR 46.102(f) or 21 CFR 56.102(e)). If the case report does not qualify as human subject research, the IRB will return a formal designation indicating such. Please note that only case reports examining **completed clinical care** will qualify for an NHR (Not Human Subjects Research) determination. A case series of four or more should be submitted as a chart review and reviewed as research.

An investigator must ensure that the case report does not include any of the following patient identifiers:

- Personally identifiable private information about a living human person
- Any of the 18 protected health information identifiers (PHI) noted in the HIPAA regulations unless authorization from the individual(s) has been obtained.

Expanded Access / Compassionate Use

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 that is generally derived from clinical trials (21 CFR 312.310). When an investigator needs to obtain approval from the IRB for expanded access they should first submit

- Completed application that provides evidence that there is no comparable or satisfactory alternative available and the intended treatment plan,
- FDA form 3926,
- Investigator brochure or another source describing the risks and potential benefits of the treatment and draft consent document that uses plain language that is aimed at "patients" who expect direct benefit.
- The submission is then routed to an IRB chair or designee who is able to review and concur with the expanded access request.

Emergency use of an unapproved drug, biologic, or device

The FDA and other Federal agencies have strict regulations about the use of investigational agents in emergency situations. The regulations state "Nothing in this policy is intended to limit the authority of a physician to provide emergency medical treatment for patients who need such care" (45 CFR 46.116(f)). These regulations mean that emergency medical care for patients may be provided **without regard** to IRB review and approval. However, it is important to speak to the IRB as soon as possible when a potential situation arises. Please call 216-844-1529 to contact the IRB Administration office to discuss the situation.

Emergency use of an unapproved **drug or biologic** in a life-threatening situation without prior IRB review is "research" as defined by FDA, the individual getting the test article is a "subject" as defined by FDA, and therefore is governed by FDA regulations for IRB review and informed consent.

Emergency use of an unapproved **device** without prior IRB review is not "research" as defined by FDA and the individual getting the test article is not a "subject" as defined by FDA. However, FDA guidance recommends following similar rules as for emergency use of an unapproved drug or biologic.

DHHS regulations (45 CFR 46) do not permit DHHS-regulated **research activities** to be started, even in an emergency, without prior IRB Committee review and approval. When emergency medical care is initiated without prior IRB Committee review and approval, the patient may not be considered a research subject as defined by DHHS regulations. However, the patient is a research subject under FDA regulations. Therefore, it is the UHCMC IRB policy that data obtained when an Investigator utilizes the emergency use provisions found in the FDA regulations for the administration of investigational, drugs, agents, biologics, or devices, the data may not be claimed as DHHS-regulated research, although the data must be claimed as FDA-regulated research. Data regarding such care may not be included in any report of a DHHS-regulated research activity, but may be used in a report of an FDA-regulated research activity that is not DHHS-regulated.

When the urgency of the patient's treatment **does not** permit consideration at a convened IRB meeting, the emergency use of the test article may proceed. Emergency use of an investigational drug, biologics, or device may only occur if the **all** FDA requirements (21 CFR 56.104(c)) for emergency use are met:

- The patient is in a life-threatening or severely debilitating situation. The criteria for life threatening do not require the condition to be immediately life threatening or to immediately result in death. Rather, the subjects must be in a potentially life-threatening situation requiring prompt intervention.

- There is no standard acceptable treatment available.
- There is insufficient time to obtain approval from the IRB at a convened meeting
- Any subsequent use will be reviewed by a convened IRB.

IRB must either grant approval at a convened full Committee meeting (may use the data for research), or if the conditions of 21 CFR 56.104(c) are met and it is not possible to convene a quorum within the time available, the emergency use may proceed without IRB approval (may not use the data for research). The investigator will need to decide if the patient's need for treatment is such that the emergency request can be considered at a convened IRB meeting before the treatment is administered. Since the IRB meets on a weekly basis, it may be possible for the proposal to be added to the agenda of a scheduled meeting. If the patient's condition allows waiting for review at an IRB meeting, then the FDA Emergency Use restrictions do not apply, the IRB approves the protocol, and the patient consents, and the investigator may use the data for research purposes.

If there is no time to make contact, reference the "WORKSHEET: Emergency Use (HRP-322)" in the SpartaIRB Library for the regulatory criteria allowing such a use and make sure these are followed. You will need to submit a report of the use to the IRB within five days of the use.

Even in an emergency situation, the investigator is required to obtain written informed consent from the patient whenever possible. Use the "TEMPLATE EMERGENCY USE CONSENT DOCUMENT (HRP-506)" to prepare your consent document. The consent form is not approved or stamped by the IRB. The IRB is willing however to review the consent and offer suggestions.

An exception to the requirement for informed consent may be made if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- The subject is confronted by a life-threatening (or severely debilitating) situation necessitating the use of the investigational drug or biologic;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- Time is not sufficient to obtain consent from the subject's legal representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If, in the investigator's opinion, immediate use of the investigational drug or biological product is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the investigator should make the determination and, within 5 working days after the use of the investigational drug or biological product have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

If you fail to submit the report within five days, the IRB will notify Research Compliance.

The emergency use provision in the FDA regulations is an **exemption** from prior review and approval by the IRB. It allows for **one** emergency use of a test article without prospective IRB review. Any subsequent

use of the investigational product **at the institution** must have prospective IRB review and approval. Investigators must understand that an emergency use procedure be done only once for a single investigational drug, agent, biologic or device. The Investigator is to evaluate the likelihood of a similar need for the drug, agent, biologic or device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IND or IDE for subsequent use. If investigators think they may need to use the investigational drug, agent, biologic or device again, a complete IRB protocol must be submitted in time for full Board review

When an emergency use report is discussed at an IRB meeting, the Board will consider if the use of the investigational agent meet the requirements of 21 CFR 56.104(c) and 21 CFR 50. If not, the matter will be handled as non-compliance.

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Chapter 4- Required Training Necessary to Conduct Human Subject Research

This chapter describes the training required to conduct Human Subjects Research at University Hospitals. You may have additional training imposed by other federal, state, or institutional policies.

Investigator Training:

If you are a Principal Investigator, you are required to complete the investigator training course. This course is a series of modules consisting of a collection of short videos with corresponding assessments/quizzes. Instructions for the completion of these modules can be found here.

CITI Training:

Principal Investigators and all research staff must complete the Collaborative Institutional Training Initiative (CITI) human subjects online training program.

In order to complete training for CITI, visit the Continuing Research Education Program webpage for specific instructions.

Once certified, investigators are to maintain valid certification by participating in ongoing continuing research education programs. The UHCMC IRB follows the CWRU requirements for re-certification. Certified investigators and research staff members are required to earn 12 CRECs (Continuing Research Education Credits) every three years to maintain their certification in human subject protections.

The IRB coordinator will not process IRB submissions until all investigators and study personnel have completed the required HSP training.

Note: When conducting community-based research that utilizes community partners on study teams, the UH IRB will consider, on a case-by-case basis, allowing the use of CIRTification in place of CREC. Please contact the UH IRB office for instructions on how to apply.

Research Credentialing:

Any non-University Hospitals employee requiring access (for research purposes) to 1) UH Protected Health Information (PHI), 2) UH patients, or 3) UH property, must complete the research credentialing process unless they have privileges. For policy information, please reference “R-46 - Clinical Research Credentialing.” For detailed information about how to submit your Research Credentialing application, please read the SOP labeled, “GA 103: UH Research Credentialing.” The SOP is a step by step guide explaining the process for submitting initial, renewal, and medical student applications.

The IRB coordinator will not process IRB submissions until all non-University Hospitals Investigators and study personnel have completed the required training and submitted the necessary documentation to become UH research credentialed.

Good Clinical Practice (GCP) Training:

GCP training is required by the NIH for all NIH funded studies and by many industry sponsors. This training is not tracked / verified by the UH IRB, but it is important to comply with the requirements of your sponsor. GCP training is available as an optional training through the CITI program.

Other personnel requirements and notes:

All study personnel conducting research activities must be appropriately trained, certified and credentialed to perform the tasks to which they are designated, at the location at which they are designated to perform them. For example, individuals designated to take blood must be certified phlebotomists. Any individual performing a medical procedure must have UH privileges to act in that capacity at that specific location. Individuals must be appropriately licensed to prescribe medication or order labs. Study personnel found to be acting outside of their scope of practice will be reported to Hospital and Research Compliance.

It is not appropriate to include minors as key study personnel. Occasionally, in an effort to expose interested individuals to research, minors will be included as research interns or volunteers. When minors are engaged as interns or volunteers with UH research projects, they would not be listed as study personnel because they would not be responsible for study activities. The PI of the project is responsible for ensuring the below requirements are followed:

- Minor must be supervised at all times.
- Minors should not be responsible for completion of study interventions or procedures.
- Minors cannot consent participants, or have any direct unsupervised contact with participants.
- No access may be provided to UH systems, particularly systems that contain Protected Health Information (PHI).
- Datasets containing PHI may not be shared with minors.
- Limit access to sensitive information. This may mean that participation in certain study team meetings or research visits is inappropriate.
- Minors should not be included in any research visit without advance permission from participants. It should be made clear that the minor is a volunteer / research intern here for educational purposes, and that it is okay to decline.
- Follow other relevant institutional policies for volunteers.

Chapter 5- Research Staff Responsibilities

This chapter includes the responsibilities specific to the Principal Investigator and other research staff

UH Principal Investigator Requirements

The PI of studies that includes UH patients or data must be a University Hospitals employee. In instances where the study is No Greater than Minimal Risk, individuals who have appropriate hospital privileges may be listed as the PI. Individuals who do not meet these requirements will need to identify a UH PI to take responsibility for the hospital-based activities. The designation of a UH PI is intended to ensure that UH personnel are primarily responsible for research using UH patients. In rare cases and with ample justification, the Clinical Research Center will consider individuals for an exemption to this policy.

It is important that the UH PI understands the serious responsibility involved in sponsoring and overseeing the sharing of UH data and access to patients with non-UH employees. Acting as a PI "in name only" is not acceptable as, under the federal regulations, the listed PI accepts ultimate authority for the conduct of the study at that site, and that responsibility may not be delegated. The UH PI holds all of the below listed Responsibilities of the Principal Investigator, and would be named on any research compliance audits or IRB actions, including reporting of non-compliance to OHRP and/or the FDA.

If the study is a Clinical Trial, a UH faculty member must be listed as PI. Trainees (student, resident, fellow, etc.) may not be PI of a Clinical Trial. Additionally, the PI must be able to provide oversight of the conduct of the study, meaning that the PI must have the time, proximity, and appropriate credentials to effectively supervise the study.

PIs that have outstanding compliance issues on an existing study should resolve those issues before submitting other new studies. The IRB may hold on reviewing new studies until compliance issues have been addressed.

Responsibilities of the Principal Investigator

The Principal Investigator (PI) is ultimately responsible for the conduct of the study, for assuring compliance with Institutional Review Board (IRB) policies and procedures, and with Federal regulations. The primary responsibility of the PI is to acknowledge and accept the responsibility and ethical obligations for protecting the rights and welfare of human research participants in compliance with current federal regulations and IRB requirements governing human subject research. Even though a PI may delegate specific tasks to other members of the research team, he or she cannot delegate the responsibility for ensuring that those tasks are completed according to institutional and federal regulations.

There are additional regulations governing the responsibilities of UH investigators when conducting human subject research under DHHS, FDA, etc. This information can be found in specifically designated chapters of this manual.

The PI is obligated to ensure that all human subject research receives IRB approval prior to the initiation of the research. The implications of engaging in activities that qualify as "human subject research" without

obtaining prior IRB review and approval are significant. Results from such studies may not be published or presented unless IRB approval had been obtained prior to collecting the data. To do so is in violation of UHCMC Policy. It is also against UHCMC policy to use inappropriately collected human subject research data to satisfy thesis or dissertation requirements.

Prior to the initiation of the research, the PI is responsible for completing all financial and contractual obligations including, but not limited to, the following: ensuring appropriate funding is available to support the proposed research, obtaining budget approval, execution of the contract, an attestation of clinical trial qualifying status, ensuring a coverage analysis is completed, and ensuring that all necessary and appropriate contracts between UH and other parties are executed prior to the conduct of the study.

It is the responsibility of the PI to assure and document that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed, otherwise qualified, and appropriately research trained or credentialed to perform them.

The PI should conduct a site initiation visit prior to conducting any study-related activities to promote adherence to the IRB-approved protocol. The PI is responsible for informing all study staff about the current protocol and consent form(s). In addition, the PI is responsible for conducting the study in accordance with the currently approved protocol and consent forms. The PI does not institute any changes to the IRB-approved protocol and/or consent form document without first obtaining IRB approval for such changes. If the PI is conducting sponsored research, the study sponsor is notified of an investigator's intent to modify the protocol or consent form. In rare instances, an investigator may deviate from the protocol without first notifying the IRB in order to eliminate immediate hazard to a study participant. Any such protocol deviations are to be promptly reported to the IRB via a "Reportable New Information (RNI)" submission. Failure to comply with this requirement can result in an allegation of non-compliance. Documentation surrounding the event is also placed in the research record and the medical record, if applicable.

Other PI responsibilities during the conduct of the study include the following:

- Ensuring subjects are recruited via the protocol-approved recruitment methods
- Confirming that each subject enrolled meets eligibility criteria based on the inclusion and exclusion criteria detailed in the current IRB approved protocol
- Ensuring the requirements for obtaining informed consent are met
    - Although it is not required for the PI to obtain consent personally, the PI must ensure appropriate study team members are delegated (listed in the IRB forms, listed in the delegation log, has appropriate training, can adequately answer study-related questions, etc.).
- Maintaining documentation of research regulatory documents and other essential documents including, but not limited to: IRB approvals, protocols, consents, submission forms, grant applications, investigator's brochure, Investigational Device Exemption documentation, IND or IDE application, correspondence with the IRB, sponsor, FDA, signed consent forms, etc.
- Compliance with federal and institutional time periods for record retention
- Responding to subjects who have an adverse event

- Keeping subjects fully informed of any new information
- Providing timely reports to the IRB as required
- Making records available for inspection by UH Research Compliance, CWRU Compliance office, study sponsor, the FDA, OHRP, or any hospital or program accrediting body.
- Ensuring accountability of Investigational Drugs, Devices, or Biologics
- Protecting subject privacy and maintaining the confidentiality of data by following the plan in the approved protocol
- Maintaining documentation of any subject complaints or concerns and their resolution
- Providing a Data and Safety Monitoring Plan to the IRB
- Submitting an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
- Ensuring that no study personnel accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
- Ensuring that no study personnel accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")
- Contacting the CRC if your study has been selected for an FDA or OHRP audit.
- Posting one IRB-approved version of a consent form that has been used to enroll participants on a public federal website designated for posting such consent forms after recruitment closes and no later than 60 days after the last study visit if your study is a clinical trial
- Maintaining additional requirements of various federal agencies in Chapters 22-26 (these represent additional requirements and do not override the baseline requirements of this section.)
- Any study meeting the definition of a Clinical Trial (or otherwise required to register) must register on ClinicalTrials.gov in accordance with the policies governing use of that site. For more information, please review SC 401: *Registration of Clinical Trials in ClinicalTrials.gov*

If, due to a leave of absence, a PI is temporarily unable to perform these duties they should delegate responsibilities to qualified study team members. A leave longer than 3 months should prompt a formal transfer of the PI role for the study. Alternatively, the study team can place the study on administrative hold (via a submission to the IRB) until the delegation log is created, and / or a new PI is identified.

Submission of New Human Subjects Research to the IRB

The PI, or designee, is to complete the New Study SmartForm in SpartaIRB and attach all necessary documents. First, send your completed study for department scientific review (DSR). Once the department has completed their review, the PI must submit the study to the IRB by clicking "Submit". Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Before submitting the research for initial review, the PI must verify that:

- They have reviewed the protocol and acknowledge their responsibilities as Principal Investigator.
- The information in this submission accurately reflects the proposed research.
- They accept responsibility for assuring adherence to all applicable Federal, State, and local research regulations and policies in carrying out this research.

Responsibilities of the Research Team

Co-investigators, study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures, to adhere rigorously to all protocol requirements, to inform investigators of all serious and unexpected adverse reactions or unanticipated problems involving risk to participants or others, to oversee the adequacy of the informed consent process, and to take whatever measures are necessary to protect the safety, rights and welfare of participants. The research team must be licensed, or otherwise qualified, and appropriately research trained and/or credentialed to perform research tasks.

Regardless of involvement in research, each member of the research community is responsible for promptly notifying the IRB of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware, whether or not they are directly involved in the research.

All Investigators are required to promptly (but in no case later than 48 hours) report to the UH Clinical Research Center (i) any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections, (ii) any litigation, arbitration, or settlements initiated related to human research protections, and (iii) any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the Organization's HRPP. Investigators should not directly report any of these outside of UH, unless required by law or to protect the immediate safety of a human subject. UH CRC will report all incidents that are required to be reported as required by applicable law, the FDA, HHS or AAHRPP.

Financial Interest Disclosure

All individuals involved in the design, conduct, or reporting of research are required to disclose financial interests:

- On submission of an initial review.
- At least annually as part of continuing review.
- Within 30 days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

The UH IRB has the final authority to decide whether the interest and its management, if any, allows the research to be approved.

Failure to appropriately report research related Financial Interests per UH Policy CE-08 may be considered non-compliance. Failure to appropriately document a conflict of interest within an IRB submission, or failure to follow an approved management plan may be considered non-compliance. These instances will be considered by the IRB and referred to Hospital Compliance (per CE-08) and Research Compliance for remediation and education. Any investigation into possible failure to comply with Conflict of Interest policies and procedures will include education regarding those policies and procedures.

Within 30 days of a substantiated instance of non-compliance with Conflict of Interest policies and procedures, a formal education will be provided to the Investigator.

Departing the Institution

In order to ensure compliance with applicable law and Institutional policies, faculty listed as Principal Investigators (PI) on IRB approved human subjects research studies must contact an IRB Specialist in the IRB Administration Office at 216-844-1529 at least 60 days before departure to discuss the status and plan for all open studies, existing data, and records. Once the IRB/HRPP is notified that an investigator is leaving UH, they are not permitted to begin any new research without first speaking to an IRB Specialist about the plan for continued oversight.

Faculty have four potential options for handling active IRB protocol(s) when they are leaving the institution:

1. Submit a study closure to the IRB to completely close the study without plans to transfer or continue the study.
2. Submit a study closure to the IRB to close the study at UH and transfer the project to the new institution. *Please note that data and materials collected under research protocols belongs to UH and may not be taken without prior approval / contract in place.*
3. Keep the study open at UH and at the new site. *Please note that a reliance agreement may need to be put in place.*
4. Keep the study open solely at UH and submit a modification to the IRB to designate a new PI.

If a PI leaves the institution without implementing one of the above four options, a notice will be sent to UH Research Compliance and the study may undergo an audit or be suspended, terminated, or administratively closed. Best practice is to submit a study closure form or PI change modification at least 30 days before departure.

In all cases, a plan for the sharing and storage of all study-related datasets and documents should be in place before the PI leaves. As applicable, information on clinicaltrials.gov should be made including transfer or closure of the record(s) if the PI is designated as the Responsible Party.

Study Administratively Discarded due to Lack of Response

The study team has 30 days to respond to a request for modifications, clarifications, or deferral stipulations for a new study. The system will send out courtesy reminders every 15 days. If a meaningful response is not resubmitted within 30 days, IRB staff may administratively discard the submission. At that point, a new study must be created if the study team wishes to move forward.

Investigator Quality Improvement Assessment

Investigators and study teams can utilize the Investigator Quality Improvement Assessment (HRP-430) document located in the SpartaIRB Library in order to conduct a self-assessment. Research Compliance posts other self-assessment tools on the CRC Website (https://www.uhhospitals.org/for-clinicians/research-and-clinical-trials/for-researchers).

Chapter 6- IRB Submission Components

This chapter contains information about the required components for submissions to the IRB as well as the various types of study submissions.

SpartaIRB System

All IRB submissions (e.g., continuing reviews, modifications, continuing reviews with modifications, new studies, and reportable new information submissions) are to be created and submitted to the UH IRB via the SpartaIRB system (https://spartairb.case.edu). The SpartaIRB Library contains various templates and forms. If you have questions about which template is appropriate, please contact the UH IRB administration office.

Personnel Table

The UH IRB requires real time review of the personnel table. All individuals engaged in the research should be listed on the personnel table in the IRB submission. Individuals listed on the personnel table must have up-to-date training as required, and appropriate certifications. It is the PI's responsibility to determine whether individuals meet criteria to be engaged in research. Please use the following guidelines to make that determination.

Individuals are generally considered to be NOT engaged in research when all of the following are true:

(a) The services performed do not merit professional recognition or publication privileges;
(b) The services performed are typically performed by those individuals for non-research purposes; and
(c) The individual does not administer any study intervention being tested or evaluated under the protocol.

Submission Requirements

The research protocol describes the study and is used by the IRB to assess the scientific and ethical merits of the proposed study. There is no limit to the number of pages; however, the length of the protocol should be proportionate to the complexity of the study. The IRB encourages the use of tables and flowcharts when they make the protocol easier to understand. The protocol should include a selective list of references that are related to the protocol. In a new study submission, the protocol is to be uploaded to the Protocol section of the Basic Information page in the study's smart form.

Information in the protocol/supplemental form should include:

- Introduction/background

- Justification/rationale/significance of the study
- Purpose, including specific aims and/or hypotheses
- Study population (inclusion and exclusion criteria), as well as required sample sizes. Note: maximum enrollment goal must be provided.
- Study procedures
- Recruitment procedures
- Risks and discomforts and how minimized
- Benefits to subjects
- Costs to the subject
- Alternative(s) to participation
- Payment to the subjects (include both reimbursement and incentives)
- Plan for obtaining informed consent
- Provisions for subjects from vulnerable populations
- Plans for the subjects at the end of the protocol
- Data safety monitoring plan or Data safety monitoring board or committee*
- How will data (electronic and hardcopy files) be maintained
- How long will research data be stored by the PI after study closure
- Subject privacy
- Data/Sample confidentiality and security plan
- Data analysis plan
- References

*Ongoing study monitoring by the Principal Investigator is required for all studies to assure adherence to protocol and participant safety. Study teams should, at minimum, monitor the data at least every four weeks to ensure subject safety, that the data is complete, accurate and the study is being conducted in accordance with the protocol.

Greater than minimal risk studies, including complex or multi-site studies, FDA-regulated studies including an IDE or IND, those with high-risk interventions, blinded or masked treatments, and those including vulnerable populations, are expected to include a DSMB (Data and Safety Monitoring Board) whose composition and schedule of meeting and reporting are delineated.

Greater than minimal risk studies of lower overall risk, for example with a single site, a single intervention or bundle of interventions of lesser risk, or including washout, delay or placebo, are expected to have a SMC (Study Monitoring Committee) or an Independent or Safety Medical Monitor whose name(s), credentials and planned details of oversight are provided. Studies where the greater than minimal risk designation is solely due to the risk of radiation exposure will be exempt from this requirement.

Medical Monitors should be independent of the study, should have no real or apparent conflict of interest, and should not report to or be supervised by the Principal Investigator. In general, the Medical Monitor has the responsibility to review and evaluate information relevant to safety during the conduct of the trial. They serve as an individual who is medically qualified to independently review the safety of the trial and have responsibilities including:

- Review protocol halting rules

- Advise protocol team on safety oversight
- Evaluate adverse events/SAEs and reviews safety reports
- Review of deviations that affects the safety, rights, and welfare of the patient

Supplemental Form

In most situations, a completed Supplemental Form (HRP-503SUPP) is required for review and approval of a study proposal. The Supplemental Form is in addition to the protocol document, and explicitly addresses many criteria for approval. If the information being requested can be found in the protocol document, in most cases it is sufficient to reference the protocol page where that information can be found. This form also includes prompts for other required reviews – careful reading of the instructions can help streamline the overall review process.

The Supplemental Form is not required if the study is using the Chart Review Data & Specimens Protocol (HRP-503DATA), the Exemption Protocol (HRP-503EXEMPT), or the Not Human Subjects Research Protocol (HRP-503NHR).

Writing a Consent Document

If consent will be obtained, the use of the appropriate consent template is **required**. Consent templates are located in the Templates tab of the SpartaIRB library and can be tailored to the needs of the study. Please make sure that you use the consent template designated for the UH IRB, not the Case IRB.

All consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure. The template heading, title of protocol and page numbers must appear on all pages. This ensures that auditors can verify all pages are in order and from the same document.

It is recommended that you date the revisions of your consent documents to ensure that you use the stamped, most recent version approved by the IRB.

Additional information on the consent requirements can be found in the General Consent Requirements Chapter of the Investigator Manual.

In a new study submission, the consent document is to be uploaded to the Consent Forms section of the Local Site Documents page in the study's smart form.

When making any changes to the consent with a modification to the study, ensure to utilize the "Update" button found next to the original consent in the study's smart form to essentially stack revisions on top of older versions. To clarify, each item under a section is seen as its own entity so if documents are not stacked appropriately, it looks like the study has more than one consent form.

Study Modifications

The IRB reviews and approves all modifications (i.e., revisions or addenda) to an IRB approved research protocol. **Please note that research must continue to be conducted without inclusion of the**

modification(s) until IRB approval is received, except for reasons directly related to patient safety. In these cases, please contact the IRB immediately.

Modification Examples:

- Revisions to a protocol including:
  - Sponsor amendments
  - Administrative or editorial changes or addenda
  - Changes or additions to eligibility criteria
  - Changes to a procedure
  - Addition of a procedure
  - Addition of investigative sites in multi-site research
- Single subject protocol exceptions
- Changes to enrollment numbers
- Revisions to consent or assent form
- Changes to study investigators
- Changes in study personnel
- Changes in recruitment practices including:
  - Change in research population
  - Letters to potential participants
  - Notifications and/or letters to research participants
  - Advertising materials
  - Recruitment materials

Approval from the Department Review Committee and/or Department Chair or Clinical Director is required if the modification significantly alters the design of the study, impacts the risk/benefit ratio, or if requested by the IRB.

When making any changes to documents with a modification to the study, utilize the “Update” button found next to the original document in the study’s smart form to essentially stack revisions on top of older versions.

In order to add research sites to previously approved protocols, a modification must be submitted to the UH IRB for review and approval. The modification must include the site-specific information, including but not limited to consent forms, conflict of interest management plans, etc. to be used at the relying site. When no significant changes to study procedures are requested / included by the relying site, this may be considered a minor modification that can be reviewed via expedited review.

Continuing Reviews

The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) have specific regulations regarding IRB continuing review of ongoing research, to ensure that the rights and welfare of human subjects are protected.

The aims of continuing review are to reappraise the research to ensure:

- The risk/benefit ratio is still acceptable.
- The measures taken to safeguard subjects are adequate.
- The approved protocol is being followed.
- The protocol reflects changes in the regulations for human subjects' research that have been implemented since the last approval.
- To review the progress of the protocol since last review and the plans for the future based on the progress to date.
- Review adverse events, untoward reactions, or unanticipated problems that occurred since the last review.
- Evaluation of new significant findings that might relate to the participant's willingness to continue and which should be provided to participants.
- All local requirements are still being met, including verification of current study personnel certifications.

Continuing Review submissions include general information about the study progress. Please select all applicable study milestones.

Study teams will be asked to report any new financial interests, protocol deviations and enrollment numbers (which must not exceed the IRB approved enrollment numbers).

Note: enrolling over the number listed on the IRB forms is not permitted and could be considered non-compliance. Enrolled subject means the number of eligible subjects who have signed consent (if the study consents), number of people who have responded to the questionnaire (if there is a consent waiver), or the number of charts from which you have actually pulled data (if chart review).

Continuing Review submissions must report details of events that occur under the purview of the IRB (at any UH site(s) or any site(s) relying on the UH IRB) if any of the following occurred within the past year:

- Subjects experienced unexpected harm*
- Anticipated adverse events have taken place with greater frequency or severity than expected*
- Subjects withdrew from the study*
- Unanticipated problems involving risks to subjects or others*
- Complaints about the study*
- Publications in the literature relevant to risks or potential benefits
- Interim findings
- Multi-center trial reports
- Data safety monitoring reports
- Regulatory actions that could affect safety and risk assessments
- Summary or log of protocol deviations*
- Summary or log of Adverse Events*
- Other relevant information regarding this study, especially information about risks

*Reporting required for internal events only (See Chapter 20: RNI for definition of internal)

The study team must also confirm that:

- In the opinion of the PI, the risks and potential benefits are unchanged
- All modifications to the protocol have been submitted to the IRB
- All problems that require prompt reporting to the IRB have been submitted

Although continuing reviews are usually assigned an expiration date of 1 year, the Board may require certain projects, as determined by an evaluation of the risk-benefit ratio, to be reviewed more frequently than yearly. This can be either after a fixed period of time (such as at six months) or after a certain number of subjects have been enrolled. For studies approved under the Pre-2018 Common Rule, the IRB may also grant an extended period of approval of up to 2 years for research that is not federally funded, not greater than minimal risk, and not subject to COI review.

Unless the UHCMC IRB determines otherwise, continuing review of research approved under the 2018 Common Rule is not required for:

1. Research eligible for expedited review
2. Research reviewed by the IRB in accordance with limited IRB review;
3. Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
    i. Data analysis, including analysis of identifiable private information or identifiable biospecimens, **or**
    ii. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

The UHCMC IRB may determine that continuing review is required for any research protocol that falls within the above criteria. For example, the IRB may determine that continuing review is required when:

1. Required by other applicable regulations (e.g., FDA);
2. The research involves topics, procedures, or data that may be considered sensitive or controversial;
3. The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability;
4. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
5. An investigator has a history of noncompliance

When the UHCMC IRB determines that continuing review is required for such research, it will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

The expiration date (if any) for an IRB approved study is clearly indicated on the IRB approval or initial approval letter and is the last day that the study has IRB approval.

The Principal Investigator is responsible for ensuring that the research is submitted to the IRB for continuing review in an appropriate time frame, in order to avoid a lapse of IRB approval. The date by which a protocol must receive its continuing review is listed on the approval letter and indicates the date

that the protocol is approved through. In order to avoid a lapse in approval, the investigators must plan ahead to meet the required continuing review dates specified by the IRB. The UH IRB recommends that a Continuing Review is submitted at least 6 weeks prior to the expiration of the study. The SpartaIRB system sends courtesy notices out at 30, 60, and 90 days.

When a continuing review application is submitted less than seven (7) days before expiration to the IRB, the Principal Investigator, Co-Investigators, and study staff may be required to complete Continuing Review Education offered by Research Compliance.

If the continuing review involves modifications to previously approved research, it is usually best to submit those modifications as a combined Modification and Continuing Review in the electronic system.

Addressing a Lapsed Study

If the approval of human subjects research lapses, all human subjects research procedures related to the protocol under review must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing human subjects research procedures is a significant violation of policy. If current subjects will be harmed by stopping human subjects research procedures that are available outside the human subjects research context, provide these on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping human subjects research procedures that are not available outside the human subjects research context, immediately contact the IRB Office and provide an explanation as to why they will be harmed by stopping human subjects research procedures.

If the investigator continues to conduct the research after the study has expired (without prior approval from the IRB that it is in the best interest of the current subjects to continue activity), this becomes an issue of non-compliance and will be referred to Research Compliance

If you fail to submit a continuing review form to close out human subjects research, you may be restricted from submitting new human subjects research until the completed application has been received.

If a continuing review submission is not reviewed and approved by the IRB before the study expires, the IRB will inform the investigator that the study approval has expired and that no research activity, including data analysis may occur during the lapse in approval. Both automatic and manual notices will be sent via the electronic system. If a continuing review submission is not received for review within thirty (30) days of the expiration date, the IRB office can administratively archive the study, and the study will be considered closed. All responses to IRB stipulations on an expired study must be received within 2 weeks, or the process for administratively archiving will continue. Once a study is closed in SpartaIRB it CANNOT be reopened. If the IRB administration office archives a study with a greater than minimal risk designation, notification of that action will be sent to the Research Compliance.

Annual Check-In for Studies with No Expiration Date

Under the Revised Common Rule, certain studies can now be approved without an expiration date. However, the UH IRB and HRPP are still required to maintain oversight of all open research. Thus, it is still UH IRB policy to require a study closure form when the research is complete. Until a closure form has been processed by the IRB, notifications will go out to study teams on a yearly basis to prompt the

study team to close the study, if possible, and submit any necessary modifications. Please respond to these notices with a brief confirmation of study status or by submitting a closure form. Study teams that do not respond will be referred to Research Compliance to investigate study status. Please note that while a formal Continuing Review is not required by the updated regulations for these studies, all research is still subject to, and must comply with, federal and local research regulations and policies, including random Research Compliance audits.

Study Closure

Complete the Continuing Review SmartForm in the electronic IRB system and attach all requested documents. To request a study closure, select the first four research milestones under #2 in the SmartForm. Once completed, the PI or PI Proxy will need to click "Submit" to send the submission to the IRB. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Please be mindful that certain sponsors, including the NIH, might have additional record retention policies. If your human subjects research is sponsored, contact the sponsor before disposing of human subjects research records.

After a protocol has been closed, the IRB does not accept further submissions unless they impact the rights and welfare of participants. The investigator should keep all non-reported adverse events on file for review by regulatory agencies.

After study closure the study no longer has IRB approval and all human subject research activity must cease.

Important: Once a study closure has been submitted and processed by the IRB the study **cannot** be re-opened.

Record Retention

Regulations and study sponsors require investigators to retain research data not only while research is being conducted but also after the research is complete. See also SOP HRP-072: IRB Records Retention for more information.

Regulatory Authority / Oversight	How long to retain records
UH IRB Policy	3 years after study completion
FDA	• 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, • If no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified **Reference Chapter 23 for more FDA guidance*
OHRP	3 years after study closure

HIPAA	Signed Authorizations (i.e., consent forms) for 6 years after study completion
Sponsor	Comply with any term for record retention detailed in the contract

Other IRB Submissions

Please refer to subsequent chapters for more information regarding Reportable New Information (RNI) and reliant review submissions.

Chapter 7- Required Reviews and Approvals

This chapter includes information about required department approvals, as well as additional required reviews and approvals needed before submission.

Department Scientific Review of Protocols

It is the policy of the UH IRB that each Department reviews all protocols prior to submission to the IRB. The review must address the scientific merit, ethical issues, and the availability of Departmental resources to carry out the research. Departmental review allows the Chair of the Department to be aware of Departmental research activities and provides information for allocation of Departmental resources.

Principal Investigators submitting new protocols to the IRB must submit to their Department for review and approval. Review by the Department applies to new protocols and modifications with major study design changes or changes that alter the level of risk to subjects. The IRB will not review or approve any protocol that has not been reviewed and approved by the Department.

The Department of Medicine has delegated the departmental review responsibility for cancer related protocols to Protocol Review and Monitoring Committee (PRMC).

Research taking place at Community Hospitals (Ahuja, St. Johns, Geauga, Parma, etc.) should submit via department approval at UHCMC.

Functions and Organization of Department Scientific Research Review

The function of the department's research review is to:

- Review the scientific merit of a protocol.
- Review the available resources (including qualified staff, appropriate population and adequate facilities) to carry out the proposed research within the Department.
- Determine if the PI and study team have appropriate expertise to conduct the study.
- Review the proposed time to conduct and complete the research.
- Review ethical concerns related to the study risk especially as it relates to the discipline represented by the Department.
- Review the protocol and consent form to ensure that the required elements are present before forwarding the protocol to the IRB for review.
- Review amendments to approved protocols if the amendment adds significant risk to the subjects or significantly alters the study design or procedures.
- Serve as an educational resource for faculty and staff of the Department on human subject protections.

Each department's research review will:

- Ensure timely and prompt review of new protocols submitted for review.
- Designate support staff that will receive and distribute protocols to other members of the Department Research Review Committee for review (if applicable).

- Organize a timely and efficient review process for protocols submitted in their Department.
- Ensure timely submission of protocols to the IRB.
- Refer protocols to the UHC Ethics Committee for review and recommendations when either the Chair or committee members believe it is appropriate.

Secondary Department Reviews

Protocols involving medical care or treatment of subjects not under the primary care of the Principal Investigator's Department must also obtain approval from the Department responsible for the subjects' care.

If a protocol includes a Co-Investigator from the responsible Department, review by that additional Department is at the discretion of the IRB and will depend on the nature of the study.

Additional Required Reviews

Human subject research protocols may require review and approval from entities not represented by the Principal Investigator's UH Medical, Academic or Administrative department responsible for the conduct of the research under UH Human Research Protection Program policies. Human subject research conducted at UH or its affiliates which involve any of the following procedures (experimental or otherwise) will require additional review from the appropriate departments of committees prior to IRB approval:

- Biological hazards
- Human cell or tissue samples
- Select chemicals
- Controlled substances
- Biologics
- Recombinant DNA
- Electrical device use
- Cellular therapy
- Stem cell use
- Ionizing radiation
- Lasers

If additional reviews are required, documentation of the additional approval should be submitted to the IRB before the IRB will approve the research. In general, documentation can be provided via ancillary review sign-off.

Examples of departments and committees that may be required to conduct additional reviews of human subject research proposed for conduct at UH or its affiliates are listed below. Additional internal and/or external entities not listed below may also be required to review proposed human subject research as indicated by the IRB Administration Office.

UH Departments/Committees Utilized for Additional Reviews:

Grants and Contracts Office

The CRC Grants and Contracts Office must review all industry-sponsored protocols and research contracts for the purposes of ensuring coordination of legal review, ensuring that investigators follow fiscal guidelines, and ensuring regulatory compliance with research billing policies. Grants and Contracts Office approval is not required prior to IRB submission although approval is required prior to subject enrollment.

Research Finance Office

The Research Finance Office must review all protocols that involve clinical patient care to assess the need for a coverage analysis. Based upon national and local coverage determinations, the Research Finance Office will craft a coverage analysis for your trial to ensure that UH continues to meet research billing and compliance requirements. Research Finance Office approval of your coverage analysis is required prior to study initiation and subject enrollment.

Special Care Units

Protocols involving subjects in areas of special care, such as intensive care units or respiratory care units, require the approval of the director of that area, as well as the approval of the Department Chair.

Newborn Nursery: Protocols involving subjects in the Newborn Nursery require the approval of the Department of Pediatrics Research Review Committee and the signature of the Chair of the Department of Obstetrics and Gynecology. The Chair of the Department of Obstetrics and Gynecology may choose to have the protocol reviewed by the Obstetrics and Gynecology Department Research Review Committee.

Electrical Safety Office

If the protocol involves subject contact with new or nonstandard (non-FDA approved) electrical equipment, the equipment and the protocol must be submitted for approval to the UHCMC Electrical Safety Office. Electrical safety is also a requirement when the equipment's grounding is attached to the unit's casing. Each protocol must include sufficient information to determine whether electrical safety is an issue. The protocol must identify all experimental or investigational electrical equipment used in subject contact by manufacturer model and serial number (if known) and an IDE number (if applicable). The protocol must describe how the equipment is to be used, as well as its location. All equipment must be approved before use on subjects. A copy of the approval should be submitted to the IRB with the protocol. Final approval by the IRB cannot be given until Electrical Safety Office approval is complete.

Department of Pharmacy Services

The Department of Pharmacy Services has the sole responsibility for the procurement, storage, distribution, and control of all medications for patients at UHCMC/RBC. The Department provides information and assistance on the clinical use, pharmacokinetics, administration, and adverse reactions of medications.

Pharmacy Services dispenses investigational only in accordance with the current protocol approved by the IRB. All investigational products are dispensed through Pharmacy Services unless an Investigational Drug Services Exception Request has been reviewed and approved by the Investigational Pharmacy and the

Clinical Research Center. The conditions outlined in the request (documentation, storage requirements, temperature control) is monitored periodically by an independent group responsible to the Clinical Research Center.

Investigators using an investigational product as part of their protocol must contact IDS to discuss how and by whom the drugs will be dispensed, whether an investigational new drug (IND) application with the FDA should be considered, and to review any other special considerations for feasibility assessment. IDS may be reached at IDS@UHhospitals.org and 216-844-7000.

Radiation Safety Committee (RSC)

Protocols that use ionizing radiation (such as x-ray, CT, scintigraphy, PET, SPECT, etc.) in human subjects for research purposes outside standard clinical care require review and approval by the Radiation Safety Committee of the institution in which the procedure is to be performed. This requirement is based not on the nature of the procedure but on whether the person would receive the radiation only because he/she is participating in the research. Conversely, if the person would receive the radiation for his/her clinical care, regardless of the enrollment status, RSC review is not required.

If there is any question if radiation exposure is part of a subject's standard of care, investigators or the IRB may ask for a determination by either **1)** submitting a written, signed report from the review committee of the department that performs the procedure which exposes humans to radiation or, **2)** submitting the protocol to the RSC for its determination. In the event of a disagreement whether the proposed radiation use is within the standard of care, the matter is brought to the RSC for evaluation. This evaluation includes input from the department proposed to perform the procedure that exposes humans to ionizing radiation.

Forms and policies related to the Radiation Safety Committee are available at UHCMC's radiation safety website. Investigators who plan to use radiation in their protocols are advised to confer with Radiology and/or Radiation Oncology physicians who would be the Authorized User of record for the protocol. The RSC will advise the investigator and IRB of additional review and approvals that might be required, mainly in the case of an investigational radiopharmaceutical: Radioactive Drug Research Committee or FDA Investigational New Drug.

Department of Radiology

Department of Radiology must review:

- All protocols originating in Radiology
- All protocols where imaging takes place in the UH Radiology Department

Please note that the Department of Radiology has a Policy Manual that addresses a variety of requirements, such as use of contrast in research MRIs (RE-3).

Department of Pathology

Protocols that include research use of surgical tissue that is sent to the Department of Pathology require the approval of the Department of Pathology Research Review Committee. This requirement does not apply if a member of the Pathology faculty is an investigator on the protocol, or if the tissue is obtained under an IRB approved protocol for tissue banking.

Research IT

ResearchIT reviews all protocols with (1) previously un-approved methods of data storage; (2) protocols involving the use of an electronic application; (3) all methods of electronic consent; or (4) any other data storage / extraction / transmission methods that have not been previously approved. Protocols involving the aforementioned study procedures are required to undergo ResearchIT review prior to IRB approval. For more information about ResearchIT, please contact ResearchIT@uhhospitals.org. REDCap is the preferred storage method for research data.

Letter of support for Investigator initiated trials with no or limited outside financial support

Studies with medical interventions that intend to enroll UH patients typically have a sponsor or NIH funding. However, in situations where the study is investigator initiated and there is no, or limited, outside financial support, the IRB will require that study teams provide a letter of support from the Department Chair acknowledging that:

- The study is unfunded, or with limited funding
- Any cost incurred by the study will be the responsibility of the department
- That the Chair or the Chair's designee will be responsible for financial oversight of the study

UH Ethics Committee

The IRB may refer protocols to the UH Ethics Committee for review and recommendations when either the Chair or Board members believe it is appropriate.

Relevant Hospitals Policies

University Hospitals has system-wide policies that can impact research but are not owned or managed by the UH CRC or UH IRB. When applicable, the IRB will assist with compliance with those policies making study teams aware. These policies include, but are not limited to, IS-22, RE-3 and GM-23. Compliance with all UH policies is required. Each Hospital within the UH System has its own requirements and policies. While these are unlikely to impact the normal process of research it is important to be aware of them.

Conflicts of Interest (UH)

On an annual basis, all employed physicians and advanced practice providers (e.g., physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiologist assistants, certified nurse midwives) complete a "Relationships of Interest" Questionnaire in the COI Smart application to disclose financial interests and participation in certain outside activities that could be determined as a Conflict of Interest. When entering into a new or renewing outside interest, practitioners are required to complete a request for Approval questionnaire in the COI-Smart application. For more information about which outside interests request advance approval, please see UH Policy CE-20.

UH CRC DSMC

The UH Clinical Research Center's (CRC) Data Safety Monitoring Committee (DSMC) is a data and safety advisory group available to UH Investigators that conduct greater than minimal risk research and do not have external monitoring. The CRC's DSMC will not oversee Industry-sponsored or cancer-related trials.

The purpose of a DSMC is to provide independent safety review and trial guidance during the course of a study. DSMCs review study data, evaluate adverse experiences, judge whether the overall integrity and conduct of the study remain acceptable, and make recommendations to Investigators.

Non-UH Departments/Committees Utilized for Additional Reviews:

Institutional Biosafety Committee (IBC)
All protocols that include research involving the deliberate transfer of recombinant DNA or RNA, or DNA or RNA derived from recombinant DNA, into one or more research participants must be approved through the Case Biosafety Committee before final IRB approval may be granted. Additionally, research utilizing live, recombinant or attenuated microorganisms for the purposes of vaccination of one or more human participants must be approved before final IRB approval may be given. Research activities may not begin until both the Biosafety Committee and IRB approval have been granted.

Case Comprehensive Cancer Center Protocol Review and Monitoring Committee (PRMC)
The Protocol Review and Monitoring Committee (PRMC) is responsible for reviewing the scientific merit, scientific priorities, and the scientific progress of proposed and ongoing cancer/cancer-related human subject research conducted at UH. The PRMC review is required as an additional specialized review in conjunction department review and any applicable committee noted above In some cases, PRMC review will fulfill the "department review" requirement needed for IRB review of human subject research. Protocols reviewed by PRMC must attach the PRMC approval letter with their IRB submission. The IRB will consider any issues raised by PRMC during their review

Case Conflict of Interests Committee
The Conflict of Interests Committee administers the University's Policies on conflict of interest with the aim of preserving the integrity of the University and its members and maintaining compliance with applicable federal regulations, while respecting academic freedom and encouraging outside scholarly and entrepreneurial activities.

The Center for Regenerative Medicine's Cellular Therapy Review and Monitoring Committee (CTRMC)
The Cellular Therapy Review and Monitoring Committee (CTRMC) conducts specialized, expert scientific protocol review that supports clinical cellular therapy and regenerative medicine research conducted at UHCMC. The CTRMC review informs the IRB on the scientific merit, feasibility and ethical issues related to cellular therapy protocols. CTRMC review may be required as an additional specialized review in conjunction with any of the committees noted above as well as department review.

Case Stem Cell Research Oversight Committee (SCRO)
The Case Stem Cell Research Oversight Committee within the Department of Bioethics provides ethical guidance and technical support as it relates to all forms of stem cell research and translation to clinical practice. The Stem Cell Ethics Center may be required to additionally review proposed human subjects research to present insight regarding directed application of stem cell ethics in the complex array of cultural, social, political, and economic issues.

Please note: In some cases, officials from the various review committees may contact the IRB directly to communicate concerns or provide documentation of approval. The IRB staff verifies that required

documentation is on file prior to issuing an approval. Final approval of the protocol by the IRB may not be given until all required approvals are complete. Resubmission of continuing reviews does not require re-review by the special centers unless there have been changes in the protocol that would affect its specialized review (i.e., alteration of the level of risk or the addition of new procedures).

Chapter 8- Special Considerations

Studies with Sensitive Questions

If surveys or interviews address sensitive or potentially emotionally distressing conditions or topics, the study should include appropriate local psychological resources, both urgent and referral. These should be easily available in a handout or at the conclusion of the survey. The protocol must include an appropriate written plan for monitoring responses and mitigating risk. For example, if questionnaire responses could reasonably be construed to indicate significant anxiety, resources for treatment of anxiety should be provided. Other potential areas that need to be mitigated include but are not limited to food insecurity, drug/alcohol abuse, domestic abuse, and infertility.

Please note, the following must always be reported per federal/state regulations: if child or elder abuse is disclosed, or if an individual appears to present an immediate harm to self or others. If germane to the study, consider disclosing this reporting requirement in the consent form.

Suicide Risk Mitigation

In the event that a research study includes formal depression screening, an individual with clinical experience and expertise assessing for depression and suicide risk must be a study team member and must be prepared and available to conduct the relevant clinical assessment. Depression screening results should be reviewed and scored in real time (optimally in person at the time of survey completion, and if the survey is being completed remotely no later than 24-48 hours after completion of the screen) by qualified individuals who know the appropriate clinical cutoff for assessment. Any participant who screens above the clinical cut-off must be contacted by the study team member who is a qualified clinician (in-person contact at the time of screening is optimal, and if the survey is being completed remotely, by phone call, not email communication) and assessed for active suicidal ideation with a plan or intent. If assessment is negative, refer either to the participant's own mental health provider if he/she has one, or to community resources (study team must have a list prepared and included in the submission). If the assessment is positive for suicide risk, Frontline (or an equivalent provider, Frontline is optimal in Cuyahoga County 216-623-6888) and/or 911 must be contacted on behalf of the participant. The informed consent must make participants aware that depression screening is included in the study, that the results will be assessed, and that the study team will reach out if appropriate. In addition, the informed consent must be transparent about the mitigation plan in the case of active suicidal ideation, with a plan or intent. A phone number for the participant must be obtained as part of the data set. The HIPAA section must include possible sharing of information with FrontLine. The protocol must include a detailed mitigation plan as part of the study procedures to address clinically significant depression scores and suicidal crisis.

Questionnaire/Survey

The need for written informed consent for questionnaire studies will vary depending on the involvement of the subject and the nature of the information being collected. An information sheet may be substituted for the written consent, indicating the nature of the study, the time requirement for the subject, and other

information required for consent. The information sheet must indicate that completion of the questionnaire implies consent. A protocol must contain specific justification of the use of an alternative (i.e., information sheet) to written informed consent. The use of an information sheet requires an IRB waiver of the need for written consent.

The use of REDCap for electronic surveys is encouraged.

Additional Considerations for Focus Groups or Interview Studies

It is important that the training and supervision of focus groups is thoughtfully considered. When submitting studies that propose to use group discussion or interpersonal interviews, please include the training of, or supervision plan for, the moderators or interviewers.

A script or outline of discussion topics or interview questions that reflect the overall structure of the group or interview must be submitted

When focus groups or interviews are discussing sensitive topics, extra attention should be paid to privacy and confidentiality concerns.

Focus group sessions should open with a discussion about group standards and expectations. The consent for focus group studies should include statements that address the following issues.

- The risk of inappropriate behavior or interpersonal discomfort. Other group members may say or do something that make participants uncomfortable. It is important to start the first session with a group agreement regarding behaviors during discussions. Participants should be told that if another member makes them uncomfortable or approaches them outside of the group, the study team / moderators should be informed.
- The limits of confidentiality given the group setting. While researchers can take precautions to maintain confidentiality, the nature of focus groups prevents the researchers from guaranteeing confidentiality. Participants should be reminded to respect the privacy of fellow participants and not repeat what is said in the focus group to others.

*Focus group and interview studies consents should include statements that address the legal requirements to report to the appropriate individuals and authorities any information that is disclosed concerning child or elder abuse or neglect or potential harm to the participant or others.

Often investigators wish to record and transcribe focus group or interview sessions. This information must be in the consent. If outside transcriptions services will be utilized, this must be disclosed in the consent and Privacy of Protected Health Information section. All audio or video records of participants should be treated as PHI. Facial images and voice prints are both considered PHI. Further, conversations often inadvertently contain elements of PHI such as names or dates. Therefore, these records need to be stored securely according the UH IT requirement and they should not be shared with transcriptions services without an appropriate legal agreement.

Additional Considerations When Research Visits Take Place in the Home

If home visits are expected or offered, it must be disclosed in the consent. The consent must also include provisions for mandated reporting.

When research coordinators or other study team members are planning to offer in-home visits, a safety plan must be included in the protocol. It is recommended the following provisions are considered

- Confirm details of the visit including: location, estimated arrival time, address, and parking
- Visits should be conducted in teams of two wherever possible, if not, identify a study team contact to be knowledgeable of the visiting coordinator whereabouts
- If any safety concerns arise at any location, the study visit will be terminated and the study team member will consult with the PI regarding next steps and document the incident.

Blood Drawing

All blood drawn for research purposes must be done with an IRB approved research protocol and consent plan. Written consent for venous blood drawing should include the amount of blood in lay terms (teaspoons, tablespoons, ounces, or cups), the number of samples, the number of needle sticks, whether an indwelling catheter will be used, and risks of infection, discoloration, and some pain. Consent forms should indicate what will be done with the blood including what will be measured, how long the blood will be stored, and whether results will be available to the subjects. If personal identifying information will be removed from the sample this should be stated along with whether or not these samples may be used in future research studies.

When the research subjects are patients who are acutely ill and subject to multiple clinically indicated blood tests, the investigator must discuss in the protocol what measures will be taken to ensure that research samples will not cause the total amount of blood removed (including clinical samples) to exceed the allowed limit. This applies to both children and adults.

Studies involving arterial blood drawing of any amount require written consent and must include the amount of blood in lay terms, a statement that a test for patency of collateral circulation (Allen test) will be performed, and the risks involved, i.e., gangrene, blood clot, possible loss of limb, as well as infection, discoloration and some pain.

Studies that include a blood draw for research are typically required to obtain signed consent. Multiple blood drawing, regardless of amount of blood to be drawn, will always require written consent / assent.

<u>Adults</u>

Protocols typically may take a single collection of blood up to one unit (475 ml). Subjects may repeat participation in a single blood draw study as long as more than 475 ml is not taken within 2 months (including clinical and research samples); however, consent must be obtained for each blood draw and this possibility must be discussed in the protocol. In general, a signed consent is required for blood draw studies. Pregnant women would have additional considerations.

Research Samples Requiring Additional Venipunctures

If extra blood samples are obtained for research purposes, written consent and assent are required. As a general rule blood samples for clinical plus research purposes should not exceed 5 cc/kg over 2 months.

Multiple Samples

Frequent blood draws such as frequently used for pharmacokinetic studies should be done through indwelling access and not multiple venipunctures.

Children

Extra blood sticks should be minimized whenever possible. Investigators should align research bloods draws with clinical blood draws or, if already placed for clinical purpose, IV or lines should be used. When enrolling children as controls, blood samples must be obtained at the time of clinical blood draws and the enrollment of minors must be justified. Research that obtains blood draws from minors who are less than two years of age, or seeks to collect blood more than twice a week, will be subject to Full Board review.

Maximum acceptable pediatric blood volumes drawn for research:

Timeline	Total Blood Volume*
Over 24 hours	No more than 2ml/kg
Over 4 weeks	No more than 4ml/kg

*The Investigator should consider both clinical and research blood draw volumes

In order for risks to be minimized, the amount drawn should not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week. Studies that include larger, or more frequent, blood draws for minors will need to make evident the prospect of direct benefit for the individual subject; or, justify how the investigation will yield generalizable knowledge about the subjects' disorder or condition, which is of vital importance for the understanding or amelioration of the subjects' disorder or condition.

In any case, Investigators should consider the overall health of the child participant and the amount of blood they will obtain, and limit when possible blood draws in sick patients (e.g. low anemia, low cardiac output, pulmonary or hematopoietic problems). Please be aware that extra monitoring and mitigation plans may be necessary if enrolling a particularly sick population or taking a large volume of blood.

DNA and Genetics (blood and/or tissue)

All studies using blood or tissues for DNA or genetic studies (excluding discarded, anonymous tissue studies) must discuss how data will be kept confidential. The protocol and consent form must discuss what results, if any, will be told to the participant. In regard to paternity issues it may be appropriate to include the disclaimer statement "It is the policy of this institution not to report information regarding paternity." If the genetic studies are only a part of the protocol, subjects should have the option to "check off"

participation or refusal in the genetic part of the study. Subjects cannot be asked to sign away any rights to such materials. Consent forms must discuss future use of samples and data. Further details and suggested consent language are contained in the IRB Consent Form Template and Tutorial.

Use of Fetal Tissue

There is a law in Ohio and a City of Cleveland ordinance that restricts the use of the products of human conception in research. The laws state: "No person shall experiment or sell the product of human conception which is aborted irrespective of the duration of the pregnancy." However the law does allow for research to be conducted using human fetal tissue that was spontaneously aborted, such as a stillbirth, if the woman donating that tissue gives informed consent, and the research is conducted in accordance with Federal regulations (45 CFR 46.206).

Chart Review and Discarded Tissue Studies

Research activities involving the use of chart reviews or discarded tissues must be reviewed and approved by the IRB prior to beginning. If children are involved, parental permission and assent must also be obtained unless the criteria for waiving parental permission and waiving assent are met. The IRB's main concern with chart reviews for research is the possible invasion of privacy and the use of confidential and privileged data or information. As such, unless the data is kept in REDCap, investigators are required to state the specific secure data storage location, and attach to their submission a copy of the data collection sheet and corresponding linking sheet. The data collection sheet should not contain any elements of PHI. All elements of PHI should be on the linking sheet. The two sheets should both contain a unique study number that is not derived from any patient identifiers.

For any study to qualify as a chart review all the data accessed must have been collected (or will be collected) as part of routine clinical care. As with discarded tissue studies, informed consent must be obtained unless a waiver can be fully justified and meets the regulatory requirements. If an investigator has support to obtain consent from a subject and if practicable according to applicable regulations, they must do so as usual under the human subject protection regulations. The consent process and all requests for waivers must be addressed in the protocol/research plan.

Large Datasets

Due to concerns of privacy (including UH responsibilities related to HIPAA) and the protection of UH data, the IRB will require additional provisions for studies that include 500 or more patients/subjects/charts.

- The study team must provide a scientific justification for including 500 or more patients/subjects/charts. Scientific justifications should not include subjective rationales. In general, a sample size calculation based on the main outcome measure is needed.
- An annual continuing review may be required.

- A well thought out and secure data storage plan is imperative. If multiple storage locations are being used, a detailed explanation will be required to ensure the security and confidentiality of the data.
- REDCap is generally required for studies with 500 or more patients/subjects/charts.
- A study "startup visit" may be required to ensure the entire study team is aware of privacy related policies and procedures. This helps to prevent compliance issues or data breaches once data is actually being collected.

Research Repositories

Data registries or biorepositories are protocols that describe the collection of data and/or samples specifically for future research. The establishment of either data or sample repositories for research must, therefore, consider the procedure for future use of those data or samples. When reviewing the proposed repository, the IRB will require a plan that describes the circumstances under which data or samples will be shared, and with whom they will be shared. The plan should include the process by which researchers should request data and/or samples (for example, the form that researchers will use to request data and/or samples) and how decisions will be made to grant requests. The plan should also describe whether data / samples can be shared outside of the institution, whether it will be shared in a deidentfied, linked / coded, or identifiable way and an attestation that no data or samples will be shared without verification of IRB review of the proposed use.

Consent forms for repositories should always include information about how data and samples will be used for future research, and any applicable options about use.

When researchers submit projects to the UH IRB to use data or samples from established repositories, the UH IRB will request documented permission from the repository.

Pilot Studies

A pilot study is generally defined as a small-scale, preliminary study to help design methods and procedures to be used within a larger clinical trial. Pilot studies that include participants or data and involve an intervention or interaction for purposes of collecting or sharing data require IRB review regardless of the size of the study or the intent of the investigator.

Clinical Trials

A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
If your study is a clinical trial and supported by a Common Rule agency, one IRB-approved version of a consent form that has been used to enroll participants must be posted on a public federal website designated for posting such consent forms. The form must be posted after recruitment closes, and no later than 60 days after the last study visit. Please contact the study sponsor with any questions.

Any study meeting the definition of a Clinical Trial must register on ClinicalTrials.gov in accordance with the policies governing use of that site.

Use of Placebos

Protocols that use a placebo will receive full Board review. A placebo-controlled trial may be conducted with IRB approval provided that all the following criteria are met:

- The study is ethically and scientifically justified.
- There is a clear and detailed rationale for the use of a placebo in the protocol.
- Potential risks are identified and minimized.
- The subject is adequately informed of the potential use and risks of the placebo in the study.

Situations in Which Placebo is not appropriate:

A placebo arm is inappropriate whenever withholding an active (proven effective) treatment would increase the risk of more than minor harmful consequences or when minor or minimal harmful consequences due to withholding an active treatment or to the placebo itself are likely to be irreversible, or when there is no scientific justification for use of a placebo.

Informed Consent and Use of Placebo

Participants must be fully informed of the use of placebo as part of the study and the possible risks, including discussion of exacerbation of current condition/symptoms as part of being assigned to the placebo group. The informed consent form must include the following information:

- A statement indicating that subjects may be given a placebo.
- A clear lay definition of the term “placebo,” Such as “a pill/injection that has no active medicine in it,” “a pill with no medicine”, etc.
- The rationale for using a placebo must be explained in lay terms to the subjects.
- If applicable, subjects must be informed of any viable medical alternatives to being placed on placebo.
- The duration of time that a subject will be on a placebo, degree of discomfort, and potential effects of not receiving medication must all be explained.
- Any consequences of delayed active treatment must be explained to the subjects.
- A statement in the “Risk” section of the consent document that the subject’s condition may worsen while on placebo.
- A discussion in the “Benefits” section that subjects who receive placebo are not expected to receive the same benefit as those who receive active treatment if that treatment is effective.

If all subjects are receiving active treatment throughout the trial, the above issues need to be addressed only for the placebo component of the trial.

Use of Washout

Protocols that involve washout periods (with or without the use of a placebo) present similar concerns about risk to subjects as protocols using placebos because both involve withholding available, proven therapy from subjects. Therefore, similar attention should be paid to the justification of the use of a washout period including methods to minimize risks to subjects.

Subjects must also be fully informed of the use of a washout period and any potential risks associated with this procedure. The informed consent form must include the following information:

- A statement indicating that the research will involve a washout period;
- A clear lay definition of the term "washout" (e.g. a period of time without any active medicine);
- A statement explaining which medications or treatments must be withheld during the washout period if washout does not include all medications or treatments that the subject is taking;
    - The duration of time the subject will be asked to withhold treatment during the washout period;
- The risks associated with the washout period, including potential deterioration of the subject's condition and/or exacerbation of the subject's symptoms.
- Clear instructions to the subject stating who should be contacted if the subject experiences an adverse event during the washout period and what symptoms to watch for.

Chapter 9- General Consent Requirements

This chapter includes information on general consent requirements

The IRB requires that all informed consent documents include the **nine basic elements** of informed consent listed below (45 CFR 46.116(a) and 21 CFR 50.25(a)). The IRB may also require any or all of the **six additional elements** of informed consent (45 CFR 46.116(b) and 21 CFR 50.25(b)), depending on the nature of the research.

There may not be discrepancies within the informed consent documents, the IRB application forms, the sponsor's or investigator's protocol, the investigator's brochure, or the contract regarding the purpose, risks, and benefits of the research. The Informed Consent document must be in a language understandable to the participant or the participant's legally authorized representative (45 CFR 46.116 and 21 CFR 50.25). Verbal or telephone consent is not acceptable unless the IRB has specifically waived the requirement for a written consent (45 CFR 46.116(c)). Consent must be obtained before initiation of any study procedures unless delayed consent is approved by the Board.

The investigator must provide a detailed description of the intended method for obtaining informed consent in the protocol. All informed consent documents (full written documents, oral scripts, assent forms, etc.) must be submitted for review and approval by the IRB prior to use. Any changes in the informed consent documents must be submitted as an amendment to the IRB for review and approval prior to use.

The location and timing of the informed consent process must ensure privacy and (except in the case of emergency research) sufficient time for the potential participant to make a decision; additionally the circumstances must ensure that the potential participant is not under mental or emotional duress or in physical pain, or scientifically justify any deviation from this plan.

Informed consent documents must be written in language that is at the appropriate reading and comprehension level for the targeted population. The target language level for consent forms is 6^{th} – 8^{th} grade reading ability. Use of a readability score tool is recommended. Two frequently used readability tools are Flesch-Kincaid and SMOG – these formulas can be accessed for free by searching online.

The informed consent documents must be in lay language and should not include complex language that would not be understandable to all participants. Technical and scientific terms should be adequately explained using common or lay terminology. The IRB discourages the use of lists of medical terms followed by the lay term (e.g., syncope (fainting), rhinorrhea (runny nose)) and prefers the use of only the lay term. Generic names are preferable when describing pharmaceuticals unless the brand name is more commonly known and understood. Regardless of which name is preferred, it should be used consistently throughout the informed consent documents.

No informed consent, whether written or oral, may contain any exculpatory language through which the participant or their legal authorized representative is made to waive or appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

For all research involving test articles regulated by the U.S. Food and Drug Administration (FDA), informed consent documents should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies are not appropriate when the purpose of the study includes determination of safety. In studies that also evaluate the effectiveness of the test article, informed consent documents should include that purpose, but should not contain claims of effectiveness. In addition, participants need to be informed that their records may be inspected by the FDA.

No unproven claims of effectiveness or certainty of benefit, either implicit or explicit, may be included in the informed consent documents.

When a Board approves a protocol and waives the requirements for obtaining a signed informed consent document, the meeting minutes must document the required regulatory determinations made by the Board in accordance with the above criteria as well as including the protocol-specific information for the justification of the waiver.

UHCMC Standard Research Consent Language

It is the requirement of the IRB that the Standard Research Consent Language be included in all written consent forms unless specifically waived by the IRB. However, research that is not being regulated by the FDA, the following sentence may be deleted, “If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records.”

Authorization to Use and Disclose Protected Health Information (PHI) for Research Purposes

All research studies enrolling patients or collecting protected health information (PHI) must abide by the Health Insurance Portability & Accountability Act (HIPAA) enacted April 14, 2003. This regulation, also known as the “Privacy Rule”, establishes conditions under which researchers may have access to and use an individual’s PHI to for research purposes. Clinical HIPAA Authorization DOES NOT cover use or disclosure of PHI for research purposes. Permission must be obtained via signed Authorization for use and disclosure of PHI for research purposes. The UHCMC IRB requests that the language relating to HIPAA and authorization for use and disclosure is included in the consent document. When PHI will be shared outside of the study team (for example, with business associates such as home health services, ride services, or transcription services), this should be accurately reflected within the HIPAA section of the consent.

Waiver or Alteration of Informed Consent Requirements

The IRB may approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. Alteration or Waiver of Informed Consent is defined as a variation from the traditional informed consent process. However, this

process still includes a considerate and thorough discussion of the study with the participant and verification that the participant understands the study and will participate voluntarily. The IRBs may alter or waive the requirement for informed consent of participants. In order to approve such a waiver or alteration, the IRB must find and document the following:

- The research involves no more than minimal risk to the participants;
- The waiver or alteration will not adversely affect the rights and welfare of the participants;
- The research could not practicably be carried out without the waiver or alteration;
- Whenever appropriate, the participants will be provided with additional pertinent information after participation; and
- The research is not greater than minimal risk under FDA regulation.

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds *and documents* that:

- The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    - public benefit or service programs;
    - procedures for obtaining benefits or services under those programs;
    - possible changes in or alternatives to those programs or procedures; or
    - possible changes in methods or levels of payment for benefits or services under those programs
- The research could not practicably be carried out without the waiver or alteration; and
- The research is not greater than minimal risk under FDA regulation.

The IRB may allow the alteration of informed consent in research involving no more than minimal risk, which can only be conducted when participants are less than fully informed and the missing information does not increase participant risk (e.g. behavioral studies). In these situations, the IRB may determine that consent, which does not disclose information about all elements of informed consent, can be obtained for initial enrollment. However on completion of the research, or after participation, each participant must be informed of the true nature of the study and be offered the ability to decline participation. The records must document why the IRB judged that each criterion listed above was met for the protocol. Research that includes participant deception is not eligible for expedited review.

Electronic Consent

Investigators are able to obtain consent electronically, and this process may substitute for paper-based informed consent. The eIC (electronic informed consent) must contain all elements and meet all regulatory criteria for informed consent outlined by HHS and FDA in 45 CFR 46.116 and 21 CFR 50.25. The eIC may contain hyperlinks and other electronic strategies to enhance comprehension, but must be easy to navigate with sufficient time allowed for understanding, and the potential subjects' electronic literacy must

be considered. Assent may also be obtained electronically but the capabilities of the child to assent using electronic methods must be considered.

The process of informed consent requirements still apply with electronic consent, and the following must be included in the protocol:

- Measures to ensure that subjects have access to all the consent related materials
- Plan to ensure all hyperlinks are active and working
- Plan for providing subjects with a written copy of the consent form
- Plan for how the date of the electronic signature will be captured

If the consent process takes place in person, then additional verification of identity is not required. However, "If any or all of the consent process takes place remotely and is not personally witnessed by study personnel, the electronic system must include a method to ensure that the person electronically signing the informed consent is the subject who will be participating in the research study or is the subject's LAR (see 21 CFR 11.100(b))" FDA regulations do not specify any particular method for verifying the identity of an individual and accepts many different methods, however the proposed method (e.g. driver's license or birth certificate, in addition to security questions, for example) must be described and approved by the IRB. The regulations found at 21 CFR part 11 permit a wide variety of methods to create electronic signatures, including using computer-readable ID cards, biometrics, digital signatures, and user name and password combinations. FDA does not mandate or specify any particular methods for electronic signatures, including any particular biometric method upon which an electronic signature may be based.

"IRBs, investigators, and sponsors may rely on a statement from the vendor of the electronic system used for obtaining the electronic signature that describes how the signature is created and that the system meets the relevant requirements contained in 21 CFR part 11."

When an electronic system is used there must be a time-stamped audit trail, full record retention (either electronic or paper), and the ability to provide copies and permit inspection (FDA 21 CFR Part 11). A copy must be provided to the subject.

Consent Documentation

It is the policy of the IRB to assure that for research involving human subjects, provisions are made to obtain legally authorized informed consent from each prospective participant or legally authorized representative. However, the IRB may grant a waiver of informed consent if conditions presented are in accordance with the requirements for a waiver or alteration of informed consent. Any such waiver or alteration must be consistent with applicable Federal and Ohio state laws and regulations.

The IRB also requires that documentation of informed consent be obtained from all participants unless alternate procedures are approved by the IRB. The IRB will review all informed consent documents to

assure the adequacy of the information contained in the consent document and adherence to Federal regulations regarding the required elements of informed consent.

All approved informed consent forms must have the UHCMC IRB stamp, which contain the UHCMC protocol number, IRB approval date, IRB effective date, and the consent expiration date. The IRB requires that the most recently approved and non-expired consent documents be used when obtaining consent from participants.

The signature section of the UHCMC Standard Research Consent Language has signature blocks for the following study categories: 1) adults able to provide informed consent; 2) adults with decisional impairment; 3) minors where the IRB has determined that the permission of one parent is sufficient; and 4) minors where the IRB has determined that the permission of one parent is not sufficient unless the other parent is deceased; unknown; incompetent; not reasonably available; or one parent has legal responsibility for the care and custody of the child. Both the research subject and the person obtaining consent must sign and print their names.

It is important to complete the Informed consent documentation checklist during each consent process (a template is available on the CRC website).

The following are the requirements for long form consent documents:

The subject or representative signs and dates the consent document.
The individual obtaining consent signs and dates the consent document.
Whenever the IRB or the sponsor require a witness to the oral presentation, the witness signs and dates the consent document.
For subjects who cannot read, a witness to the oral presentation signs and dates the consent document.
A copy of the signed and dated consent document is to be provided to the subject.

The following are the requirements for short form consent documents:

The subject or representative signs and dates the short form consent document.
The individual obtaining consent signs and dates the summary.
The witness to the oral presentation signs and dates the short form consent document and the summary.
Copies of the signed and dated consent document and the summary are provided to the person(s) signing those documents.

Individuals designated by the PI to obtain consent for this project must be listed as such on the study personnel table, and must have all required training / credentialing. Individuals obtaining consent must be knowledgeable about the study and capable of answering study-related questions posed by participants.

Informed consent must be obtained under circumstances that give the individual sufficient opportunity to consider whether to participate in the research study, and that minimizes possible coercion or undue influence. This includes providing the participants or his or her legally authorized representative adequate time to read the consent, ask questions, and consider the risks and/or benefits to participation in the research study prior to obtaining their signature. In the interest of ensuring that there is a full and valid consent process it is not appropriate or permissible to obtain consent in pre-op areas, or on labor and

delivery wards, without compelling justification and a description of how an adequate consent process will be ensured.

It is the principal investigator's responsibility to assure that the informed consent process is an ongoing exchange of information between the research team and the study participant throughout the course of a research study. Informed consent is a continuous process of communication over time, not just a signed document.

In order to approve research, the IRB must determine that informed consent will be documented in writing unless documentation can be waived in accordance with the Common rule (45 CFR 46.117) and FDA regulations (21 CFR 50.27). Documentation of written informed consent must be obtained as a standard written informed consent that embodies the elements of informed consent required by 45 CFR 46.116 and 21 CFR 50.25 and which is signed and dated by the participant or his/her legally authorized representative.

Standard Consent Form Document

This form may be read to the participant or the participant's legally authorized representative however the investigator must give either the participant or the representative the adequate opportunity to read it before it is signed (45 CFR 46.117(b)(1)) and dated. The participant or the participant's legally authorized representative must sign the document and a copy must be given to the person signing the document. For complex studies the IRB strongly encourages giving the consent documents to the potential participant several days in advance of the time he or she will be asked to sign the consent form. The IRB approved and stamped informed consent document may be sent via standard mail, fax, electronic mail, etc.

The IRB allows for illiterate persons who understand English and individuals who are seeing-impaired to participate in research studies. In these situations the consent document must be read to the participant and the process documented in the research file. For illiterate participants, the consent should be subsequently signed by the participant "making their mark" on the signature section of the consent document, in order to document their understanding. The IRB also requires an impartial third party witness to be present to confirm the consent process has taken place. Both the witness and the person obtaining informed consent or interview to obtain permission must sign and date the consent document. If someone other than the Principal Investigator conducts the interview and obtains consent, the Principal Investigator should formally delegate this responsibility, and the person delegated, should receive appropriate training to perform this activity.

For treatment studies or studies that include patient care, a copy of the informed consent document must be included in the participant's medical record. The principal investigator must retain the original signed informed consent document in his or her research records for 3 years after the completion of the study or otherwise designated by the study sponsor.

The person obtaining consent should document the consent process in the participant's medical record or the participant's research record. This may include:

How and where consent was obtained;

The participant's level of comprehension (did they appear to understand, did they ask questions, were they able to reiterate or verbalize the main purpose of the study, procedures, risks, etc.);
The participant's decision-making capacity at the time of consent (were they alert and oriented?);
Whether others were involved in the decision-making process;
The time given for the participant to review the consent document, consider the research, and ask questions to their satisfaction;

Identify who was present during the consenting process;

A copy of informed consent document was provided to participant; and
The participant signed and dated the ICF before any study procedures were performed.
The requirement for documenting the consent process applies to all interventional protocols and any protocol for which additional documentation would be warranted. A sample Informed Consent Documentation Checklist is available and may be used.

A copy of the currently approved and IRB date-stamped informed consent documents must be given to the participant or his or her legally authorized representative. If an unsigned copy is given to the participant it must be an exact copy of the signed consent form.
Any revisions to the informed consent process or documents will be submitted to the IRB for review and approval.

Use of Fax, Mail, or Email to Document Informed Consent

For minimal risk studies (e.g., studies involving questionnaires, surveys) the IRB may approve a process that allows the informed consent document to be given to the potential participant by fax, mail, or email. Original, signed consent forms should be returned by mail. Unique situations or alternative approaches should be discussed with the IRB.

For greater than minimal risk protocols, generally, using fax, mail, or email to obtain documentation of informed consent is not appropriate. For these situations, an electronic consent process that includes a live conversation should be used. Plans for the process of obtaining consent should be outlined in the IRB Submission.

Waiver of Signed Written Consent

If the IRB waives documentation of informed consent, the investigator still needs to obtain informed consent from the study participant, but does not need to document the circumstance of that consent on paper (i.e.; verbal consent). An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all participants if the IRB finds either:

- That the only record linking the participant and the research would be the consent document, the principal risk would be potential harm resulting from a breach of confidentiality. **Or**
- That the research presents no more than minimal risk or harm to the participants and involves no procedures for which written consent is normally required outside of the research context (45 CFR 46 117(c)(2) and 21 CFR 56.109(c)(1)).

When the IRB waives the requirement to obtain written documentation of the consent process, the IRB will review a written script of the information to be provided to participants and the script must include all the required and appropriate elements of consent disclosure. The investigator should provide the participants with a copy of the script.

When to Re-Consent Subjects

When changes occur in the conditions or the procedures of a study that would affect an individual subject, the investigator should once again seek informed consent from the subject. If the re-consent process includes a revised consent form, it must be submitted to the IRB as a protocol modification prior to use.

Active subjects

Subjects who are presently enrolled and actively participating in the study should be informed of the change and re-consented if it might relate to their willingness to continue or affect their participation in the study. For example, adverse events may occur during a research activity that would directly affect whether prospective or enrolled subject would wish to continue in a particular research activity.

Subjects who have completed active participation

Federal regulations do not require re-consenting of subjects who have completed their active participation in the study. However, the IRB may require re-consent of subjects when specific conditions are met; particularly when there is new information that participants should be aware of. In addition, study sponsors may also require re-consent of subjects.

Examples for when re-consent is required:

A) Re-consenting Children Who Become Adults While Participating in a Research Study

When a child who has been enrolled in a research study reaches 18 years of age, the subject must be re-consented as an adult.

B) Addition of Risks or Significant Revision to Consent Form

Enrolled subject must sign a revised consent form if the consent has been significantly revised and/or includes the addition of risks to the subject. The changes from the original consent form should be explained to the subject. If the only change to a consent form is an update to the UHCMC's standard research consent language, re-consent is not required.

C) Decisionally Impaired Research Subjects

If consent has been obtained from a legally authorized representative, and if the subject regains the capacity to consent, the subject must be re-consented using standard consenting procedures. If the subject

refuses consent, any data previously collected cannot be used for research purposes. In protocols where a return to normal cognitive functioning is likely, investigators must include their plan to re-consent the subject, including the time frame. Consent must be obtained as soon as possible, once a subject has regained the capacity to provide consent

D) As Part of Compliance Review

As a consequence of a compliance determination by the IRB, a corrective action may require re-consenting subjects before previously collected data can be used for research.

E) When the Principal Investigator is Changed

Participants who are active in a study must be informed when the PI changes. Re-consent is recommended when active participants are still coming in for study visits, however, in certain situations, it could be appropriate to use a signed notification to document the participant was informed. A copy of this signed notice must be still be given. If participants are still active but attending study visits yearly or less frequently, notification may be made by mail. When participants are no longer active, and all study participation is over, notification is not required.

Certificate of Confidentiality (COC)

A Certificate of Confidentiality is an assurance issued to protect subjects' privacy and ensure the confidentiality of their data. The Certificate prevents researchers from having to release identifying information about human research subjects in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings. This protection is afforded by the Public Health Service Act 301(d), 42 USC 241(d).

Any person engaged or intending to engage in research that will collect identifiable and "sensitive" information about participants should apply for a Certificate. Sensitive identifiable information includes all information that identifies an individual or for which there is at least a very small risk, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual. Sensitive information specifically consists of includes (but is not restricted to):

- Information regarding sexual practices or preferences
- Information regarding the use of alcohol, illegal drugs or other addictive products
- Information concerning illegal behavior
- Information that can be destructive to the subject's financial standing, employability or reputation within the community or might lead to social disgrace or prejudice
- Information regarding the subject's psychological state or mental health
- Genetic information or tissues samples

NIH-funded researchers are automatically issued a CoC with their award. This applies to NIH-funded research commenced or ongoing since 12/13/16 and new research. Other Department of Health and Human Services (HHS) agencies issue CoCs to researchers that they fund. Investigators not funded by NIH or HHS agencies can continue to apply for CoCs through NIH or FDA as appropriate. If you need to apply for a Certificate of Confidentiality, please contact the UH IRB office for assistance (UHIRB@UHhospitals.org) – we will submit a request on your behalf.

Chapter 10- Remuneration

This chapter includes information about remuneration for research subjects.

If a study offers remuneration in exchange for participation in the research study, the remuneration offered is not considered a benefit of research but is for the time and effort devoted to participation in research by individuals. Payment amounts, timing, and method of payment must be justified and described in the protocol and consent form. The IRB does not view the remuneration as a benefit to offset research risks in deciding whether a protocol should be approved. Risks that are otherwise unacceptable cannot be made acceptable by offering increasing amounts of money to participants. The IRB will consider the cultural, financial, and educational status of potential participants when determining whether proposed compensation plans are appropriate.

Determining Appropriate Subject Remuneration

Investigators may compensate participants using any (one or combination) of the following models: "reimbursement," "hourly wage," "market" (higher pay for high risk/low benefit studies), "fair share" (fixed proportion of the per-subject reimbursement to the investigators' institution), or other methods, provided undue inducements and inequitable selection are avoided.

The consent document must list what is being paid for, when and in what manner the participant will be paid, including the total amount the participant will receive and how it will be prorated. The proposed payment schedule must be included in the research protocol. Any change in the payment to participants must be submitted to the IRB as an addendum to the protocol with appropriately modified consent/assent forms.

Subject payments should generally be made upon completion of each study visit, unless justified in the research protocol. In certain circumstances it may be acceptable to withhold some or all of the payment until the end of the study. In these situations, payment or credit for payment must accrue as the study progresses to be paid out once participation is complete. If a subject withdraws from the research study or is discharged from the study any payments that have accrued as a result of participation must be provided promptly unless the protocol and consent form states otherwise. A small proportion of the study payment may be held and paid as a completion bonus as long as the IRB determines the amount would not coerce the subject to stay in the study against their better judgment. The IRB encourages describing reimbursement of expenses separately from payment of an incentive for time and effort.

Remuneration in Research Involving Minors

In protocols involving minors as participants, the division of payment for time and discomfort between the parent and child must be age appropriate and stated in the protocol and consent/assent forms. In general, for subjects under 7 years, the payment is provided to the parent; for subjects 7-13 years, half the payment goes to the parent and the other half to the minor; and for subjects 14-17 years, the entire payment is to the minor. This schedule presumes that the minor is the one undergoing the research interventions. Payments should never be so large as to induce a subject to submit to research that they might otherwise reject.

Financial Reporting Requirements

Tax laws and HIPAA regulations regarding the privacy of personal health information must be followed when the decision is made to provide remuneration to research participants. Participants receiving payment are required to complete an IRS W-9 form, which requires a social security number. Participants receiving more than $600 in one calendar year must be informed that a 1099-Misc form will be issued to the Internal Revenue Service. In addition, a copy of the 1099-Misc form will be mailed to the address provided on the W-9 form for tax purposes. The payments they receive may be considered taxable income and the following language must be in the consent form:

> *"To receive payment you must agree to complete a W-9 form which requires you to provide an address and social security number to the accounting department. This payment to you may be considered taxable income by the IRS. You will be issued a 1099-Misc form only if payment exceeds $600 from all studies in which you are participating, in a fiscal year*".

Records containing social security numbers should be stored securely and separately from the research record. Individuals objecting to completing an IRS W-9 form should be informed that they may not be able to participate in the research study. Individuals inquiring about the option of participating with a waiver of payment may be informed that this is an acceptable option. The participant's inquiry and agreed upon plan must be documented in the research record.

Requests for Subject Payments

It is required that all payments to participants be processed through the UHCMC Patient Stipend Reimbursement System (PSRS) for tracking purposes. Grant awards managed through Case Western Reserve University (CWRU) must follow the applicable CWRU procedures.

Chapter 11- Drugs

This chapter contains information on the use of investigational drugs or biologics in research

The Clinical Research Center, Regulatory/FDA Guidance Core and the IRB Administrative Office will work with the investigator and manufacturer to determine the need for an Investigational New Drug Application. The proposed research is not allowed to begin until a valid IND is in effect, or until it has been determined by the IRB or FDA that the research meets exemptions from the requirement for an Investigational New Drug Application under 21 CFR 312.2(b). This includes recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND.

In order to verify the validity of the IND, one of the following is required for review:

- Written communication from the sponsor documenting the IND number.
- Written communication from the FDA documenting the IND number. (Required if the investigator holds the IND.)

In certain cases, the IRB may require a letter from the FDA stating that an IND is not needed.

In accordance with FDA regulations 21 CFR 312.3, and Good Clinical Practice (GCP) guidelines, the requirements applicable to a sponsor-investigator under part 312 include both those of an investigator and a sponsor. The responsibilities include the following:

- Maintaining the Investigational New Drug application
- Obtaining Qualified Investigators and Monitors
- Providing Necessary Information and Training for Investigators
- Monitoring the Investigation
- Controlling the Investigational Agent
- Reporting Significant Adverse Events to FDA/Investigators
- Maintaining and Retaining Accurate Records
- Implementing and maintaining quality assurance with written Standard Operating Procedures (SOP's)

Locally Held INDs:

When a UHCMC Investigator is the sponsor of the Investigational New Drug (sponsor-investigator), the UHCMC IRB suggests the investigator meet with a representative of the Regulatory/FDA Guidance Core to review his/her FDA responsibilities as a sponsor-investigator. It is important to understand that locally held INDs are high risk to UH and carries significant responsibilities to the IND holder.

Due to the scope of responsibilities the sponsor-investigator must complete the University Hospitals Clinical Research Center investigator training modules and submit the Locally Held IND/IDE Agreement (HRP-602) with their IRB application. A sponsor-investigator of an IND at University Hospitals cannot be

a fellow or a resident, nor can a resident or fellow be the PI of an IND study. Routine monitoring of these studies is required and research compliance may audit quarterly.

The IRB will be responsible for determining whether an Investigational New Drug Application is required in accordance with the following criteria:

FDA regulations 21 CFR 312.2 states all clinical investigations that involve drugs (any use of a drug other than the use of a marketed drug in the course of medical practice must have an Investigational New Drug Application, unless the drug meets one of the exemptions from the requirement for an Investigational New Drug Application in 21 CFR 312.2(b).

In accordance with FDA regulations 21 CFR 312 and UHCMC policies, the Sponsors and/or Investigators are responsible for the proper ordering, handling, storage and disposition of investigational drugs in clinical trials at UHCMC. If the Principal Investigator does not delegate this responsibility to UHCMC Investigational Drug Services, then the Principal Investigator must complete an Investigational Drug Services Exception request form that is accepted and on file with IDS.

Chapter 12- Devices

This chapter includes guidance on the use of investigational devices in research including humanitarian use devices.

The US FDA defines an investigational device as "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 Pharmacopoeia, or any supplement to them,
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, Treatment, or prevention of disease, in man or other animals, or
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Please note:

a) Software or smart device (e. g. software that controls a pacemaker) are considered a device.
b) Certain investigational devices are billable to the subject. This is determined by the Cost Management System and linked to the FDA Investigational Device Exemption (IDE) number. The consent form must acknowledge whether the subject is to be charged.

Significant Risk(s)

A significant Risk (SR) device study is defined as a study of a device that presents a potential for serious risk to health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise prevents a potential for serious risk to the health, safety, or welfare of a subject. If the Institutional Review Board (IRB) determines the study to be SR, the sponsor must obtain an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA) before proceeding with the study.

Non-Significant Risks

The non-significant risk (NSR) category was created to avoid delay and expense where the anticipated risk to human subjects did not justify the involvement of the FDA. If the IRB determines that the study is NSR, no submission to or review by the FDA is necessary before starting studies in humans. ***Note:*** *It is very important to note that the terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.*

510(k)

A 510(k) Device is a new device that the FDA agrees is substantially equivalent to a device already on the market. 510(k) devices can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations. Because 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects will follow the same requirements.

Investigational Device Exemption(s) (IDE)

An Investigational Device Exemption (IDE) allows the investigational device to be used in a clinical trial in order to collect safety and effectiveness data required to support a Pre-market Approval application (PMA) or a Pre-market Notification [510(k)] submission to the FDA. An IDE permits a device to be shipped lawfully for purposes of conducting investigations of that device. (21CFR 812.1). The FDA assigns each investigational device exemption (IDE) to either category A or B. All clinical investigations of devices must have an approved IDE or be exempt from the IDE regulation, see 21 CFR 812.2.

FDA category A Device

Experimental/Investigational. Category A devices are novel first of a kind technology: an innovative device for which the absolute risk of the device has not been resolved.

FDA category B Device

Non-experimental/Investigational. Category B devices are new generations of proven technology.

Under FDA regulations 21 CFR 812.2(a) all clinical investigations that involve determining the safety or efficacy of a medical device must have an Investigational Device Exemption.
There are two ways that a medical device can have an Investigational Device Exemption:

1. FDA issues an Investigational Device Exemption: A copy of the FDA correspondence with information pertaining to FDA review of the device and the IDE number assigned by the FDA must be provided with the protocol submission for review by the IRB.

2. The device meets the requirements for an abbreviated Investigational Device Exemption: Research that meets all of the elements of the following category is considered to have an abbreviated Investigational Device Eexmption and does not need an FDA-issued Investigational Device Exemption: [21 CFR 812.2(b)]

Abbreviated Investigational Device Exemption

The device is not a significant risk device if:

- Is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;

- Is not purported or represented to be for a use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Does not present a potential for serious risk to the health, safety, or welfare of a subject.
- The device is not a banned device.
- The sponsor labels the device in accordance with 21 CFR 812.5;
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
- The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under §56.109(c).
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
- The sponsor maintains the records required under 21 CFR 812.140(b)(4) and (5) and makes the reports required under 21 CFR 812.150(b)(1)-(3) and (5)-(10);
- The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a)(1)(2)(5) and (7); and
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

In accordance with FDA requirements, it is the policy of UHCMC IRB that a determination of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made prior to consideration of approval of the medical device study. The Significant Risk versus Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

All devices with an Investigational Device Exemption number require full Board approval. If the IRB determines, or concurs with the assessment of the sponsor that a device study involves a Significant Risk, then it would be governed by the Investigational Device Exemption regulations at 21 CFR 812. The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:

- A description of the device;
- Reports of prior investigations conducted with the device;
- The proposed investigational plan;
- A description of subject selection criteria;
- Monitoring procedures; and
- The sponsor risk assessment and the rationale used to make the sponsor’s risk determination;
- The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment.

The IRB determination of the risk status of the device will be indicated in formal IRB minutes and correspondences to the investigator (sent via normal mechanisms), and when applicable, will identify that the IRB determination of risk status differs from that submitted by the investigator/sponsor in the application materials. When required, this determination will also be forwarded to the sponsor.

In accordance with FDA regulations 21 CFR 812.3, and Good Clinical Practice (GCP) guidelines; the requirements applicable to a sponsor-investigator under part 812 include both those of an investigator and a sponsor. The responsibilities include the following:

- Maintaining the Investigational Device Exemption
- Obtaining Qualified Investigators and Monitors
- Providing Necessary Information and Training for Investigators
- Monitoring the Investigation
- Controlling the Investigational Agent
- Reporting Significant Adverse Events to FDA/Investigators
- Maintaining and Retaining Accurate Records
- Implementing and maintaining quality assurance with written Standard Operating Procedures (SOP's)

Locally Held IDEs

When a UHCMC Investigator is the sponsor of the Investigational Device Exemption (sponsor-investigator), the UHCMC IRB requires the investigator to meet with a representative of the Regulatory/FDA Guidance Core to review his/her FDA responsibilities as a sponsor-investigator. It is important to understand that locally held IDEs are high risk to UH and carries significant responsibilities to the IDE holder.

Due to the scope of responsibilities the sponsor-investigator must complete the University Hospitals Clinical Research Center investigator training modules and submit the Locally Held IND/IDE Agreement (HRP-602) with their IRB application. A sponsor-investigator of an IDE at University Hospitals cannot be a fellow or a resident, nor can a resident or fellow be the PI of an IDE study. Routine monitoring of these studies is required and research compliance may audit quarterly.

In accordance with FDA regulations 21CFR 812 and UHCMC policies, the Sponsors and/or Investigators are responsible for the proper ordering, handling, storage and disposition of investigational devices in clinical trials at UHCMC.

Humanitarian Use Devices

A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting smaller patient populations. The U.S. Food and Drug Administration therefore, developed and published the Humanitarian Device Exemption (HDE) regulation (21 CFR 814.124) to provide an incentive for the development of Humanitarian Use Devices (HUDs) for use in the treatment or diagnosis of diseases affecting these populations. The regulation provides for the submission by a manufacturer of a HDE application. An HDE application is not required to contain the result of clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable risk of illness or injury, and that the probable benefit to health outweighs the risk of illness or injury from its use. Additionally, the manufacturer must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market. FDA approval of a manufacturer's HDE application authorizes marketing of an HUD. However, an HUD may only be used in facilities that have established an IRB to approve the use of the device to treat or diagnose the specific disease.

Humanitarian Use Device (HUD) is a medical device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in no more than 8,000 individuals in the United States per year.

The UHCMC IRB reviews and approves protocols for Humanitarian Use Devices following the guidelines in the Code of Federal Regulations 21 CFR 814.124 (Subpart H), Humanitarian Use Devices, IRB requirements:

> (a) IRB approval. The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having an IRB that can approve the original protocol and perform continuing reviews of use of the device. If, however, a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by the IRB. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the chairman of the IRB of such use. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.
>
> (b) Withdrawal of IRB approval. A holder of an approved HDE shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.

The IRB requires the review and approval for the use of a HUD before the device is administered to patients of UHCMC unless an emergency situation exists as defined above. The IRB full board will review and approve the use of the device for groups of patients meeting certain criteria, or use of the device under a treatment protocol. The IRB will review the HUD protocol for the patient's need for the device and the likelihood that the device is appropriate for the patient's condition or disease state as well as to determine if the risks to subjects are reasonable in relation to anticipated benefits.

For initial review of a HUD protocol, the IRB will perform a full board review. For continuing review, however, the IRB may vote during the initial review to use the expedited review procedures, unless the IRB determines that full board review should be performed.

For initial IRB approval of a HUD protocol, an investigator must provide the following documentation:

- The HUD manufacturer's product labeling, clinical brochure, and/or other pertinent manufacturer informational materials.
- A description of the device
- The patient information packet that may accompany the HUD
- The FDA HDE approval letter.
- UHCMC Departmental Review Committee approval to confirm that it has approved the HUD for clinical use.
- HUD protocol including a statement from the investigator specifying a description of any screening procedures, the clinical indication, where and by who the HUD will be used, and any patient follow-up visits, tests or procedures within UHCMC environment.
- A clinical consent form to address the proposed clinical use of the HUD. Since the HUD is approved for clinical use by the FDA, words such as "research" or "study" should be avoided in this clinical consent form.

IRB approval is required for any modifications of the device and/or proposed clinical use of the device. An HDE holder may collect safety and effectiveness data to support a PMA under the approved HDE (i.e., no IDE is needed). If the HUD is the subject of a clinical investigation, (one in which safety and effectiveness data is being collected to support a PMA), UHCMC IRB approval and informed consent are required.

The HDE holder is responsible for submitting updated information on a periodic basis to the IRB of record and the FDA demonstrating that the HUD designation is still valid.

Facilities that are using the device approved under an HUD are required to submit medical device report to the FDA, the IRB of record, and to the manufacturer whenever an HUD may have caused or contributed to a death or a serious injury (see definition above.)

HUDs may be used off-label in an emergency situation, but certain patient protection measures should be followed before the use occurs. Because UHCMC IRB review and approval is required before a HUD is used within its approved labeling, a HUD should not be used outside of its approved labeling without similar restrictions. In an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient, but the physician and HDE holder should follow the emergency use procedures governing such use of unapproved devices. Before the device is used, if possible, the physician should obtain UHCMC IRB Chair's concurrence, informed consent from the patient or his/her legal representative, and an independent assessment by an uninvolved physician. In addition, authorization from the HDE holder would be needed before the emergency use of the HUD. After the emergency use occurs, the physician should submit a follow-up report on the patient's condition and information regarding the patient protection measures to the HDE holder and UHCMC IRB.

A HUD may be used for compassionate use. As discussed for emergency use, the physician should ensure that the patient protection measures are addressed before the device is used. In addition to addressing the

patient protection measures, prior FDA approval of the HUD for compassionate use is required just as it is for compassionate use of any unapproved device. According to the FDA's IDE policy on compassionate use, a physician who wishes to use a device for compassionate use should provide the IDE sponsor with a description of the patient's condition and the circumstances necessitating treatment with the device, a discussion of why alternative therapies are unsatisfactory, and information to address the patient protection. For compassionate use of a HUD, the physician should provide this information to the HDE holder, who would then submit it as an HDE amendment for FDA approval before the use occurs. FDA will review the information in an expeditious manner and issue its decision to the HDE holder.
If the request is approved, the physician should devise an appropriate schedule for monitoring the patient, taking into consideration the limited information available regarding the potential risks and benefits of the device and the specific needs of the patient. Further discussion of the post-approval procedures for compassionate use, including the submission of a follow-up report can be found at FDA, Guidance on IDE Policy and Procedures

Chapter 13- Minors

Inclusion of Minors in Human Subjects Research

For children who are potential research participants, it is the responsibility of the principal investigator and the study team to obtain permission from the parent(s) and/or guardian(s). A guardian is a person appointed by a court to handle the affairs of a minor child or incompetent adult. A guardian of the person can consent on behalf of a child to general medical care; however, a guardian of the estate only cannot. In order to provide medical consent, including permission to participate in a clinical trial, the guardian must prove that he or she was appointed by a court. The guardianship cannot be based on informal agreements by the parents or established by current living arrangements (e.g., a child living with an aunt does not make the aunt legally authorized to consent on behalf of that child to general medical care unless the authorization has been made by a court). Documentation that shows a person is the legal guardian of a person is required.

In general, children who are wards of the state may participate in research either because the research (1) relates to their status as wards, or (2) is conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. Pragmatically, for research designated as 45 CFR 46.404 or 45 CFR 46.405 that incidentally or purposely includes a ward of the state, the minor's DCFS (Department of Children and Family Services) worker can be contacted in order to assist in identifying the individual who will represent the state as that minor's legal guardian (to provide parental/legal guardian consent and parental/legal guardian permission to approach the child).

Children who are in the custody of a state agency, or are in foster care, are generally referred to as wards of the State. Parents of children in the custody of the state may, and most often do, retain the right to consent to participation by their child in clinical research. However, depending on the circumstances, the state agency and even court consent may also be required. If the parent(s) has sole legal custody, only parental consent is necessary for the child to participate in a research study. If the state agency has sole or joint legal custody, consent from the state agency is required and consent of the parent may also be required. A state agency may withhold consent in situations in which parents cannot be located, a petition to terminate parental rights has been granted, a child has been surrendered for adoption, or reasons specific to a family's or child's circumstances and needs.

For situations when children begin a study and then become a ward of the state, the investigator is required to let the state agency charged with care of the child know so they are aware of the participation and any questions can be addressed. Since these situations are complex, investigators who wish to enroll wards should contact the IRB and/or the legal department for guidance in complying with all federal and state regulations pertaining to the inclusion of wards in research.

For research designated as 45 CFR 46.406 or 45 CFR 46.407, "the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child, and must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research. The advocate should represent the individual child subject's interests throughout the child's participation in the research. The HHS regulations further require that the advocate not be associated in any way (except in the role as advocate or

member of the IRB) with the research, the investigator(s), or the guardian institution." Pragmatically, this advocate may be the child's guardian ad litem (GAL, who represents his/her best interests during the period of being a ward of the state) or a Court Appointed Special Advocate (CASA), and thus contacting the minor's DCFS worker may assist in identifying such an individual who is already engaged with the minor. However, "each institution is likely to rely on a different process for appointing an advocate. In some cases it might be a member of the Institutional Review Board (IRB), a representative from an institution's health advocacy or ombudsman's office, or a case worker, social worker, or counselor responsible for the child's rights and welfare."

Investigators who are studying conditions that have an increased frequency in foster children (e.g., AIDS, child abuse) are encouraged to develop a plan for including children in foster care in the protocol. This is especially true for treatment protocols where non-research treatment alternatives are inferior or not available. This is consistent with the Belmont Report expectation for equipoise in selecting research participants.

If research is planning to obtain and document assent

The child should be given an explanation of the proposed research procedures in a vocabulary and language that is appropriate to the child's age, experience, maturity, and medical condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate in the study.

If assent is solicited, the investigator must respect the child's decision. If the child is asked for assent and refuses, the child's parent(s) or guardian may not override the child's decision.

To obtain valid written assent, the investigator must use the current IRB approved and stamped assent or consent form. Assent expires when a child becomes an adult. At that time the subject must sign the IRB approved adult consent form for the study

Parent(s) or a guardian is encouraged be present during the process of obtaining assent but this is not required. Parent(s) or a guardian are encouraged to be present during the research procedures, especially if a young child will be exposed to significant discomfort or if the child will be required to spend time in an unfamiliar place.

Age Guidelines for Assent

1) 6 Years of Age or Younger, Verbal or Written Assent Is Usually Not Required

Consent is based on the permission of the parent or guardian, and no assent is required. A brief verbal explanation of the research procedures should be provided to the child. A verbal script is an option for explaining the research to the child and can be submitted to the IRB for review.

2) Between the Ages of 7 to 13, a Separate Assent Form Is Required

In addition to the parents' consent form, a separate assent form is required for the child. It should be in language appropriate for children 7-13 years of age, typically at 2nd-3rd grade reading level. The assent form should outline what is involved for the child, and emphasize the voluntary nature of the study.

Depending on the research study, it will usually be one to two pages in length. Each assent process must at a minimum involve communication of the information in the assent form to the child, a comfortable opportunity for the child to ask questions, and obtaining of the child's verbal agreement to participate in the study.

The plan to obtain and document the assent process must be fully described and justified in the protocol/research plan. The IRB will make the final determination of the assent process.

3) 14 to 17 Years of Age, a Consent or Assent Form May Be Used

Children 14 to 17 years old may give assent after the information in the assent form has been communicated to them and the child's verbal agreement to participate in the study has been provided. The IRB may determine that the child can sign the Informed Consent document that has been signed by the parent(s) or guardian. A separate assent form may also be provided to the child if the investigator believes it would better describe the information provided to the child about the nature of the study. This would most likely apply to 14 or 15 year old subjects in very complex studies, or children with mild cognitive impairment. The plan to obtain and document the assent process must be fully described and justified in the protocol/research plan. The plan should describe how the minor will be encouraged to ask questions and attain an understanding of what is involved in research participation, and of the purpose of the research. The IRB will make the final determination of the assent process.

4) Assent for Minors with intellectual disability or limitations to decision-making

If a minor (of any age <18 years) has intellectual disability, or a medical condition that includes cognitive limitation, the assent process must respect this. Assent may then need to be primarily verbal, and use props such as plush toys or picture boards, to provide explanation. It may be appropriate to waive assent on an individual case by case basis but careful justification is needed and the IRB will make the final decision. Assessment of the individual's abilities in order to plan the assent process may include use of formal school-based testing results such as an Individual Educational Plan or other testing results, and the parents'/guardian's knowledge about the child, including reading level and comprehension and learning style, should be incorporated into the assent plan.

Request for Waiver of Assent (45 CFR 46.408 & 46.116 Subpart A)

There are circumstances in which the IRB may determine that assent is not a requirement for children to be enrolled in a research protocol. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. **The investigator must specifically justify why obtaining assent is not appropriate, in the protocol/research plan.**
Below are the circumstances under which an IRB may determine that assent is not a requirement:

1. If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in 45 CFR 46.116, Subpart A and paragraph (b) of this section, provided an appropriate mechanism for

protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate.

2. If the IRB determines that the capability of some or all of the children 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 children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with 45 CFR 46.116, Subpart A.

Waiver of Parental Permission:

Under the federal regulation 45 CFR 46.408(c) for DHHS funded research, if the IRB determines that a research protocol is designed for conditions or for a child subject population in which parental or guardian permission is not a reasonable requirement to protect the child subjects (i.e.; neglected or abused children), the research is not subject to FDA regulations, and the waiver is not inconsistent with applicable federal, state or local laws, then the IRB may waive the consent requirements. However, the investigator must provide an appropriate mechanism for protecting the children who will participate as subjects in the research as a substitute.

Under the FDA regulations (21 CFR 50.55) the FDA does not permit such a waiver of parental permission.

Special Circumstances That Alter Standard Consent or Assent Criteria:

1) Emancipated Minors

If a minor qualifies as an emancipated minor, he/she may consent to research. Emancipated minors are defined as persons under age 18 who are either married or members of the Armed Forces and fully supporting themselves independently of their parents. Parenthood alone does not emancipate a minor. If there is no documentation that proves emancipation (court order, marriage license, military ID) then contact legal to help determine the legal status of the minor.

2) Consent for the child of a Minor Parent

In Ohio, a parent under the age of 18 can give consent for his/her minor child but cannot give consent for themselves, unless he or she is considered an emancipated minor.

3) Parent Conflict of Interest

Parental permission may sometimes be insufficient to proceed with the research. In cases involving transplants (e.g., of bone marrow or a kidney) between siblings the parents' concern for the afflicted child may interfere with their consideration of the best interests of the healthy donor. Therefore, the IRB may consider asking for additional protections for the healthy donor, such as the presence of an independent physician or a court appointed guardian, if applicable, to represent the healthy donor.

4) Waiver of Assent for Experimental therapies for Life-threatening Diseases

When research involves the provision of experimental therapies for life-threatening diseases such as cancer, investigators should be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made by the parents in conjunction with the investigator, child's physician, and the child. If the child is a mature adolescent, waiver of assent is usually not appropriate.

5) Child Abuse or Neglect

In research on child abuse or neglect, there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. In these cases, there must be alternative procedures for protecting the rights and interests of the child asked to participate, including, perhaps, the court appointment of special guardians. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

6) Children who are Wards of the State

Research involving children who are wards of the state or any other agency, institution, or entity (including children in foster placement) must have consent for research given by the agency that has custody of the child. This usually requires the agency to appoint a child advocate with the appropriate background and experience to act in the child's best interests. The advocate must not be associated with the investigator, the guardian institution of the research (except in their role as advocate or IRB member). For research approved under 45 CFR 46.406 or 45 CFR 46.407, an advocate for each participating ward must be appointed, and this person should represent the individual child subject's interests throughout the child's participation in the research. The inclusion of children who are wards of the state usually requires that the research is:

- Related to their status as wards.
- Conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as subjects are not wards.

- A treatment protocol in which the majority of participants are not wards.

7) Research at Ohio Agencies

Ohio's Department of Mental Health has an additional requirement (Ohio Administrative Code 5122-28-05A(5)), “When a community mental health board or agency conducts, participates in, or is the site of research activity with human subjects, this research activity shall comply with the following requirements: An overt refusal to participate by either the adult or child subject or the parent or guardian is to be taken as final.” If the research involves an agency, the agency director shall also provide consent. If the research involves a community mental health board, the community mental health board director shall also provide consent.

Chapter 14- Decisionally Impaired Subjects

This chapter includes important safeguards for the inclusion of decisionally impaired subjects in research

Institutions and investigators conducting research on decisionally impaired subjects must balance the societal commitment to advance important scientific knowledge with the ethical obligation to protect the rights and welfare of human research subjects. Special protections must be considered by the IRB when reviewing research involving subjects with impaired decision making capacity. Therefore, the principal investigator, in concert with the IRB, is responsible for providing specific additional safeguards appropriate to the research study. However, few regulations or guidance documents specifically address research involving adults with impaired decision-making capacity. The IRB has developed these guidelines to assist investigators in addressing this issue. These guidelines also align with GCP training.

Important Issues for Research in the Decisionally Impaired

1) Fundamental Principles

For studies proposing to include adult subjects with impaired decision making capacity, the following principles always apply:

- Decisionally impaired subjects must comprise the only appropriate population, and the research question must focus on an issue relevant to this subject population. If the research question can be answered using non-impaired subjects, then subjects with impaired decision making capacity should not be included without compelling justification.
- If the research involves greater than minimal risk, the risk must be commensurate with the degree of potential benefit to the individual subject.
- If a study presents greater than minimal risk, and offers no possibility of direct benefit, the study must be reviewed by the UHCMC Ethics Committee.
- Whenever possible, the wishes of the decisionally impaired individual should be respected.

2) Issues with Consent

Because decision-making capacity is task specific, some decisionally impaired individuals remain capable of making informed decisions for themselves regarding research participation. Similarly, many people in the early stages of cognitive impairment remain capable of making a wide variety of decisions, including deciding whether to participate in research. Thus, the determination of cognitive impairment does not automatically entail decisional incapacity for affected individuals. The capacity to obtain informed consent should be assessed in each individual, for each research protocol being considered. Procedures should be developed to enhance the possibility that subjects can consent for themselves. The setting in which consent is sought, as well as the person seeking consent, should be conducive to promoting a potential subject's ability to comprehend and appreciate what is being asked. Because there are no generally accepted criteria for determining capacity to consent to research, the investigator must propose criteria for assessing potential subjects, and the criteria must be reviewed by

the IRB. Criteria for determining capacity vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gains can be anticipated.

There have been several approaches proposed to assess a subject's ability to give informed consent. Whatever approach is taken, it is essential to document the plan in detail in the research protocol. Examples may include:

- A screening standard mental status examination, such as the MINI-Mental Status Exam (MMSE). A MMSE score less than 24 suggests impaired cognitive ability and would require further assessment of the potential research subject's decision making capacity, or exclusion of that subject from the research. This test, while brief and relatively easy to administer, is not sufficient evidence of capacity to participate in high risk or burdensome protocols.
- The study investigators may ask a physician/psychologist outside the research team to evaluate the potential subject's decision-making capacity.
- Investigators and the IRB may also consider involving an independent person or witness to observe or monitor the consent process as an additional safeguard for a specific protocol, especially if the protocol is complex, difficult to understand or involves increased risk as compared to benefit.

<u>Recommended approach to assessment and consent</u>

While there are a variety of appropriate ways to approach assessing and consenting in a potentially decisionally impaired population, the following is a recommended process.

First, an initial global assessment, which if passed is followed by a consent discussion, and then use of a post-consent quiz.

The initial global assessment includes the following:

1. Is the subject alert and able to communicate with the investigator/study team?
2. Is the subject sufficiently comfortable as to be able to communicate?
3. Is the subject medically stable such that a consent process is feasible?

If the answer is "no" to any of these 3 questions, the investigator should consider whether it is possible to return to the potential participant to repeat the assessment within a timespan compatible with study enrollment, and if so, this is optimal. If not possible, then the legally authorized representative of the potential participant should be sought.

If the answer is "yes" to all 3 questions, then the investigator should engage in the consent process with the potential participant if he/she is willing. If the individual declines, no further engagement is pursued.

If the individual agrees, then following the consent process, the investigator should document the results of a post-consent quiz. If the potential participant does not pass, the investigator/study team member can review the material with the individual and re-administer the quiz one time. If the individual does not pass the second time, but appears to have interest in the study, then the legally authorized representative of the potential participant should be sought.

Post-consent Quiz:

1. Tell me in your own words the purpose of the study.
2. Just so I'm sure you understand, could you please explain to me what we're asking you to do?
3. What are the possible risks of this study?
4. What are your choices if you decide not to participate?
5. What more would you like to know?

Subjects who were initially enrolled with the use of a legally authorized representative or whose decisional capacity changes during the course of the study have the right to be informed and consented for their involvement in the study when they regain their decision making capacity. For these subjects, we recommend the following (1) regular assessment of the subject's capacity using the suggested initial global assessment, which if passed is followed by (2) a consent discussion, and then (3) use of a post-consent quiz.

Temporary Decisional Impairment

This policy applies to individuals who have acute or temporary cognitive impairment with the expectation of recovery. In addition to individuals with seizures, strokes, etc., acute cognitive impairment also includes individuals who have normal brain functioning, but are unable to make research decisions due to effects of medication/anesthesia. Individuals with temporary cognitive impairment rarely have advance directives or guardians, so next of kin consent may be appropriate in some instances. As soon as research subjects regain the ability to consent, their consent must be obtained. The plan to reassess decisional capacity, including how/frequency of reassessment, and a plan for re-consent must be clearly described in the supplemental form. If the subject refuses consent then any data collected must not be used for research. If the subject has not regained full decisional capacity, but is able to engage in conversation, assent (see below) for continued participation should be sought, and if the individual declines further research involvement this must be respected.

In instances when it is likely that the subject's capacity may become impaired over time, efforts should be made at the outset to identify the process for making or obtaining effective advance directives, durable powers of attorney for health care, or guardianship.

Assent

Assent (an expression of agreement), whenever possible, should be obtained from the decisionally impaired subject even though consent is obtained from his or her LAR (legally authorized representative). Depending on the type and structure of the study, assent might be verbal or written. The plan for obtaining assent should be outlined in the IRB supplemental form. A verbal script with a succinct lay description of the research with key information is preferred. The objection of an adult subject with limited decision-making capacity should be binding, except in rare cases when the IRB makes and specifically documents that the intervention is expected to provide a direct health benefit to the subject and the intervention is available only in the context of the research. Assent in the context of decisional impairment should not be confused with assent obtained as per federal regulations from a minor following the permission of their parent/legal guardian (see Chapter 13).

Risk with No Direct Benefit

Research protocols that do not hold out a reasonable prospect of direct benefit to the participating subjects, and that expose subjects to more than a minor increase over minimal risk, should be offered only to those subjects who either retain decision making capacity or those who have indicated in a research advance directive that they would be willing to be enrolled in such studies. Guardian, LAR, or next of kin consent is rarely acceptable in these situations.

Limiting Risks

Investigators must include in the protocol a description of appropriate psychological or medical screening criteria to prevent or reduce the chances of adverse reactions to research. Other health care providers may need to be consulted to ensure that proposed research procedures will not be detrimental to the subject's non-research treatment plan. Consideration should also be given to the effects of separation from supportive family or friends during research procedures, which may be a significant risk for this population.

Institutionalized Subjects

Research involving persons with impaired decision-making capacity, and who have restraints on their personal freedom due to residence in an institution, need additional protections. An institutional setting can be advantageous to the conduct of research because the population is easily accessible, under close supervision to prevent extraneous influences, and medical monitoring is available. However, persons who are totally dependent on an institution may be vulnerable to perceived or actual pressures to conform to institutional wishes for fear of being denied services or privileges. Also, with little or no opportunity to make decisions regarding their daily living, the ability of institutionalized subjects to make choices may be further diminished. Protocols should explicitly address how institutionalized individuals will be protected throughout the research, including approach and enrollment.

Guidance Regarding Legally Authorized Representatives and Research Consent

If the subject is determined to have impaired decision making capacity, investigators must determine whether there is a legally authorized representative. Documentation purporting to establish appointment as a legally authorized representative must be carefully evaluated to determine the validity of the appointment and scope of authority granted to make decisions regarding procedures involved in the research.

Instructions in advance directives for research are likely to be imperfect at best as they are based on knowledge at one point in time, but are applied in the future. The individual's condition, available treatments, and other factors may change, so the legally authorized representative retains the right to decline enrollment or withdraw the subject from a trial if the legally authorized representative determines that enrollment would either not be in the subject's best interests or would not be consistent with what the subject intended, even if the decision would conflict with the subject's advance directive.

Legally authorized representatives should be provided the same information that would be given to potential research subjects. If there are ongoing decisions during the study regarding the subject's participation or changes to the study, the legally authorized representative must be willing to remain involved in the decision process. Investigators must clearly describe the consent process in the protocol/research plan, including how the consent process will be documented.

Legally authorized representatives are prohibited from receiving any financial inducement for providing consent. This does not prohibit the legally authorized representative from being compensated for his/her time and reasonable expenses the legally authorized representative incurs, related to the legally authorized representative's own participation in the research.

Additional Guidance Regarding "Next of kin" and Research Consent

If a subject has impaired decision-making capabilities, there is no advance directive, durable power of attorney for health care or guardian, then the ability of a next of kin to consent may be considered. The appropriateness of the use of a next of kin needs to be assessed in relation to the risk-benefit analysis of the protocol. In assessing benefit the importance of the knowledge that may reasonably be expected to result may also receive some consideration, but never substitutes for the assessment of the benefit to the subject. The plan to obtain consent from a next of kin must be documented in the protocol and approved by the IRB.

Consent by the subject's next of kin may be obtained from any of the following potential persons who have reasonable knowledge of the subject, in the following descending order of priority:

- The spouse of the subject.
- An adult child of the subject or if there is more than one adult child, a majority of the subject's children who are available within a reasonable period of time for such consultation.
- A custodial parent of the subject.
- Any adult sibling of the subject or if there is more than one adult sibling, a majority of the subject's siblings who are available within a reasonable period of time for such consultation.
- The nearest adult who is related to the subject by blood or adoption, and who is available within a reasonable period of time for such consultation.

A major consideration in evaluating next of kin is that he or she knows the subject well enough to be able to make the decisions concerning research participation that the subject would make if he or she were able to do so. It should be kept in mind that a next of kin may be subject to conflicting interests because of financial pressures, emotional attachments, or other feelings common in such close relationships. Characteristics to consider include:

- Has reasonable knowledge of the subject.
- Is familiar with the subject's degree of impairment.
- Has knowledge of the subject's wishes and value system.
- Is willing to serve as the substitute decision-maker.

- Understands the risks, potential benefits, procedures and available alternatives to participation in the research protocol.
- Makes decisions based on the subject's known preferences, and where the subject's preferences are unknown, makes decisions based upon judgment of what the subject's preferences would be even if they are different from the next of kin's.
- Is willing to remain involved in speaking for the subject until the study is complete or the subject can speak for him or herself.
- If there is more than one next of kin who qualifies to provide consent (e.g., several adult children), it is important that the majority are in agreement before the subject is enrolled in the research.

Proposed protocols should include provisions to document the next of kin's (1) willingness to serve as the substitute decision-maker; (2) relationship to the subject; (3), reasonable knowledge of the subject's condition and preferences. The Law Department should be consulted for questions relating to guardianship in appropriate cases.

Chapter 15- Other vulnerable populations

This chapter includes information about safeguards for the inclusion of additional vulnerable populations in research

Pregnant Women

In order to approve the inclusion of pregnant women in a research protocol, the following conditions listed in 45 CFR 46.204, Subpart B must be met. You may also refer to HRP-412-Checklist-Pregnant women in the SpartaIRB Library for a list of criteria required for approval. The research protocol must address how these criteria are met and provide sufficient justification for inclusion of pregnant women.

What if the Pregnant Subject is a minor?

In addition to the regulations outlined by OHRP and FDA, including 45 CFR 46

Subpart B, if the pregnant subject is also a minor, there are additional considerations that must be accounted for under 45 CFR 46 Subpart D, Additional Protections for Children Involved as Research Subjects.

Prior to inclusion of pregnant minors in research, parental permission must be obtained or the IRB must approve a waiver of the requirement for parental permission in accordance with 45 CFR 46.116 or 45 CFR 46.117.

What if my research involves pregnancy testing of subjects who are minors?

In research protocols that involve pregnancy testing of subjects who are minors, the following is required:

- If the female age 13 years or younger, positive results of the pregnancy test must be shared with both the child and the parent or legal guardian. In addition, the pregnancy must be reported to the local public children's service agency (DCFS – Department of Children and Family Services) per UHCMC reporting requirements (see UHCMC Clinical Policy 1.2 "Child Abuse and Neglect") and per state law. This must be documented in the research record.
- If the female is age 14 years or older, the results of the pregnancy test must be shared with the minor. The results do not automatically have to be shared with the parent or legal guardian unless the parent or legal guardian asks for the results. This must be documented in the research record.
- If the research study is a clinical trial and the investigator wishes to obtain information and/or enroll the minor pregnant partner of a currently enrolled male research subject, the following additional protections are required:
- If there is no known risk to the pregnancy as a result the male partner's participation in the research study, the study staff may ask the male partner to talk to the minor female partner to see if she wishes to participate in the research study with her parents' consent. If the female pregnant partner wishes to participate, she and her parent or legal guardian can contact the study staff to discuss participation in more detail.

- If there is a known or theoretical risk to the pregnancy as a result of the male partner's participation in the research study, the male subject should instruct his pregnant partner to contact study staff. The study staff should disclose relevant information about the study, including possible risks to pregnancy and potential follow-up. The pregnant partner should discuss this with her parent or legal guardian, who should then contact the study staff for follow-up.

What happens if a Woman Becomes Pregnant after Enrollment in the Research Study?

If a research protocol intends to allow participants who become pregnant during the course of the research study and/or collect pregnancy follow-up and outcome information from the participant who has become pregnant, the provisions as they pertain to the protection of pregnant women as outlined under OHRP and FDA regulations, including 45 CFR 46 Subpart B, are applicable and criteria for inclusion must be met. The protocol and consent form must address the following:

- Whether research procedures will be continued;
- If research procedures will be discontinued, how this will be done to ensure participant safety;
- What clinical information will be collected about the pregnant women and how long will the information be collected;
- What clinical information will be collected about the fetus/newborn and how long the information will be collected

If the IRB did not previously make a determination regarding the inclusion of pregnant women in the currently approved research protocol, then a modification to allow the inclusion must be reviewed and approved prior to inclusion.

Neonates

The IRB may approve research that involves the following categories of neonates: neonates of uncertain viability, non-viable neonates, viable neonates, if all of the following are met (45 CFR 46.205, Subpart B), as well as additional criteria listed for each special population below:

<u>1) Neonates of uncertain viability</u>

- A neonate whose viability has not yet been ascertained may only be involved in research if all of the following additional conditions are met:
- The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means, and there will be no added risk to the neonate resulting from the research; and
- The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of the unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is

obtained, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

2) Nonviable neonate

- After delivery, a neonate that is living but is not considered viable may be involved in research if all of the following additional conditions are met:
- 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 added 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.
- The legally effective informed consent of both parents of the neonate must be obtained. If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements.

3) Viable neonates

- A neonate determined to be able to survive to the point of independently maintaining heartbeat and respiration ("viable") upon delivery may be included in research to the extent permitted by and in accordance with OHRP (including
- Subpart D) and FDA requirements

Prisoners

The inclusion of individuals in a research protocol who are considered "prisoners" involves special ethical considerations and requires meeting additional regulatory requirements to safeguard prisoners' interests and protect them from harm. Prisoners constitute a research population who are at risk for coercion due to their legal status or confinement. Prisoners may be under constraints because of their incarceration, which could affect the ability to make a truly voluntary decision with respect to participation as subjects in research.

A research protocol is considered to include prisoners when:

- Prisoners are the target population that will be recruited; or
- The subject is a prisoner at the time of enrollment; or
- A currently enrolled subject becomes incarcerated during the course of the trial.

Permitted research involving prisoners includes those studies that aim to examine conditions, practices and antecedents specifically relevant to prisoners, prisons and incarceration (see 45 CFR 46.306).

When a research protocol involves the inclusion of prisoners, the IRB will review the research in accordance with institutional policy, with OHRP and FDA regulations, and with respect to 45 CFR 46 Subpart C (additional protections pertaining to research involving prisoners). Additional rules as determined by Federal, state, county, and local regulations may also apply. If a prisoner is pregnant or a minor, IRB policy regarding these vulnerable populations (45 CFR 46 Subparts B and D respectively) also applies

It is important to know that prisoners cannot be involved in emergency research where the requirement for informed consent has been waived by the Secretary under the authority of 45 CFR 46.101(i) 45 CFR 46.101(i).

What happens if a research subject becomes a prisoner?

If a subject becomes a prisoner after enrolling in a research study, the investigator is responsible for immediately reporting the event in writing to the IRB through submitting a "Reportable New Information" form (NOTE: This is not required if the study was previously approved by the IRB for prisoner participation.). The investigator should provide detail on the subject and the incarceration, as well as the extent of the subject's participation in the research trial up to becoming a prisoner, what remaining study activities the subject has to complete and the plan for either inclusion or exclusion of the subject from further research activities.

If the study was not previously reviewed and approved by the IRB in accordance with the requirements of 45 CFR 46 Subpart C, all research interactions and interventions with, and obtaining identifiable private information from the prisoner must cease until the requirements of Subpart C are satisfied. If the investigators would like the subject to continue in participation in the research protocol, a modification must be submitted with revisions to the protocol and consent form to detail how continuation of the prisoner meets applicable criteria under 45 CFR 46 Subpart C

In special circumstances in which the investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the subject may continue to participate in the research until the requirements of subpart C are satisfied. The investigator must promptly notify the IRB of this occurrence, so that the IRB can review the study. Note that in these circumstances, some of the findings required by 45 CFR 46.305(a) may not be applicable; for example, the finding required under 45 CFR 46.305(a)(4) regarding the selection of subjects within the prison may not be applicable, if the subject was recruited outside of an incarcerated context.

Non-English Speaking Participants

Participants who do not speak English must be given study documents, including an informed consent document, written in a language understandable to them. If an investigator intends to enroll participants who speak a language other than English, a translated version of the informed consent form, including

HIPAA authorization, and appropriate study documents must be submitted to the IRB for approval prior to use. The principal investigator must provide the qualifications of the individual or the service that was used to translate study documents. The principal investigator may wish to delay translating study documents until the IRB has granted approval for the English version(s) to avoid extra translation costs.

Informed Consent Considerations:

A person who is fluent in both English and the participant's language must participate in the informed consent process. If the person authorized to obtain informed consent in the research protocol is not fluent in the participant's language, an interpreter or interpreter service may be obtained. Consistent with UH Policy "CP-2-Access to Interpretive Services", family members and friends of the potential participant should not act as the sole translation/interpretation source for enrollment and participation in a research protocol unless the situation is emergent and there are no other means of communication readily available. In addition, there must be a witness signature block in the informed consent. Please note that the MARTTI system is not acceptable as the sole translator for the consent process. Please review the related Informed Consent Process for Research (HRP-090).

Other Considerations:

Other study related documents that will be filled out by the participant (e.g., log sheets, data collection forms, self-assessment tools, etc.) must also be translated into the participant's native language. If the study involves more than one study visit, a plan must be developed to ensure that an appropriate party is available to conduct all study visits in the participant's native language. IMPORTANT NOTE: If the participant will spend the night in the hospital, there should be an appropriate round-the-clock plan for the duration of the planned hospitalization. The plan should take into account the risk level of the research protocol, and also the ability to plan in advance. For example, a participant in a Phase I clinical trial will need to have a very strong plan to report side effects that may not be anticipated, but the visits can probably be planned well in advance.

Research NOT actively recruiting participants who are Non-English Speakers

Many protocols include the provision to include individuals who do not speak English as they are often a part of the general participant population; however, they are not the targeted population. As non-English speaking individuals are not the targeted population, often informed consent and HIPAA Authorization documents are not yet translated into other languages as the needed language is not yet known. In all cases, a translated consent should be used if at all possible. For potential participants where there may not be sufficient time to obtain a fully translated version of the written consent form and HIPAA Authorization in the participant's native language, a "short-form" informed consent process may be used if described in the IRB approved study submission. The short form must either come directly from the IRB office, or be a certified translation of the English version of the short form from the IRB administration office. A "short form" consent form is a document that contains key information about the study and a brief paragraph that affirms all the elements of informed consent (as required by the Federal Regulations) were reviewed with the participant in a language understandable to the participant. There

must be a witness signature block. Subsequent to the use of this process, a full translated consent must be created and submitted to the IRB for review as soon as possible.

What other Vulnerable Populations can be included in my Research Study?

1) Students and Employees

- Justification of the intention to enroll UHCMC or Case Western Reserve University employees, house staff, or students must be provided in the protocol. The actions to prevent coercion or undue influence must also be detailed in the protocol. Anyone with an employment or academic relationship to Case or UHCMC must be informed that their participation in a study, or refusal to do so, will in no way influence their grades, employment, or subsequent recommendations. Employees must never be made to feel that their job, promotion, salary, or status in any way depends on participation in research studies.
- The Principal Investigator or any co-investigator may not be responsible for directly recruiting and/or obtaining informed consent from any person under his or her direct supervision.
- Direct recruitment of students and employees may be undertaken using IRB approved recruitment language via standard recruitment methods (e.g., IRB approved language in the UH Daily News email bulletin, recruitment flyers placed in staff/student mailboxes).
- A Principal Investigator may not enroll his or herself into his or her own research protocol unless provisions are made in the research protocol to allow for the enrollment. In these cases, the IRB may allow the inclusion if the study outcomes are objectively measured and provisions are there with respect to recruitment, consent, and affirmation of eligibility (e.g., by a study co-investigator).
- Individuals listed as Study Personnel for a study should not, in general, enroll as a participant in that study. Issues of privacy, coercion, subject rights, and confidentiality would need to be considered and addressed with the IRB.

2) Principal Investigator's Clinical Patient Population

Many research protocols may involve recruitment from one's own clinical pool of patients. To avoid any potential for undue influence that may result from the doctor-patient relationship, the informed consent process should not be conducted solely by the physician who has a clinical relationship to the patient that will be enrolled. (e.g., research study coordinator). An additional person should be available to confirm eligibility (e.g. co-investigator) and cosign the checklist. If possible, someone who does not have a clinical relationship to the potential participant should act as the "person obtaining informed consent".

3) Family members of the study team

A Principal Investigator or any other member of the study team may not recruit and enroll any direct familial relation. Provisions must be made in the IRB approved protocol to allow for study personnel with appropriate expertise to recruit and enroll another study team member's direct familial relation.

4) Illiterate/Seeing Impaired Participants

The IRB allows for illiterate persons who understand English and individuals who are seeing-impaired to participate in research studies. In these situations, the consent document must be read to the participant and the process documented in the research file. For an illiterate participant, the consent document should be subsequently signed by the participant "making their mark" on the signature section of the consent document, in order to document their understanding. The IRB also requires an impartial third party to serve as the witness to be present during the entire consent process. Both the witness and the person obtaining informed consent must sign and date the consent document. As such, there must be an additional signature line and date for the witness on the consent document.

5) Participants Who Are Mentally Capable Of Consenting But are Physically Unable To Sign the Consent Document

The IRB allows participants that are mentally capable of consenting to research studies but are physically unable to sign the consent document to participate in research as long as a witness is present. The witness must verify that the informed consent process has taken place and sign and date the consent document. In addition, if participants are capable of doing so, they must place a mark or cross on the signature line of the consent document, to confirm their participation in the research study. This process must be documented in the research file. If the reason that prevented signing the consent form resolves, the participant should be asked to sign and date the consent form. Protocols actively enrolling individual participants who are physically unable to sign the consent document should include a witness line on the consent document

Chapter 16- Recruitment

This chapter includes information on appropriate recruitment methods for various types of studies

Recruitment of study subjects is an essential part of the research protocol and must be presented in sufficient detail to allow the IRB to fully assess the investigator's plan. Recruitment of participants must be equitable and include racial, ethnic, educational, socioeconomic, and gender diversity appropriate to the condition that is studied. Exclusion of any specific group (e.g., women of child-bearing potential) must be justified in the protocol. Both the benefits and risks of research participation must be equitably distributed.

All recruitment efforts must respect personal rights to privacy and confidentiality and be compliant with HIPAA regulations. The recruitment plan must avoid coercion of participants. Financial compensation, reimbursement for expenses, or other inducement for participation must not be coercive and should be reasonable for the expenses, discomfort, or inconvenience of participating. In addition to IRB requirements, the HIPAA regulations put further restrictions on research recruitment activities.

The IRB must review all of the research documents and activities that bear directly on the rights and welfare of the participants of proposed research; this includes the methods and material that investigators propose to use to recruit participants.

If the research involves recruitment of subjects <u>not</u> from the department from which the PI is employed, then at least <u>one</u> of the following requirements must be met:

1. A letter of support from the department(s) from which the subjects are being recruited.
2. A co-investigator is listed on the study team members table from the department(s) from which the subjects are being recruited.
3. The study is sent to the department(s) from which the subjects are being recruited via the "Manage Ancillary Reviews" activity in SpartaIRB. Through this activity, the department(s) can indicate their approval electronically.

If the research involves recruitment of subjects outside UH, a letter of support from the organization assisting in recruitment may be required.

Recruitment Methods

<u>Recruitment of Subjects by Physicians</u>

A physician who has a treatment relationship with a prospective research participant may approach that patient about participation in IRB approved research. The physician may approach the potential participant about participation in his or her own protocol or on behalf of another investigator as long as the physician is listed on the study team members table. It is recommended that the permission of the potential participant is obtained before identifying information is given to the study investigator.

An investigator with no treatment relationship to the prospective research participant must inform the treating physician before approaching potential participants for all Greater than Minimal Risk studies unless those patients are from the investigator's department.

For all potential participants who are inpatients, the attending physician must be notified of the study and the plan to approach the patient. The attending physician must be notified before approaching the patient for consent if the proposed study has any effect on medical treatment.

Contacting outpatients for recruitment to research studies is usually allowed but the method of obtaining names and contact information, who will contact the potential participants, how permission will be obtained from the treating physician, and how data confidentiality will be protected, must be presented in detail in the protocol.

Contacting Potential Participants by Phone

Unless there is a compelling rationale, a letter or email providing basic information should always be sent out beforehand that informs the potential participant that he or she will be receiving a call from the study staff. This communication **must** include how to opt out of being contacted if he or she chooses to do so. Opt out can involve calling a phone number or sending back a postcard, for example, and must be simple and easy. A brochure that explains what research is can be enclosed (this free brochure from the Office of Human Research Protection (OHRP) is recommended). A template letter and email can be found on the IRB Website or in the Templates tab of the SpartaIRB Library. In general, the initial letter or email will be very general and should not contain any protected health information.

The IRB strongly discourages cold calling of potential research participants. (*Cold calling is when a person not known to the potential research participant initiates contact with the potential participant based on their prior knowledge of private information*.)

Please note that there are specific requirements for sending letters and emails. All letters must have a UH return address, and all emails must be sent via a UH email address. Each step of the recruitment process must be laid out in the protocol and/or supplemental form.

Research coordinators must follow a script when calling prospective subjects for recruitment. Scripts read by the researcher or other individuals assisting in the recruitment of participants must be submitted to the IRB for review and approval. If the study team member who is calling is the potential subject's own physician or a member of the care team known to that person, a script is not required but is always recommended. The IRB must review these procedures to assure that they adequately protect the rights and welfare of the prospective participants.

When recruiting by phone, a UH phone number should be used. Subjects should only be given UH phone numbers where messages are actively monitored.

Note: If a treating physician is not part of the study team, it is recommended that the study team notify the treating physician before recruitment begins, even for minimal risk studies. If the project originates from another department, department approval or support must be obtained from both departments.

If pre-screening questions to determine eligibility are a necessary component of telephone recruitment, please know that these items must be directly related to inclusion or exclusion criteria as listed in the protocol. It is preferable to conduct prescreening via medical record review under a HIPAA waiver whenever possible, for accuracy and respect for persons. Additionally, to avoid collection of unnecessary and sensitive information, eligibility items should be read as a whole, with an attestation at the end as to whether the potential participant either meets or does not meet criteria without a requirement that the individual disclose specific details.

Contacting Potential Participants by Text

It is acceptable to advertise with a phone number that interested individuals may text for further information, so long as the potential participant initiates the contact. As always, scripts and templates of all follow-up communication should be included in the IRB submission. Text reminders of study appointments and other study related information can be utilized if the participant has specifically provided permission for such. In all cases, text messages should only be sent if the patient has agreed to receive text messages.

Contacting Potential Participants Using Email

When recruiting by email, a UH email must be used when sending out emails to UH patients. A plan should be included about how the email will be monitored, particularly if an individual email address is used (instead of a group or general email box).

If a study team is conducting an electronic survey, the, "UH Survey Recruitment Form" can be found on the IRB Website or in the Templates tab of the SpartaIRB Library. Use of UH REDCap is usually required when sending surveys to UH patients. In general, the initial email message should be general and not include any diagnosis, treatment, or private information. The email should contain a link to the secure survey and the first page of the survey should be the study specific information sheet.

Advertisements

Advertising materials are part of the recruitment process and must be approved by the IRB. Advertisements are directly related to the informed consent process and must be consistent with prohibitions against coercion and undue influence. The IRB must ensure that appropriate safeguards exist to protect the rights and welfare of research participants. Advertising or soliciting for study participants is the start of the informed consent and participant selection process. The IRB reviews the advertisements to assure that informed consent is given freely and coercion or undue influence is avoided. In order to evaluate this, the protocol must state who the participants will be, what incentives are being offered, and describe how the material will be used, distributed, and/or posted. This is especially critical when a study may involve participants who are likely to be vulnerable to undue influence.

Advertisements should be submitted as part of the initial IRB application. If advertising materials become available after the initial approval or the approved material is changed, the advertising must be submitted as an amendment to the study. The material may not be used until IRB approval is received.

Advertising materials must include the following information:

- Statement that the study is research.
- The condition under study and/or the purpose of the research in summary form.
- The criteria that will be used to determine eligibility for the study in summary form.
- The location of the research.
- Information about the person or office to contact for further information (e.g., a work-related phone number, email address, etc.).
  Please note: UH addresses, phone numbers, and emails must be used when recruiting UH patients, and are always preferred. If the only recruitment is posting a flyer in the community (not on

hospital property) then a Case email or phone number might be approvable with appropriate justification.

When appropriately worded, the following items may also be included in advertisements:

- A brief list of participation benefits, if any (e.g., a no-cost health examination).
- The time or other commitment required of the participants.
- Compensation may be mentioned, but not as a specified amount or as a benefit.

Advertising materials should not include the following:

- Claims, either explicitly or implicitly, that the drug, biologic, device or other type of intervention is safe or effective for the purposes under investigation.
- Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, device or intervention.
- Terms such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational.
- Promises of "free medical treatment," when the intent is only to say that participants will not be charged for taking part in the investigation.
- Mention of a specific amount of financial remuneration or overemphasize in the materials that remuneration is available.
- Any exculpatory language.
- Photographs or graphics that could be considered attention-grabbing but not study related.

<u>Advertising that does not require IRB review:</u>

If the involvement of UH personnel is limited solely to handing out flyers for research, those advertisements do not need to be formally submitted to the IRB. This would mean that UH personnel are not discussing the study, not consenting, not collecting data, and they are not a co-investigator. Those advertisements should be forwarded to IRB leadership or the general IRB inbox for review before dissemination to UH staff or patients for a review of local policy adherence.

The following do not qualify as an advertisement and do not require IRB review:

- Communications intended only to be seen or heard by health professionals, such as letters to physicians.
- News stories where reporters or other non-study personnel are responsible for the final content.
    - Please note: When participating in an interview it is important that the study team send a knowledgeable representative. Study teams may share basic study information and provide contact information for interested persons. When being interviewed it is important not to overpromise benefits or inaccurately represent risks, present the hypothesis as fact, or discuss interim results as if they were final. It is recommended to use terms such as we "think," "hope," or "expect" and please avoid terms such as "miracle" or "cure."

<u>Advertising Using Social Media</u>

All Internet recruitment materials directed at potential participants are considered advertisements and the same rules apply. This includes information posted on social media websites (e.g., Twitter, Facebook, YouTube, etc.). Social media ads should not have a "hot link" back to the study unless there is a disclaimer explaining the risk of loss of confidentiality for the recipient when clicking such link.

Posting of Advertisements

Advertisements should only be posted in physical locations (no bathrooms or elevators) or to electronic accounts with appropriate permission from the responsible parties/entities or account holders. All advertisements posted physically or electronically must be approved by the IRB. If you are posting or handing out flyers at recruitment fairs, on social media, or within the UHHS system, you do not need to list specific locations in your UH IRB application in order to post.

Recruitment Registries / Trial Finders / Research Listing Services

When information about a study is presented on a website for purposes such as trial finders, research listing services (National Cancer Institute's cancer clinical trial listing and the government-sponsored AIDS Clinical Trials Information Service), or recruitment registries (e.g., ResearchMatch), IRB approval of the information is not required if the information is limited to the following:

- Study title
- Purpose of the study
- Protocol summary
- Basic eligibility criteria
- Study site location(s)
- How to contact the study site for further information

Inclusion of information exceeding the above basic listing information (including description of risks and potential benefits, mention of incentives, or solicitation of identifiable information) requires IRB review and approval.

All recruitment methods should be noted in the protocol and templates and scripts for how follow up communication will occur are required. Previous research participants cannot be used as a recruitment pool unless specifically stated or agreed to in the consent for the previous study.

If a potential participant reaches out to the study team, it is appropriate to respond. However, after the initial contact, this individual should be recruited in accordance with the IRB approved recruitment plan.

Secondary Recruitment

Secondary recruitment refers to asking a study participant for identifying information about friends or family members with the intent to contact them as potential research participants. While there are important research reasons that secondary recruitment is needed, it must be approached in a manner that respects the privacy rights of the potential participants.

Investigators must include in the consent form that if a study participant provides a friend's or relative's name and address, this may reveal the subject's medical diagnosis to the friend or relative. The implications of the disclosure of the medical condition must be included in the consent form.

Preferred Method for Contact

It is against IRB policy to obtain contact information or health information about a friends or family from another participant, without their permission.

Investigators may not contact the secondary recruit unless they have provided permission to be contacted. If a secondary recruit provides the primary participant permission to share their contact information follow-up recruitment must convey this. All correspondences, including letter templates and phone scripts, must be approved by the IRB.

An investigator wishing to obtain the names of potential subjects (e.g., family members for a genetic study) could use the following method: provide a stamped envelope containing the solicitation materials (letter, study brochures, return postcard, etc.) to the subject. The participant is then asked to address the envelope to his or her relative and mail it (or give it to them). If the investigator does not receive a response from the secondary recruit, it is reasonable to ask the study participant to contact the individual to be sure that he or she received the materials but repeated or coercive reminders to the participant are of course not allowed.

Chapter 17- International Research

This chapter includes information for when research is conducted internationally by U.S. investigators

Human subject research (biomedical and behavioral) conducted internationally by U.S. investigators is subject to the same ethical guidelines and regulations as human subject research conducted within the United States. Under 45 CFR 46.101(a), research "conducted, supported, or otherwise subject to regulation by the Federal Government" that takes place outside the United States must be conducted with ethical oversight and human subject protections that are at least equivalent to those provided by the U.S. regulations, in addition to any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

Local investigators who wish to lead or participate in the conduct of human subject research conducted outside of the United States are required to secure the proper local and international approvals prior to commencement of the proposed project. The UHCMC IRB requires additional review for human subject research projects where some or all of the study subjects are located outside of the United States.

In addition to the standard IRB review process for human subject's research, the UHCMC IRB will conduct a "local context review" of the proposed research, during which local laws and cultural variances will be discussed in relation to the proposed research and U.S. ethical research standards. The UHCMC IRB requires local context review for all greater than minimal risk studies. Minimal risk studies that have obtained approval from the appropriate authorities of the host county do not require local context review, however the UH IRB has the right to request this additional review at any time.

A protocol will not have repeat local context review at the time of continuing review unless there are significant changes in the protocol or the risks to the subjects. All the usual continuing review requirements remain unchanged.

Please note that if the proposed research receives any Federal funding, a "Federalwide Assurance" (FWA) is necessary to document that the international institution/performance site will conduct the research in accordance with US Federal policy.

When submitting an International Human subject Research Proposal to the UHCMC IRB investigators should include the following:

1) All protocols that will recruit and enroll subjects and/or conduct research procedures in countries other than the U.S. must include the following additional information:
    - Explanations of cultural differences that have influenced the study design or consent process.
    - Rationale for conducting the study with an international population.
    - Specifics about the population being recruited and social norms in the specific area in the host country to clarify issues regarding recruitment, informed consent, age of majority (for enrollment of minors) and acceptability of the research procedures proposed.
    - Include information and a description of any vulnerable populations (e.g. children, women, refugees etc.) that maybe recruited for the research study and how their rights and welfare will be protected.

- Information regarding the literacy level and native language(s) of the expected subjects and how this may affect the informed consent process.
- A description of the informed consent process including methods for minimizing the possibility of coercion or undue influence in seeking consent and safeguards to protect the rights and welfare of vulnerable subjects.
- If remuneration is given to subjects, a justification for the amount of money or goods and how this relates to the average annual income of people in the host country. Information regarding the host country's IRB, Ethical Review Committee, or equivalent institution.

2) Letter(s) of agreement from the local host institution(s) to cooperate in the proposed research: The appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, should also review and approve the proposed research within the context of their own ethical requirements. Documentation of approval from the host country should be sent to the IRB (via the electronic IRB system) as soon as it becomes available. The IRB may also require meeting minutes from the committee in the host country.

3) Informed consent documents and other study materials: All consent forms and associated documents to be used with potential research subjects must be translated into the appropriate local language. The investigator must provide the name and brief description of the qualifications of the individual or the service that was used to translate the informed consent documents. If a certified translation service is used, and proof of translation is provided, the IRB will accept the proof of translation as verification of accuracy. Alternatively, the foreign IRB that reviews the study can verify the translation by indicating this on the approval letter or by use of their official stamp on the consent documents.

   As a general policy the IRB does not require independent back translation of consent documents. UHCMC IRB engages "local context reviewers" who are able to read the local language and can comment on the content of the foreign language consent form. However, for specific protocols the IRB may require a formal back translation of foreign language consent forms.

   Submission of both the English version of the informed consent document (and other study materials) and the foreign language version simultaneously is encouraged; however the IRB will review and approve English-only versions in an effort to prevent investigators from having to obtain multiple translated versions prior to final IRB approval. If the foreign language translated documents are not included as part of the initial IRB review and approval, once the translation is complete, the documents may be submitted separately as a modification to the currently approved protocol.

Special Consent Situations for International Studies:

For studies involving populations that have no written language: Use an English consent form as a template for translation and include a statement about the process for informed consent. The consent form should be signed by the interpreter, the study principal investigator, and the subject, who will make a mark or thumb print as appropriate.

For studies involving populations that utilize group consent: Describe and justify the use of group consent. Provide a method to obtain private or individual subject assent if possible. Provide a method of protecting those who choose not to participate in the study.

For studies involving minors: The requirements for assent for Minors in Research Studies (IRB Policy, Assent from Children in Research Studies) are applicable. The legal age for consent in other countries may differ from Ohio. The local legal age should be used for choosing consent versus assent documents.

Does U.S. Privacy Rule and HIPAA Authorization Apply to International Research?

The HIPAA rule does not apply at research sites outside of the United States where individually identifiable information may be collected. Once the individually identifiable health information is transferred to a HIPAA covered facility (e.g., UHCMC), this renders any individually identifiable health information PHI by virtue of its being held by a facility covered by HIPAA. Once the data is transferred to a HIPAA covered component, all HIPAA regulations apply.

If UHCMC faculty or staff is responsible for, or involved with, the use and disclosure of protected health information as defined by the HIPAA rule, then the Federal regulations apply (UH Policy, R3 “Uses and Disclosures of PHI for Research”).

The UHCMC IRB has determined that investigators conducting research outside the United States must adhere to HIPAA requirements for all studies unless the investigator requests a waiver of HIPAA based on the criteria outlined in 45 CFR 164.512.

Recognizing the impracticality of asking subjects to sign a lengthy document in technical legal language, a modified shortened form of the required HIPAA language is available for use. This language should be included in both the English version and all translated versions of the Informed Consent forms.

Chapter 18- Resources and Facilities

This chapter contains information about research resources and facilities available for individuals conducting studies at University Hospitals

Dahms Clinical Research Unit

The Dahms Clinical Research Unit (DCRU; including both the DCRU main site and the Coleman Clinical Research Suite in Seidman Cancer Center) provides research-dedicated facilities and staff to create capacity, opportunity and a supportive environment for clinical and translational research at the academic medical center and in the community.

The Dahms Clinical Research Unit team partners with investigators from all disciplines to support pediatric and adult clinical research visits, and will work with you to plan your study budget and implement your protocol from recruitment to study visit. The Dahms Clinical Research Unit provides:

- Inpatient and outpatient facilities, or scatter visits throughout the main campus.
- Highly trained clinical research staff, including research nurses, bionutritionists, sample processing, analytical lab and bioinformatics professionals
- Specialty services, including:
    - Creation of protocol-specific order sets and flow sheets to conduct GCP-compliant research visits
    - Sample collection for pharmacokinetic studies and specialty procedures/equipment including adult and pediatric SphygmoCor, biopsies, endoscopies, bronchoscopies
    - A metabolic kitchen and dietary counseling, 24 hour dietary recalls and dietary analysis, research-dedicated DXA scans for whole body composition and bone density across the lifespan, anthropometric measurements
    - Remote sleep monitoring
    - Special chemistry analytical lab that can test for a range of cytokine tests using ELISA technology
    - Complete biospecimen management including customized sample collection and processing instructions, sample processing and shipping, DNA extraction and isolation of PBMCs in a sterile environment

Contact 216-844-4720 or 216-844-4902 or dahmscru@uhhospitals.org for more information.

CRC Research Support Core

CRC Coordinator Core

The University Hospitals Research Coordinator Core supports all phases of clinical research with expertise in every aspect of the clinical research process and extensive knowledge in all areas of medicine.

The Coordinator Core provides:

- Fee-for-service staffing to support investigators and their study teams.
- Resources for investigators and their research staff to help conduct studies at all UH sites, non-UH sites in the community, and outside institutions.
- A "float pool" of experienced nurse and non-nurse coordinators available to support all responsibilities for protocol implementation.
- Recruitment Specialist to help teams meet and exceed enrollment goals.
- Protocol development, study start-up, recruitment and enrollment, complete study coordination, project management, and clinical data management support.
- Hiring, HR oversight, mentoring, and training support for study coordinators.

To inquire about specific services available, please contact Heather Tribout, Manager, Research Support Core at Heather.Tribout@UHhospitals.org or 216-286-0765.

The FDA & Regulatory Support Core

The FDA & Regulatory Support Core are a team of dedicated support staff who are well versed in the regulatory approval and startup processes of the FDA and the Institutional Review Board (IRB). As a fee for service team, the FDA & Regulatory Support Core can provide flexible services based on the individual needs of each department/investigator and can begin at any point in the research trial.

Upon request, services from the core can begin immediately and be maintained on a short- or long-term basis. In addition, the FDA & Regulatory Support Core are available to provide consultation services prior to the start of a clinical trial to assist investigators with drug/device/biologic pre-clinical questions, biostatical support, and guidance on the correct regulatory pathway with the FDA and IRB.

FDA support services include:

- Protocol review and evaluation
- Drug and device risk determination
- IND/IDE application assistance
- Regulatory document/binder creation
- Source document creation
- FDA regulatory monitoring
- Long term FDA maintenance
- Biostatistician support

Regulatory support services:

- IRB application and study start-up support
- Regulatory document/binder creation
- Investigator and study team education/training

- Regulatory prep/clean-up for monitoring visits
- Long-term regulatory maintenance
- Study closure support

Requests for service can be sent to FDAregsupport@uhhospitals.com or contact Heather Tribout, Manager, Research Support Core at Heather.Tribout@UHhospitals.org

Biostatistics support services:

The Clinical Research Center Biostatistics Core offers a range of statistical support services to UH faculty and investigators conducting clinical research at any stage of the research process. These services include sample size estimation or simple consulting up through dataset analysis and reporting statistical results. Our team works directly with the investigator or investigative team to assess and plan the approach to each project, and maintains a consistent line of communication for the project duration. As a pro bono service, our primary goal is to assist investigators who hold junior-faculty appointments or who are currently unfunded.

Support services include:

- Dataset Analysis
- Data Visualization of Results
- Power Analysis
- Scientific Interpretation of Statistical Analyses
- Statistical Consultation
- Statistical Plans

Requests for services can be sent to biostatssupport@uhhospitals.org

UH Institutional DSMC

The UH Institutional DSMC is an optional service for all non-industry sponsored trials opened at UH where a DSMB is required (except oncology research which is required to go through the Case Comprehensive Cancer Center's Data Safety and Toxicity Committee (DSTC)).

The UH Institutional DSMC is comprised of experienced investigators and a dedicated biostatistician, and is available free of charge to eligible trials with a UH PI.

To apply to use the UH Institutional DSMC contact the UH IRB Administration Office at 216-844-1529 or UHIRB@UHHospitals.org

Chapter 19- Research Compliance

As a central tenet of a robust Human Research Protection Program (HRPP), the UH Research Compliance team has an institutional mandate to create and maintain a culture of integrity and compliance across all aspects of the conduct of research at UH. As such, the UH Research Compliance team is responsible for implementing a program of oversight and auditing that focuses on decreasing risks to the institution; protecting the safety of research participants; promoting standards of excellence in the conduct of research; identifying and communicating best practices; and ensuring compliance with requirements and ethical standards.

Audits and Reviews

It is a requirement of the UH HRPP that all study teams cooperate fully with requests from UH Research Compliance. All human research approved by the IRB and/or conducted at UHCMC may undergo a research compliance audit in order to assure the protection of human research participants and compliance with Federal regulations, state and local law, IRB policies and procedures, and UHCMC's Federalwide Assurance with OHRP.

When study teams do not appropriately or timely respond to Research Compliance communications, the matter will be escalated to the HRPP manager, the relevant Department Chair, CRC leadership, and the IRB, respectively. The IRB will assess whether it is necessary to suspend or terminate the study to ensure subject safety.

Audits and Reviews can be either routine or directed. Routine proactive reviews or audits are conducted to assess the investigator's compliance with Federal, state and local law, and UHCMC and IRB policies. Protocols are selected for routine visits by performing a query of the IRB database, reviewing IRB minutes, or may be requested on a voluntary basis by the principal investigator, Department or Clinical Chair.

UH Research Compliance Audits

Audit is defined as a systematic and independent examination of IRB approved studies to determine whether the evaluated activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's procedural documents, GCPs and applicable requirements. [ICH 1.6].
The purpose of an audit visit is to:

- Assess adherence to Federal regulations as defined by OHRP and FDA;
- Assess adherence to UHCMC IRB policies and procedures;
- Assess adherence to UHCMC research policies;
- Assess adherence to Federal Privacy rule regulations under HIPAA via the Office of Civil Rights;
- Assess adherence to local and state laws and regulations;
- Assess adherence to regulations as defined by the Office of Research Integrity regarding Research
- Misconduct;

- Determine that the rights and safety of human research participants have been properly protected; and
- Provide education to investigators.

UH Research Compliance Reviews

A compliance review is defined as targeted review of a particular piece of the process of conducting research. The reviews will usually focus on examining a specific piece of IRB approved research project, but can expand if issues are identified.

Typical areas for Compliance Reviews may include:

- Observation of the informed consent process
- Research conflict of interests
- Biorepositories/Databases/Big Data studies (>500 records)
- IDS Exceptions with no internal or external monitoring oversight
- A specific issue of concern has been identified, but does not warrant a full audit without further discussion

Routine reviews/audits

Routine reviews and audits are typically in the following areas (but may also evolve to include other targeted areas of interest): Locally Held INDs and IDEs; Industry Sponsored GMRs; Exempt studies; Investigator Initiated (GMR) studies; Biorepositories/Databases/Big Data studies (>500 records); Reliant Reviews; Expedited (NIH funded).

Directed reviews/audits

Directed reviews or audits occur when a concern or issue is identified and a request for additional review of IRB approved research is required. The request may be for any reason including, but not limited to, the following:

- Notification of an FDA or other sponsor initiated audit;
- A response to an externally initiated complaint (OHRP, FDA or sponsor) of potential protocol violations or non-compliance;
- A response to a complaint or concern from a participant, a participant's family member, the public or anonymous sources;
- A response to a concern raised by an employee;
- An IRB directive or concern;
- An investigator with a history of poor adherence to research policies and procedures.

External research compliance reviews or audits may also be conducted in the form of prospective and directed auditing at affiliated UH sites or where the UHCMC IRB serves as the IRB of Record.

UH Research Compliance Findings

A compliance finding is defined as non-compliance with any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with one or more of the following: Federal Regulations; the IRB approved protocol or investigational plan; Policies – Institution,

IRB, Sponsor, Funding Agency; and/or Standard Operating Procedures (SOPs) – Institution or Department .

A report of results from a review or audit will note the following as applicable:

- No Findings – all actionable items corrected and completed prior to final audit report submission;
- Non-Significant Findings – administrative issues (e.g. regulatory binder; good documentation practices issues);
- Significant Findings – issues related to the informed consent process or eligibility assessment
- If study is relying on another IRB, the IRB of record needs notification; All significant findings require mandated education
- Critical Findings – issues related to participant safety; institutional risk (privacy/confidentiality); meets guideline for an IRB determination.

Any submissions on the study being audited may not be processed until the UH Research Compliance investigation is complete and responses have been received.

NOTE: A research compliance finding may require a Corrective and Preventive Action Plan (CAPA) be created. A CAPA may be written to identify a discrepancy or problem in the conduct of a research study, describe the root cause of the identified problem, identify the corrective action(s) to be taken to prevent recurrence of the problem, and to document any preventative actions instituted.

Other Research Compliance Activities

Monitoring of the Informed Consent Process

Considering the importance of the informed consent process, the IRB may require special monitoring of this process by an impartial observer (consent monitor) in order to reduce the possibility of coercion and undue influence.

Required Study Refresh Auditing

This process includes a detailed review of study documents and procedures to ensure that all study materials and processes continue to meet updated regulatory and institutional requirements which may change over time. This is a collaborative process between the IRB, the Study Team, and Research Compliance. Any study may be subject to refresh by the IRB at any time. Common categories that would prompt a refresh include studies that are over 7 years old and studies that are subject to FDA and/or NIH oversight. Study teams will be notified when a refresh is needed, but study teams are welcome to request an in-depth review at any time.

UH Research Compliance Study Start-Up

A compliance study start-up visit is an organized meeting/interview to discuss a new protocol before the research project is ready to screen and enroll potential patients and/or to collect study data. The objectives are to ensure the study team understands their obligation to adhere to the IRB approved study protocol, are trained on the study protocol, are delegated study tasks appropriately, and are prepared to initiate and implement the research project according to Good Clinical Practices and UH research policies.

Expired Study Auditing

Timely completion of continuing review is a requirement. It is a violation of federal regulations and potential non-compliance when a study's IRB approval lapses and research activities continue. An expired study audit occurs once a study has been lapsed in approval after multiple attempts have been made through the SpartaIRB system to contact the study team to submit a continuing review. A potential result of an expired study could be administrative closure of the study. See Chapter 6 – IRB Submission Components and Chapter 20- Reportable New Information for more information.

Allegations of Non-Compliance

If an allegation of non-compliance is reported from any source (including monitoring/auditing reports, subject complaints, internal allegation or investigator self-reporting), UHCMC Research Compliance in consultation with the IRB Chair or Vice-Chair, and the HRPP Manager will make an initial assessment to determine:

- whether there is sufficient information present to verify and determine if the allegation is true;
- whether additional information is needed to make a determination; and
- whether a determination of non-compliance is serious or continuing non-compliance.

The IRB, as part of their oversight responsibilities has established procedures for the evaluation of all non-compliance with human subject protection regulations and institutional policies, and the prompt reporting of any serious or continuing non-compliance with the Federal regulations or institutional policies.
All reports of alleged non-compliance or inappropriate involvement of humans in research are investigated by the Research Compliance Office. If it is determined that the non-compliance might be serious or continuing, the suspected non-compliance is forwarded to a convened meeting for Full Board review and determination.
Goals of the Research Compliance Office and the IRB in investigating and managing issues of potential noncompliance include:

- Assuring the safety, rights and welfare of human subject research participants;
- Developing action plans to prevent recurrence, and promote a culture for future compliance;
- Educating research staff to assure the understanding of DHHS (OHRP) and FDA regulations and guidelines, and UHCMC IRB Policy; and
- Reporting serious or continuing noncompliance to the appropriate regulatory agencies and institutional officials.

Allegations or potential instances of non-compliance may be identified during monitoring visits conducted by Research Compliance. Research Compliance will prepare a written summary of the observations and propose an action plan for the investigator. If necessary, Research Compliance will consult with the IRB Chairs, HRPP Manager, or the Vice President of Research. The action plan may include any, or all of the following:

- Asking the investigator to submit a Reportable New Information report (RNI) to the IRB for further review;
- Identifying the finding as minor non-compliance and request a thorough action plan to correct and/or prevent the event from occurring again;
- Require education;

- Require additional monitoring

UH Research Compliance follows UH policy R-40: "Research Misconduct" for allegations of research misconduct.

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HRPP Activities

PI Departure

Study teams and PIs should notify the UH HRPP when a PI is leaving UH employment. Once the UH HRPP is notified that an investigator is leaving UH, an email will be sent to involved parties documenting the impacted studies. The departing investigator is required to develop a plan for current research before they are no longer employed by UH. The UH HRPP will send the notice, and a follow up. If the exit date is approaching, or the individual has already left UH, without a transition plan, Research Compliance will be notified. When study teams do not appropriately or timely respond to Research Compliance communications, the matter will be escalated to the HRPP manager, the relevant Department Chair, CRC leadership, and the IRB, respectively. The IRB will assess whether it is necessary to suspend or terminate the study to ensure subject safety. For more information on departing investigator options, consult GA-109.

Research Conflicts of Interest

Conflicts of interests in research can take many forms – financial, institutional, fiduciary responsibilities, intellectual property (inventorship), proprietary, consultation, interpersonal, etc. If the UH HRPP identifies a potential for an actual, potential, or perceived conflict of interest, the conflict may be managed, reduced, acknowledged, or eliminated at the UH HRPP's discretion with input from the conflicted investigator(s). The UH IRB has the final authority to decide whether the conflict of interest and its management, if any, allows the research to be approved.

UH HRPP staff will work in collaboration with the UH IRB, UH Compliance & Ethics, UH Legal, and the CWRU Conflict of Interests Committee, when appropriate. Principal Investigators share responsibility with the UH HRPP for ensuring compliance with policies and issued management plans on their projects.

In addition to any situation where there is a suspicion of a COI, the UH HRPP staff is responsible for performing an internal research COI review on all new industry-funded, PHS-funded, and investigator-initiated studies as well as all personnel changes when a new investigator is added to an Industry-funded or PHS-funded study. For more information on research COI identification and management, refer to UH Policy R-43.

ClinicalTrials.gov

ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH).

Help is available for all aspects of ClincialTrials.gov, from registering to maintenance, to results reporting and completion. We are here to help walk you through all the different steps of working in ClinicalTrials.gov. Please email UHResearchCompliance@UHhospitals.org for more detailed information on how to access help.

FDA Requirements

FDAAA requires registration and results reporting of all Applicable Clinical Trials (ACTs). An ACT is defined as:

1. Interventional studies;
2. Studies that require an IND or IDE;
3. Studies where **AT LEAST ONE** or more of the following applies:
    a. At least one site in the US or one of its territories, or
    b. Study is conducted under an IND or IDE, or
    c. The product is manufactured in and exported from the US or one of its territories
4. Studies that evaluate at least one drug, biological, or device product regulated by the FDA
5. Studies that are not Phase 1 (drug and biological products)* or not Device Feasibility (device products)**

- *Phase 1 studies of new drugs are usually the first that involve people. Phase 1 studies are done to find the highest dose of the new treatment that can be given safely without causing severe side effects

**Device Feasibility are usually 10 or fewer people to test the safety/efficacy of the device, has to meet very specific criteria to fit feasibility. Email UHResearchCompliance@UHhospitals.org for more information.

Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial- https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

NIH Requirements

The National Institutes of Health (NIH) Policy on Dissemination of NIH-Funded Clinical Trial Information requires registration and results reporting, and applies to all clinical trials funded by NIH, regardless of whether they are subject to the FDAAA 801 and the Final Rule effective January 18, 2017. The Policy is effective for competing applications and contract proposals submitted on or after January 18, 2017 and states that all NIH-funded awardees and investigators conducting clinical trials will register and report the results of their clinical trials in ClinicalTrials.gov. Please refer to the following grants policy information from NIH's Office of Extramural Research to learn more about ensuring compliance with NIH's implementation of FDAAA 801: https://grants.nih.gov/policy/clinical-trials/reporting/index.htm

ICMJE Requirements

The ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy.

Obtaining a ClinicalTrials.gov Account

To establish an account with the ClinicalTrials.gov PRS email your request to UHResearchCompliance@UHhospitals.org. An account will be created within 2 business days. If you have forgotten your password you may also email to request it be reset.

Registering a New Study

For step by step instructions on how to register a study please see the ClinicalTrials.gov Registration User's Guide: Insert Link More information can also be found in SC-401 (insert link)

Record Maintenance

Records must be verified at least annually for accuracy. Each time you are in the record update the RVD to the current month/year. Records are also required to be updated within 30 days of any changes, i.e. changing from "Not yet recruiting" to "Recruiting". If you have stopped enrollment but are still collecting data your study status should be "Active, not recruiting". If all data has been completed the status should be updated to "Completed" or "Terminated". See glossary for complete list of status.

Results Reporting

All ACTs and NIH CTs must have results reported in ClincialTrials.gov within one year of the primary completion date (PCD). The PCD is the LAST DATE data was collected for the primary outcome measures. Secondary outcome results must be reported within one year after the final data has been collected for that outcome. ALL data is required to be posted within 1 year of your Study Completion Date (SCD). If you are required to report results, they must be entered by these dates, even if you have not yet published the data. ClinicalTrials.gov will not grant extensions due to publishing timing. The study protocol is REQUIRED to be submitted with results submissions on all ACTs and NIH CTs. For study specific results templates please email UHResearchComplaince@UHhospitals.org. You can also find out more information regarding results reporting in SC-406 (insert link).

Chapter 20- Reportable New Information

Investigators and study team members may submit Reportable New Information (RNI) to the IRB. Please note: the author of the RNI will be listed as the point of contact for the RNI submission and all communication will occur between the IRB and that individual.

A member of the study team must complete and submit the Report New Information SmartForm within **five business days** for any of the following information items:

- Information that indicates a new or increased risk, or a new safety issue. For example:
    - New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) that indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
    - An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk
    - Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol
    - Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm*
    - Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm*
    - Any changes significantly affecting the conduct of the research
    - Any adverse event, which in the opinion of the PI, are **both** unexpected and related or possibly related to the study/study participation and involves increased risk to the subject or others is considered an unanticipated problem.*
        - An adverse event is “unexpected” when its specificity or severity are not accurately reflected in the IRB approved informed consent document or protocol, or are not expected given the characteristics of the subject population being studied
        - An adverse event is “related to the research procedures” if in the opinion of the PI, it was more likely than not to be caused by the research procedures, or if it is more likely than not that the event affects the rights and welfare of current participants.
- Non-compliance with the federal regulations governing human subjects research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.*
- Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g. FDA Form 483.)
- Written reports of study monitors if applicable to IRB
- Major failure to follow the protocol due to the action or inaction of the investigator or research staff.*
- Breach of confidentiality.*
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.*

- Incarceration of a subject in a study not approved by the IRB to involve prisoners.*
- Complaint of a subject that cannot be resolved by the research team.*
- Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
- Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.*
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Event that requires prompt reporting to the sponsor such as disqualification or suspension of investigator.

*Reporting required for internal events only.

Internal encompasses events that occurs in a participant who was consented using a UHCMC IRB approved consent process. Studies approved by the UH IRB but conducted outside the United States are considered "internal" for adverse event reporting.

External encompasses events reported to a UHCMC investigator that occurred in a participant who gave consent using consent documents that were not approved by the UHCMC IRB.

External events where the UHCMC investigator is not responsible for the reporting of the event to a regulatory agency are expected to have review as described in the Data and Safety Monitoring Plan (DSMP) for the protocol. All external events reported to a UHCMC PI must be promptly reviewed by the PI and any event that changes the risk/benefit ratio of the study must be reported as information that indicates a new or increased risk. If protocol or consent form changes must be made due to a revised risk profile those changes should be submitted to the IRB as soon as possible.

All internal, unexpected, study-related deaths must be reported to the IRB within five business days of their discovery. Both internal, expected, study-related or non-study-related deaths and internal, unexpected, but not study-related deaths should be retained in the Principal Investigator files.

Failure to report in a timely manner may be considered a compliance matter and referred to the IRB for review and a compliance determination.

Any event that does not fit into the above categories does not require reporting on an RNI form. Please review the section regarding Continuing Reviews for additional reporting guidelines.

Protocol Deviations

A PI with an IRB approved protocol must conduct the protocol under the terms and specifications of the study as approved by the IRB. An investigator may not deviate from the requirements for procedures or

testing of participants as outlined in the protocol. Protocol Deviations must be reported by the PI to the IRB in a timely manner. Major Deviations are reported to the IRB within five business days of discovery. Minor Deviations are kept in the investigator's file to be reported at the time of continuing review.

Deviations are reported electronically using the appropriate category on the RNI form. Frequently, the most appropriate category is "Non-compliance" or "Researcher error," but this is not all-inclusive and other categories may be more applicable depending on the nature of the situation. The author of the RNI should briefly explain the new information and the corrective actions taken to avoid future deviations. If a change in the protocol is needed, questions 5b) and 5c) should be answered appropriately and the PI will submit a protocol amendment electronically in the electronic system. The examples listed below are a guide and are not meant to be all-inclusive.

Protocol Deviation: Any alteration/modification to the IRB-approved protocol that is not approved by the IRB prior to its initiation or implementation. Protocol deviations may result in determinations of non-compliance, serious or continuing.

Major Protocol Deviation: A more serious incident involving noncompliance with the protocol usually involving critical study parameters. Major protocol deviations generally affect the subject's rights, safety, or welfare, or the integrity of the study data. A major protocol deviation can also be called a protocol violation.

1) Examples of Major Deviations

- Failure to obtain informed consent, i.e., there is no documentation of informed consent or informed consent was obtained after initiation of study procedures;
- Informed consent obtained by someone not approved to obtain consent for the protocol;
- Use of invalid consent form, i.e. consent form without IRB approval;
- Enrollment of a participant who was ineligible for the study;
- Performing a research procedure not in the approved protocol;
- Failure to report serious adverse event to IRB; sponsor; and/or regulatory agencies;
- Study medication dispensing or dosing error;
- Failure to follow the approved study protocol that affects participant safety or data integrity (e.g., study visit missed or conducted outside of required timeframe, or failure to perform a laboratory test);
- Failure to follow safety monitoring plan;
- Continuing research activities after IRB approval has expired;
- Use of recruitment procedures that have not been approved by the IRB;
- Participant giving study medication to a third-party;
- Enrolling significantly more subjects than proposed in the IRB protocol (defined as over-enrollment by 10% or more);
- Any deviation that impacts the risk / benefit ratio;

Minor Protocol Deviation: An incident involving noncompliance with the protocol but one that typically does not have a significant effect on the subject's rights, safety, welfare, or on the integrity of the resultant data.

2) Examples of Minor Deviations

- Missing original signed and dated consent form (only a photocopy available);
- Missing pages of executed consent form;
- Failure to follow the approved study protocol that does not affect participant safety.(e.g., study procedure conducted out of sequence, failure to perform a required test, missing laboratory results, study visit conducted outside of required timeframe.);
- Use of consent forms that are outdated/expired but contain the same information as the current consent;
- Failure of a participant to return study medication.

All protocol deviations are initially reviewed by the IRB Chair or a Vice-Chair and sent for Board review as required. Board determinations will be reported to outside agencies as required. Study sponsors may have different reporting requirements than the IRB and it is the PI's responsibility to be knowledgeable about, and meet, the study reporting requirements.

Any other event that does not meet criteria of an unanticipated problem or a study-related event causing harm or increasing risk to participants does not require prompt reporting on an RNI form. Please review the section regarding Continuing Reviews for additional reporting guidelines.

IRB Compliance Determinations and Reporting Guidelines

Federal regulations 45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1) require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems, and any serious or continuing non-compliance. The IRB must comply with all applicable local, state, and federal regulations in the conduct of research studies. In keeping with these regulations, investigators are required to promptly report to the IRB unanticipated problems involving risks to subjects or others as well as major protocol deviations. The UHCMC IRB will review the reports and fulfill reporting requirements to the appropriate institutional officials and federal departments or agencies. The IRB may be required to report:

- Any determination of serious non-compliance
- Any determination of continuing non-compliance
- Any determination of an unanticipated problem involving risk to self or others
- Any suspension of part or all of a protocol

The UHCMC IRB is responsible for reviewing, on an ongoing basis, risks to human subjects. The risks may involve physical, emotional, financial, social, psychological, or legal harm to the subject (or to others). The IRB has the authority to suspend or terminate all or part of a protocol at any time in response to information regarding deviations, adverse events, allegations of misconduct, unanticipated problems, or subject complaints.

After receiving notice from an Investigator, or any other researcher, or otherwise becoming aware of a Reportable Event meeting the criteria below, UH CRC will provide AAHRPP with prompt written notice of the Reportable Event (provided, such event is substantiated, pertinent, and would not otherwise breach any obligations of confidentiality or privilege, or violate internal institution policies):
(i) any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections, (ii) any litigation, arbitration, or settlements initiated related to human research protections, and (iii) any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the Organization's HRPP.

Non-compliance*:* Failure to follow the regulations, requirements and/or determinations of the IRB.

Serious Non-compliance*:* Non-Compliance that adversely affects the rights or welfare of subjects.

Continuing Non-compliance: A pattern of Non-Compliance that suggests the likelihood that, without intervention, instances of Non-Compliance will recur, a repeated unwillingness to comply, or a persistent lack of knowledge of how to comply.

Unanticipated Problem Involving Risks to Participants or Others, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given
   - The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
   - The characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggest 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. In order to determine if an adverse event meets this criterion the OHRP assesses whether the risk meets the definition of "serious."

Adverse Event, although not defined under either the DHHS or FDA regulations, per OHRP guidance of January 15, 2007, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events uses the term to include any event meeting the following definition:

> Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. An adverse event encompasses both physical and

psychological harms; and although they most commonly occur in the context of biomedical research, they can also occur in the context of social and behavioral research.

Serious or Continuing Non-Compliance:

When the IRB Chair (or designee) determines the information regarding an alleged report of non-compliance is serious, the information is forwarded to the full IRB for review, consideration of suspension criteria, or consideration of termination. An investigation by the Research Compliance Team can occur simultaneously with IRB review for consideration of suspension. If the IRB Chair, Vice Chair(s) (or designees) has suggested suspending the research because of findings or alleged findings of serious or continuous non-compliance, the IRB will vote to confirm suspension.. If the research is federally funded, then notification of the non-compliance must be made to OHRP (Office for Human Research Protections).

If the investigator is a member of the faculty of Case and the research involves a Federal grant, or other grants awarded to Case, or the non-compliance is determined to be serious or continuing, the IRB may refer the issue of non-compliance to the Associate Vice President of Research at Case for assistance in seeking an appropriate resolution.

Non-Compliance with HIPAA (Privacy Language) Requirements

Failure to comply with HIPAA (Privacy Rule) requirements for research will be referred to the Privacy Officer for investigation and resolution.

Suspension or Termination of a Study

The IRB has the authority and responsibility to suspend or terminate approval of research that is not being conducted in accordance with the IRB policies and procedures, or that has been associated with unexpected harm to participants or others. The IRB has the ability to temporarily or permanently suspend or terminate approval for some or all research activities. Depending on the circumstances surrounding the suspension or termination action, the investigator may be required to submit a report to the IRB, detailing any adverse events and/or study outcomes that were previously unreported to the IRB for consideration. Any letter of suspension or termination of approval to an investigator must include a statement of the reasons for the action by the IRB.

The IRB Chair, Vice-Chair, or the Vice President of Research is authorized to suspend or terminate the enrollment of subjects; and the ongoing involvement of subjects in research, as it deems necessary to protect the rights and welfare of participants. This also includes compelling and urgent instances when subject safety is of concern. The IRB will review such suspensions and terminations at a subsequent convened meeting. A plan will be developed that takes into account the rights and welfare of currently enrolled subjects and those subjects who may need to be withdrawn from the study. If the agreed upon plan of action involves withdrawal of enrolled participants, the IRB will take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another researcher, and continuation in the research under independent monitoring). If the IRB determines that a suspension or termination of the research will place subjects at risk of harm, the investigator will be requested to submit a proposed script or letter for participants for IRB review and approval. The IRB

determines the information that is to be provided to subjects and the method of their notification e.g., in writing or by telephone is appropriate. This includes appropriate subject follow-up and notification of the reasons for the action.

Administrative Hold is a voluntary action by an investigator to temporarily or permanently stop some or all research activities as a modification to approved research. Although the investigator may discuss this action beforehand with the IRB Chair, Human Research Protection Program Leadership, or the Vice President of Research, the hold must be initiated voluntarily by the investigator and must not be used to avoid IRB mandated suspension or termination of reporting requirements. During administrative hold, the research remains subject to continuing review and requirements for reporting non-compliance and unanticipated problems involving risks to subjects or others. Administrative holds must not be used to avoid reporting deficiencies or circumstances that otherwise require reporting by federal agencies. Administrative holds are not considered suspensions or terminations, and do not meet reporting requirements to OHRP, FDA, and other federal agencies.

Chapter 21- Reliant Review

All research that takes place at University Hospitals (involves UH patients, data, materials, or property) falls under the purview of the University Hospitals IRB. The University Hospitals IRB (UH IRB) is willing to consider entering into reliance agreements with external IRBs. However, permission to use another IRB must be obtained, an agreement to cede IRB review must be in place, and a submission to the UH IRB for review of local requirements must be completed before submitting to another IRB.

The UH IRB is also willing to serve as the Reviewing IRB for multisite research. Collaboration in advance is required as reliance agreements naming UH IRB as the IRB of record must be in place.

The UH IRB has entered into reliance agreements with various institutions, as well as with independent central IRBs, including Advarra and Western IRB (WIRB). The UH IRB has also entered into agreements to participate in the national reliance platform, SMART IRB. The UH IRB will continue to consider new opportunities to rely on external IRBs accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

Reliance agreements outline the roles and responsibilities in the reliance relationship between IRBs; however, when using Reliant Review for a research study it is important for investigators to recognize that University Hospitals and the UH IRB still retain important institutional responsibilities for the oversight of the research study. The relying institution must ensure that local ancillary reviews required to conduct research at this site are completed and that local requirements and context unique to UH are communicated to the IRB of Record.

For assistance with submitting a reliant review study to the UH IRB, please reference the "Reliant Review Guide" located in the Help Center of SpartaIRB.

Relying on an External IRB

Studies will be determined to be eligible for reliant review on a case by case basis with consideration given to the type of study, risk level, experience of the Principal Investigator and study team and availability of resources. Below describes the mechanism the UH IRB uses to make a reliance determination. UH will not rely on any IRB that is not accredited by AAHRPP. Any Phase I trial, particularly with a pediatric population, would require strong justification for relying on another IRB. UH IRB will document rationale for not relying upon a single IRB review in accordance with NIH policy on exceptions from single IRB review.

Reliance Request and Acceptance

Once it is determined that an external IRB will be used for a study and/or there is an agreement to collaborate with an investigator at another institution:

- Obtain a copy of the protocol and consent related document(s). Create UH site specific consent document(s) using the template provided by the lead site or sponsor.

  - Confirm with the IRB of Record whether or not an IRB Authorization Agreement (IAA) or Collaborating Institutional Investigator Agreement (CIIA) is necessary or if one is already in place. Contact the UH IRB for assistance with this step if necessary. There are several different types of reliance agreements. An agreement may cover one study, multiple studies, or all studies at an institution. Collaborating Institutional Investigator Agreements are also an option when collaborating with an investigator that is not covered by an IRB or FWA. The IRB office can help determine if an agreement is needed or if one is already in place.

- Submit a Reliant Review Submission to the UH IRB in the electronic system, uploading documents received. Access the Reliant Review Guide from the Help Center in SpartaIRB for step-by-step instructions on how to create and submit a Reliant Review submission.
  - The UH IRB must be notified of requests to rely on external IRBs via the Reliant Review submission. Research studies may not be implemented until the UH IRB has provided written notice of acceptance of the request and the IRB of Record has provided written notice of the approval of the study. Investigators must request reliance acceptance from the UH IRB Administration Office.
  - When requesting to rely on an external IRB, the investigator must submit a Reliant Review Submission, study protocol, and documents related to the informed consent process. Investigators assume responsibility for engaging research support offices/centers at UH with oversight responsibility for the implementation of research and provide any materials needed to those entities in order to grant approval. This includes but is not limited to, department review, Protocol Review and Monitoring Committee, radiation safety, electrical safety, research finance, grants and contracts, etc.
  - Upon receipt of the reliance request notification, the UH IRB Administration Office will review the request, will consider protocol specifics and local context and will make a final determination regarding UH's willingness to rely on the external institution. The UH IRB Administration Office will review the information included with the reliance request to confirm local context/ institutional issues, including: personnel qualification, expertise and education requirements, conflict of interest, department approval, required ancillary approval letters, the study protocol and consent documents. The UH IRB Administration Office will also communicate with UH Research Finance and UH Grants and Contracts regarding any additional requirements related to the study.
    - Please note that investigators and research staff must disclose conflicts of interest to the reviewing IRB by providing the conflict of interest management plan with site specific documents for review and approval.
  - The UH IRB Administration Office will provide an acceptance letter once local requirements have been met. If applicable, a list of suggested revisions, from either the UH IRB or from ancillary reviews, will be provided.

- Obtain study approval from the IRB of Record. The UH IRB is not responsible for the submission to the IRB of Record. The UH study team should confer with the lead study team or sponsor to determine the process for submitting to the IRB of Record for the initial review and subsequent reviews. The UH

PI is ultimately responsible for ensuring that the study has been approved by the IRB of Record before beginning the study at UH. The study should not begin at UH until the final determination to accept or decline the reliance is communicated by the UH IRB and the IRB of Record has approved the study.

A study disapproved by the UH IRB is not eligible for Reliant Review.

Informed Consent Documents

Investigators must collaborate with the lead study team, the IRB of Record and the UH IRB Administration Office to create UH specific study documents, including the consent document. If the lead site provides a template consent document, the template must be submitted to the UH IRB Administration Office with the Reliant Review Submission. If no template is provided, UH study investigators should create a site specific consent document or a consent coversheet to be used in conjunction with the main consent document. All consent documents should be submitted with the Reliant Review Submission. The UH IRB will not approve or stamp consent documents, but may, in some situations, provide a list of comments and revisions with the acceptance letter that should be incorporated and/or communicated to the IRB of Record. Submission of the final version of the consent to the UH IRB Administration Office is not required and subsequent versions in the event of an amendment are not required to be submitted to the UH IRB Administration Office unless otherwise necessary.

Post Initial Acceptance

- Obtain a copy of the reportable event reporting policy of the IRB of Record.
- Over the life of the study, work with IRB of Record via the lead study team on all required subsequent submissions, including amendments, continuing reviews, event reporting etc.
- Notify the UH IRB Administration Office of any staff changes or changes in Conflicts of Interest by submitting a personnel modification in SpartaIRB.
- Notify the UH IRB Administration Office of any modifications that may alter local approval requirements, or the coverage analysis for the study. For example, an additional CT scan would need to be submitted to the Radiation Safety Committee and the coverage analysis team for review.
- Notify the UH IRB Administration Office if the IRB of record makes any determinations of unanticipated problems posing risk to subjects or others or any determinations of serious or continuing non-compliance. UH IRB should also be notified of any study suspensions related to risk or non-compliance, any breaches or potential breaches of HIPAA, or other findings directly related to the institutional business of University Hospitals.
    - Consult the UH IRB Administration Office if you are uncertain whether an event requires dual reporting to the external IRB and the UH IRB.
- Notify the UH IRB Administration Office once the study is closed. Annual reviews should be submitted to the IRB of record. Work with the lead study team (when applicable) and the IRB of record to provide the required study information and maintain approval of the study. Submission of an annual review form to the UH IRB is not required. Once a study is closed, a Notification of Study Closure should be submitted in the electronic record to notify the UH IRB of closure.

Research Compliance staff will collaborate as necessary with the IRB of Record for a Reliant Review Study to conduct monitoring visits and compliance reviews, which are designed to identify standards of excellence and potential areas for improvement in order to promote a solid foundation for the conduct of human subjects' research.

UH IRB as the IRB of Record for Multi-Site Research

If planning to conduct multi-site research with UH IRB as the IRB of record, it is recommended that the UH IRB is contacted 60 days prior to grant submission or as soon as possible to determine if the UH IRB is willing to serve as the IRB of record. UH IRB needs to review the proposed study and subsites to be involved to determine if the availability of resources are sufficient to provide the necessary oversight of all sites. Any investigators who wish to use the UH IRB as the IRB of record for their studies must be aware of their responsibilities as the lead study team:

The Lead Study Team will be the primary point of contact (POC) for communication to and from the Reviewing IRB. Site-specific information from the relying sites will be provided to the lead study team and then submitted to the Reviewing IRB. All communication from the Reviewing IRB will flow from the Reviewing IRB to the Lead Study Team POC to the Relying Study Team POC. This includes (but is not limited to) the following:

- Preparing and submitting the study-wide application for initial IRB review and study- wide amendments to the Reviewing IRB
- Preparing and submitting the site-specific applications and site-specific amendments to the Reviewing IRB that address site variations in study conduct, informed consent language, HIPAA Privacy Rule requirements (if applicable), subject identification and recruitment processes (including recruitment materials), and any other applicable components of the research
    - In order to add research sites to previously approved protocols, a modification must be submitted to the UH IRB for review and approval. The modification must include the site-specific information, including but not limited to consent forms, conflict of interest management plans, etc. to be used at the relying site. When no significant changes to study procedures are requested / includedby the relying site, this may be considered a minor modification that can be reviewed via expedited review.
    - IRB approval must be obtained from international sites and submitted for review by UH IRB if UHCMC is responsible for a multi-site research study outside of the United States that is not required to follow requirements for single IRB review.
- Providing documentation of IRB determinations to relying site study teams
- Providing copies of IRB-approved materials to the lead study team
- Providing copies of the most current versions of IRB-approved materials to relying site study teams in a timely manner
- Providing the consent form template to relying site study teams

- Providing relevant Reviewing IRB policies to the study teams
- Obtaining and collating study-wide information for continuing review to the Reviewing IRB
- Submitting continuing review progress report to the Reviewing IRB
- Reporting reportable events to the Reviewing IRB (e.g., unanticipated problems, noncompliance, subject complaints)
- Providing the Reviewing IRB with required information when a study is closed.

Types of Reliance Arrangements

Central and Commercial IRBs

Central IRB and Commercial IRBs are external IRBs, often for-profit, providing IRB review services. The UH IRB currently has reliance relationships with the Advarra, Western IRB (WIRB), NCI Central IRB and is willing to consider others as well.

Ohio CTSA

The UH IRB previously participated in a statewide collaboration between three Ohio *Clinical and Translational Science Awards (CTSA)* encompassing eight institutions: University Hospitals, Case Western Reserve University, Metro Health Medical Center, The Cleveland Clinic, The Ohio State University, Nationwide Children's Hospital, Cincinnati Children's Hospital, and the University of Cincinnati. Participating institutions utilize the Reliant Review model to streamline the IRB review process. The Consortium utilized an online submission portal referred to as the HUB which is no longer accepting new studies. New requests for reliance with any of the CTSA institutions can be documented through the SMART IRB agreement.

Reliance Platforms

Several *reliance platforms* exist to streamline the IRB review process for multisite research relying on a single IRB. Generally, any one institution which has signed on to the platform's agreement may serve as the IRB of Record, but the platform exists as a mechanism to exchange information and/or documents to maintain a robust record of the research study for all sites involved.

SMART IRB

SMART IRB, the Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform, is an electronic system designed to harmonize and streamline the IRB review process for multisite studies, while ensuring a high level of protection for research participants. SMART IRB is funded by the National Center for Advancing Translational Sciences (NCATS) and intended to serve as a roadmap for institutions to implement The National Institutes of Health (NIH) policy on the use of a single IRB for multisite research.

University Hospitals is signed on as a participating site for the SMART IRB agreement. The SMART IRB online reliance system is the preferred method for creating and documenting reliance requests.

IRB Authorization Agreements (IAA)

IRB Authorization agreements are agreements executed between an IRB of Record and Relying IRB outlining the terms and responsibilities of each institution in the reliance relationship. IAAs will be reviewed by the IRB Administration office and the UH Legal Department and signed by the UH Signatory Official. Authorization agreements can be executed for one single study or multiple studies. Investigators interested in collaborating with an institution where the above options are not applicable should contact the IRB for more information about executing an IAA.

Chapter 22- DHHS-Regulated Research

This chapter contains additional considerations for research regulated by the Department of Health and Human Services (DHHS)

When either of the following exists, they must be submitted as part of the IRB review:

- DHHS-approved sample consent document
- The complete DHHS-approved protocol

When a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial should ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent, may continue. The investigator should explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.

Investigators are allowed to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the subject's consent, provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. This is the case even if that data includes identifiable private information about the subject.

For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, can choose to honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.

When seeking the informed consent of subjects, investigators should explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research.

When research is covered by a certificate of confidentiality, researchers:

1. May not disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
2. May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
3. May disclose information only when:
    a. Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding.

   b. Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
   c. Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
   d. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.
4. Researchers must inform participants of the protections and limitations of certificates of confidentiality (see language in HRP-502 - TEMPLATE CONSENT DOCUMENT).
   a. For studies that were previously issued a Certificate and notified participants of the protections provided by that Certificate, NIH does not expect participants to be notified that the protections afforded by the Certificate have changed, although IRBs may determine whether it is appropriate to inform participants.
   b. If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer activity participating in the study, NIH does not expect participants consented prior to the change in authority, or prior to the issuance of a Certificate, to be notified that the protections afforded by the Certificate have changed, or that participants who were previously consented to be re-contacted to be informed of the Certificate, although the IRB may determine whether it is appropriate to inform participants.
5. Researchers conducting research covered by a certificate of confidentiality, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other researchers or organizations, the other researcher or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

Chapter 23- FDA-Regulated Research

This chapter contains additional considerations for research that is regulated by the U.S. Food and Drug Administration

1. When a subject withdraws from a study:[1]
    a. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
    b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
    c. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.
    d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
    e. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

2. For FDA-regulated research involving investigational drugs:
    a. Investigators must abide by FDA restrictions on promotion of investigational drugs:[2]
        i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
        ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
        iii. An investigator must not commercially distribute or test market an investigational new drug.

[1] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf
[2] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7

b. Follow FDA requirements for general responsibilities of investigators[3]
    i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.
    ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.
    iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.
c. Follow FDA requirements for control of the investigational drug[4]
    i. An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
    ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
d. Follow FDA requirements for investigator recordkeeping and record retention[5]
    i. Disposition of drug:
        1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
        2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.
    ii. Case histories.
        1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
        2. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.
    iii. Record retention: An investigator must retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

[3] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60
[4] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61
[5] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62

e. Follow FDA requirements for investigator reports[6]
   i. Progress reports: The investigator must furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
   ii. Safety reports: An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.
   iii. Final report: An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
   iv. Financial disclosure reports:
      1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR §54.
      2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

f. Follow FDA requirements for assurance of IRB review[7]
   i. An investigator must assure that an IRB that complies with the requirements set forth in 21 CFR §56 will be responsible for the initial and continuing review and approval of the proposed clinical study.
   ii. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

g. Follow FDA requirements for inspection of investigator's records and reports[8]
   i. An investigator must upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62.
   ii. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

h. Follow FDA requirements for handling of controlled substances[9]
   i. If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely

[6] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64
[7] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66
[8] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68
[9] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69

locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

3. For FDA-regulated research involving investigational devices:
    a. General responsibilities of investigators.[10]
        i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR §50.
    b. Specific responsibilities of investigators[11]
        i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation, but must not request the written informed consent of any subject to participate, and must not allow any subject to participate before obtaining IRB and FDA approval.
        ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
        iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
        iv. Financial disclosure:
            1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.
            2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
        v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
    c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:[12]
        i. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
        ii. Records of receipt, use or disposition of a device that relate to:
            1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

[10] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100
[11] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110
[12] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140

2. The names of all persons who received, used, or disposed of each device.
3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

iii. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. Such records must include:

1. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
2. Documentation that informed consent was obtained prior to participation in the study.
3. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

d. Inspections[13]

i. Entry and inspection: A sponsor or an investigator who has authority to grant access must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

ii. Records inspection: A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, must permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

iii. Records identifying subjects: An investigator must permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

e. Prepare and submit the following complete, accurate, and timely reports[14]

[13] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145
[14] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150

i. Unanticipated adverse device effects. An investigator must submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
ii. Withdrawal of IRB approval. An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
iii. Progress. An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
iv. Deviations from the investigational plan:
    1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
    2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
    3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.
v. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Chapter 24- Clinical Trials Requirements

This chapter contains additional requirements for clinical trials under the guidelines for good clinical practice (GCP)

NOTE: The UH IRB complies with ICH GCP guidance (E6) only to the extent that it is compatible with FDA and DHHS regulations. GCP standards contained in the ICH document are not regulatory requirements in the United States.

However, for **industry-sponsored studies with contract requirements for institutional adherence to ICH GCP guidance (E6),** the UH IRB will comply with all of the GCP statements outlined in ICH-GCP guidance (E6), provided that (i) the study team specifically notifies the IRB administration office that the sponsor requires the IRB review process to comply with ICH standards, and (ii) the Grants and Contracts office confirms it is a contractual requirement.

ICH GCP requires the following:

- completion of additional training for study team members
- confirmation that all GCP standards will be followed during the research
- submission of additional materials and information in IRB to complete the review **(**PI's CV)
- PI responsibility for reporting requirements, including termination or suspension of the research study by the PI, sponsor, or IRB (see 4.12 of ICH GCP guidance E6)
- additional elements of informed consent (see 4.8 of ICH GCP guidance E6)

1. Investigator's Qualifications and Agreements
    a. The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.
    b. The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities.
    c. The investigator should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
    d. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
    e. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
    f. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

2. Adequate Resources

a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
b. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
c. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
d. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.

3. Medical Care of Trial Subjects
    a. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
    b. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.
    c. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
    d. Although a subject is not obliged to give his/her reasons for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights.

4. Communication with IRB
    a. Before initiating a trial, the investigator/institution should have written and dated approval opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.
    b. As part of the investigator's/institution’s written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator’s Brochure to the IRB.
    c. During the trial the investigator/institution should provide to the IRB all documents subject to review.

5. Compliance with Protocol
    a. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities and which was given approval opinion by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

b. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazards to trial subjects, or when the changes involves only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).
c. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
d. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial subjects without prior IRB approval opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendments should be submitted: a) to the IRB for review and approval opinion, b) to the sponsor for agreement and, if required, c) to the regulatory authorities.

6. Investigational Product
    a. Responsibility for investigational product accountability at the trial site rests with the investigator/institution.
    b. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
    c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
    d. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
    e. The investigator should ensure that the investigational product are used only in accordance with the approved protocol.
    f. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
    g. Randomization Procedures and Unblinding: The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.

7. Informed Consent of Trial Subjects
    a. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles

that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval opinion of the written informed consent form and any other written information to be provided to subjects.

b. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
c. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
d. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
e. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
f. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
g. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
h. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
i. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that

informed consent was freely given by the subject or the subject's legally acceptable representative.

j. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
   i. That the trial involves research.
   ii. The purpose of the trial.
   iii. The trial treatments and the probability for random assignment to each treatment.
   iv. The trial procedures to be followed, including all invasive procedures.
   v. The subject's responsibilities.
   vi. Those aspects of the trial that are experimental.
   vii. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
   viii. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
   ix. The alternative procedures or courses of treatment that may be available to the subject, and their important potential benefits and risks.
   x. The compensation and/or treatment available to the subject in the event of trial related injury.
   xi. The anticipated prorated payment, if any, to the subject for participating in the trial.
   xii. The anticipated expenses, if any, to the subject for participating in the trial.
   xiii. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
   xiv. That the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
   xv. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
   xvi. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
   xvii. The persons to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
   xviii. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
   xix. The expected duration of the subject's participation in the trial.
   xx. The approximate number of subjects involved in the trial.

k. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation

in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

l. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

m. Except as described above, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

n. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally. b) The foreseeable risks to the subjects are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval opinion of the IRB is expressly sought on the inclusion of such subjects, and the written approval opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

o. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

8. Records and Reports

a. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

b. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

c. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

d. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
e. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
f. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

9. Progress Reports
    a. The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.
    b. The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
10. Safety Reporting
    a. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB.
    b. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
    c. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
    d. Premature Termination or Suspension of a Trial If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:
        i. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the

investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.

ii. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.

iii. If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

11. Final Reports by Investigator: Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.

Chapter 25 - Additional Requirements for Department of Defense (DOD) research

This chapter includes additional requirements for research regulated by the Department of Defense (DOD)

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
3. Employees of the Department of Defense (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the Department of Defense cannot be paid for conducting research while on active duty.
4. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty or off-duty.
5. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
6. There may be specific educational requirements or certification required.
7. When assessing whether to support or collaborate with this institution for research involving human subjects, the Department of Defense may evaluate this institution’s education and training policies to ensure the personnel are qualified to perform the research.
8. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
    a. Prohibit an individual from receiving pay of compensation for research during duty hours.
    b. An individual may be compensated for research if the participant is involved in the research when not on duty.
    c. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
    d. Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

9. Surveys performed on DOD personnel must be submitted, reviewed, and approved by the DOD Information Management Control Officer (IMCO) after the research protocol is reviewed and approved by the IRB. When a survey crosses DOD components, additional review is required. Consult the Department of Defense funding component to coordinate this review.
10. When research involves large scale genomic data (LSGD) collected on DOD-affiliated personnel, additional protections are required:
    a. Additional administrative, technical, and physical safeguards to prevent disclosure of DoD-affiliated personnel's genomic data commensurate with risk (including secondary use or sharing of de-identified data or specimens)
    b. Research will apply an HHS Certificate of Confidentiality
    c. DoD Component security review
11. Data or information sent to a DOD component under a pledge of confidentiality for exclusively statistical purposes must be used exclusively for statistical purposes and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent.
12. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
13. The following must be reported to the applicable DOD Component Office of Human Research Protections within 30 days:
    a. When significant changes to the research protocol are approved by the IRB or EC:
        i. Changes to key investigators or institutions.
        ii. Decreased benefit or increased risk to participants in greater than minimal risk research.
        iii. Addition of vulnerable populations as participants.
        iv. Addition of DOD-affiliated personnel as participants.
        v. Change of reviewing IRB.
    b. When the organization is notified by any federal body, state agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that any part of an HRPP is under investigation for cause involving a DOD-supported research protocol.

c. Any problems involving risks to participants or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DOD-supported human participant research.

d. The results of the IRB's continuing review, if required.

e. Change in status when a previously enrolled participant becomes pregnant, or when the researcher learns that a previously enrolled participant is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart B.

f. Change in status when a previously enrolled participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with 32 CFR 219, Subpart C.

g. Closure of a DOD-supported study.

14. For human participant research that would not otherwise be approved but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, written approval from the DOD Office for Human Research Protections must be obtained through the DOD Component Office of Human Research Protections prior to research starting.

15. Other specific requirements of the Department of Defense research be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the IRB's HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Chapter 26- GDPR Requirements

This chapter contains additional requirements for research subject to the European Union (EU) General Data Protection Regulations (GDPR)

1. Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.

2. For all prospective Human Research subject to EU GDPR, contact institutional legal counsel or your institution's Data Protection Officer to ensure that the following elements of the research are consistent with institutional policies and interpretations of EU GDPR:
    a. Any applicable study design elements related to data security measures.
    b. Any applicable procedures related to the rights to access, rectification, and erasure of data.
    c. Procedures related to broad/unspecified future use consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.

3. Where FDA or DHHS regulations apply in addition to EU GDPR regulations, ensure that procedures related to withdrawal from the research, as well as procedures for managing data and biospecimens associated with the research remain consistent with Chapters above.

Chapter 27 – Emergency/Disaster Preparedness Considerations for Investigators Conducting Human Research

Investigators conducting human research should be aware of the following additional considerations associated with managing Human Research during an emergency/disaster scenario (e.g., extreme weather events, natural disasters, man-made disasters, infectious disease pandemics, etc.) related to investigators' ongoing interactions with research subjects and the institutional review board (IRB) in such cases.

During Emergency/Disaster Scenarios: Deciding Whether a Study-Specific Risk Mitigation Plan for Ongoing Research Is Needed

In general, investigators should develop a study-specific emergency/disaster risk mitigation plan for their research unless one of the following is true:

- Research does not involve in-person interaction with research subjects.
- Research can be conducted as written while adhering to additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event.
- The research is externally sponsored, and the sponsor has developed a protocol-specific risk mitigation plan for the research.
- The research has been voluntarily placed on hold for recruitment and all research procedures (except for necessary follow-up procedures to be done consistently with additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event).

Tools and Resources for Developing Study-Specific Emergency/Disaster Risk Mitigation Plans for Ongoing Research

Review "HRP-108 - FLOWCHART - Study-Specific Emergency-Disaster Risk Mitigation Planning" and "HRP-351 - WORKSHEET - Protocol-Specific Emergency-Disaster Risk Mitigation Plan" for general guidance on developing study-specific risk mitigation plans.

Voluntary Holds on Human Research Activities

Investigators may voluntarily elect to place all recruitment, enrollment and research procedures on temporary hold during emergency/disaster scenarios if doing so will better ensure the safety of research subjects and would not create any additional risks to the safety and welfare of research subjects. Such voluntary holds on research activity do not require IRB notification or review.

Submitting Study-Specific Emergency/Disaster Risk Mitigation Plans for IRB Review

If immediate modification of the research is necessary to eliminate an apparent immediate hazard to a subject, take action and notify the IRB within five business days following the standard pathway to submit reportable new information.

For all other study modifications made to ensure the ongoing safety of research subjects during emergency/disaster scenarios, submit a study amendment and all relevant new or modified study materials to the IRB.

Other Reportable New Information Considerations During Emergency/ Disaster Scenarios

The IRB's list of reportable events includes two items for which additional clarification and guidance may be helpful during emergency/disaster scenarios:

- "Failure to follow the protocol due to the action or inaction of the investigator or research staff." Emphasis on action or inaction of the investigator or research staff has been added because this requirement does not include action or inaction of the research subject. For example, study teams may notice an increase in the number of subjects who do not arrive for scheduled research visits under emergency/disaster circumstances. Failure of a research participant to appear for a scheduled research visit is not noncompliance due to action or inaction by the investigator or research staff, and therefore does not require reporting to the IRB.
- "Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject." During emergency/disaster scenarios, there will be cases where there is sufficient time to receive IRB approval of any proposed modifications to previously approved research, and in such cases, investigators should follow standard IRB procedures for submitting modifications. However, there will be other cases where investigators must make more immediate changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants. Such changes may be implemented without IRB approval, but are required to be reported to the IRB within five business days afterward in accordance with IRB policies and procedures for submitting reportable new information.