



IRB POLICIES AND PROCEDURES MANUAL	
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## Section 1: Introduction

### 1.1 Background Information

Review of the history of human subjects research provides us with many examples of unethical and inhumane treatment of human research subjects. Perhaps the most infamous examples were perpetrated by Nazi physicians during World War II, but there are several other examples of unethical research activities that took place in the United States.

As a result, several international codes arose that addressed the issues of ethical treatment of research subjects. In 1947, the Nuremberg Code established ten major ethical principles for human subjects research and later the World Medical Association established its own code of research ethics at a meeting in Helsinki, Finland and revised it several times over the years to keep pace with the changing technologies and types of human subjects research.

In the United States, concern over the rights and welfare of humans involved in research prompted changes in grant policy. In 1974 Congress enacted the National Research Act (P.L. 93-348) establishing a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In 1979, the National Commission published the now well-known Belmont Report that identified three basic ethical principles as relates to human subjects research. The principles are: respect for persons, beneficence, and justice. In January 1981, human subjects regulations were amended to provide a common framework within which Institutional Review Boards (IRBs) could review human subjects research. The regulations were codified in 1991 under Title 45, Part 46 of the Code of Federal Regulations. Subpart A of the codification was accepted by 17 Federal Agencies as “the Common Rule.”

### 1.2 Mission

#### 1.2.1 The Republic Specialized Scientific & Practical Medical Center for Hematology

1.2.2 The mission of The Republic Specialized Scientific & Practical Medical Center for Hematology (RSSPMC for Hematology) is to achieve excellence in the interrelated areas of clinical treatment, research, and public health. The Center contributes to the advancement of society through research, creative activity, scholarly inquiry and the development of new knowledge.

#### 1.2.3 The RSSPMC for Hematology’s Human Research Protection Program (HRPP)

Coupled with the research programs, the Center strives to protect the rights and welfare of human subjects who choose to participate in biomedical or socio-behavioral science research and has an organized and systematic program in place for the protection of research subjects that includes a commitment to the principles and guidelines for protecting research subjects contained in the Belmont Report. Central to this program, the Center will apply for a U.S. Federal Wide Assurance (FWA) of Compliance (hereafter referred to as “Assurance”) with the U.S. Department of Health and Human Services’ Office of Human Research Protections (OHRP). This Assurance will be updated periodically and commits the Center to applying federal regulations to human subjects research as required. The Center may apply equivalent policies and procedures for research not covered by regulations.

Based on the principles of the Belmont Report – respect for persons, beneficence, and justice – the over-arching goal of the Human Research Protections Program (HRPP) is to protect the rights and welfare of human research subjects at the Center.

The Center’s HRPP encompasses faculty, staff, and students who conduct human subjects research as

well as many administrative components including:

- Institutional Review Board – Responsible for reviewing and approving human subjects research activities
- Conflict of Interest Program – Oversees efforts to ensure objectivity in research
- Institutional Biosafety Committee – Ensures institutional compliance with regulations governing research involving recombinant or synthetic nucleic acid molecules and the use of biohazardous materials in research
- Institutional Radiation Safety Committee – Oversees the use of radioactive materials in research
- Office of Sponsored Projects – Serves as the coordinating office for externally funded research and sponsored projects
- Office of Industry Engagement – negotiates all research contracts funded by private industry
- Office of Technology Commercialization – Responsible for the transfer of Center’s discoveries to the marketplace for the benefit of society

The Office of Research Support and Compliance provides the interface between the various components of the HRPP as needed to ensure human subjects research is conducted with integrity and in compliance with applicable regulations.

### 1.3 Institutional Commitment

The RSSPMC of Hematology’s leadership is committed to upholding the it’s Assurance, improve the research infrastructure to ensure a strong HRPP and, through evaluation and assessment, initiate required improvements in the HRPP. At the Center, the individual designated by the Director as ultimately responsible for the Assurance and implemental of the Center’s HRPP is the **Vice President** for Research, Scholarship, and Creative Endeavors (VPR), also referred to in the Assurance as the Institutional Official (IO). The IO is the Center official responsible for ensuring that the HRPP has the resources and support necessary to comply with Uzbek National and U.S. federal regulations and guidelines that govern human subjects research. As an agent of the institution, the IO is legally authorized to represent the institution in matters regarding human subjects research, is the signatory official for all Assurances and assumes the obligations of the Center’s Assurance. The IO is also responsible for review and evaluation of reports on HRPP performance and Quality Improvement (QI) activities. In collaboration with the ORSC Director, the IO periodically evaluates resource needs to ensure optimal operation of the IRB and administrative support. The IO is responsible for further institutional review and approval or disapproval of research approved by the Center’s Institutional Review Board (IRB) (neither the IO no any other Center official can approve research that was disapproved by the IRB). All correspondence and reports sent to national regulatory agencies regarding investigator or institutional noncompliance are signed by the IO.

The ORSC Director implements needed improvements and follow-up actions relating to the principal investigator (PI) and institutional compliance of the Center’s HRPP. The ORSC Director is responsible for monitoring changes in national and international regulations, policies and guidelines relating to the HRPP, ensuring that the IRB and IO are informed of the changes and assuring compliance with all requirements.

In general, however, it is the responsibility of all faculty and research staff, IRB members, IRB staff, Center’s staff negotiating with research sponsors, and anyone else involved in human subjects research to uphold the ethical standards delineated in the Belmont Report and assure that the highest level of human subjects protections are in place and implemented at all times.

## 1.4 Human Subjects Research Oversight

### 1.4.1 Uzbek National and U.S. Regulations in regards to Human Subjects Research

The [Office of Human Research Protections](#) provides leadership on human subjects research protections and implements a program of compliance oversight for U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects - see [45 CFR Part 46](#). OHRP works to support and strengthen the nation's system for protecting those who volunteer to participate in research that is conducted or supported by agencies of Ministry of Health. OHRP also provides guidance to IRB members and IRB staff as well as to scientists and research administrators on the complex ethical and regulatory issues relating to human subjects protections in medical and social behavioral research.

Within U.S. HHS, the Food and Drug Administration (FDA) has oversight over FDA-regulated research (drugs, biologics, medical devices, and foods) as described in the FDA oversight policies Title 21, Parts 50 and 56. The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. For more information on Code of Federal Regulations visit the FDA websites at:

[21 CFR Part 50](#)

[21 CFR Part 56](#)

[The RSSPMC of Hematology IRB follows ICH-GCP guidelines as adopted by the FDA.](#)



The Center will comply with all applicable Uzbek and U.S. laws regarding human subjects research. If research takes place outside of the Republic of Uzbekistan, the IRB may consult with legal counsel, who provides interpretation and guidance to the IRB, when needed. In situations where there are conflicts between Uzbek, or other applicable laws, legal counsel will be consulted to advise on resolution of the conflicts.

#### Human Research Protection Program Oversight

The Office of the Vice President for Research, Scholarship and Creative Endeavors (VPR) is responsible for the administration and oversight of research integrity at the Center. The IO oversees the functioning of the IRB. The ORSC Director is responsible for provision of IRB administrative support. Supervisors periodically evaluate administrative support staff regarding their knowledge and interpretation of relevant policies and procedures regarding human subjects protections. In addition, and as part of the overall oversight function, in order to maximize compliance with regulations, guidelines, and policies and procedures of the institution, the ORSC Director relies on an internal QI monitoring program to assess research activities and documentation.

### 1.5 Purpose and Scope of the Manual

This manual contains a current compilation of Uzbek and U.S. federal, and the Center's rules, regulations, policies, and procedures applicable to the protection of human research subjects, sets forth appropriate mechanisms for their implementation and is regularly updated to reflect new standards, regulations and the Center's policy.

#### 1.5.1 Applicability

The policies and procedures set forth in this manual are applicable to all faculty, staff, employees, and students at the Center who propose to use human subjects in research, development, and related activities including research for which investigational devices or drugs are used, as well as to the IRB, ORSC staff who support the HRPP, and the Institutional Official.

The IRB has jurisdiction and oversight responsibilities over human subjects research in which the Center is engaged. Specific examples would include but not be limited to research:

1. For which the Center receives funding
2. Conducted by or under the direction of faculty, students, or staff of the Center in connection with their institutional responsibilities.
3. Conducted by or under the direction of any faculty, students, or staff of the Center using any property or facility of the Center.
4. Conducted by or under the direction of any faculty, students, or staff of the Center in collaboration with external researchers.
- 4.1 In the instance that Center researchers collaborate with external researchers on non-exempt, human subjects research, a reliance agreement between the participating institutions may be required.

Compliance with this policy or the procedures set forth herein will in no way render inapplicable pertinent laws of the Republic of Uzbekistan, which may bear upon the proposed activity or the Rules and Regulations of the RSSPMC of Hematology's Board of Regents.

### 1.5.2 Revision and Maintenance of the Manual

The ORSC is responsible for maintaining and updating this manual. All new or revised manual materials will be published on the ORSC website by the IRB office at <https://research.utexas.edu/resources/human-subjects/policies-and-guidance>. Updates to the manual will be communicated to the research community electronically via newsletter and listserv communications.

## Section 2: Definitions

### 2.1 Definitions Applicable to All Sections of this Manual

**Adverse events** are a subset of unanticipated problems involving risks to the subjects or others and are related to untoward or unfavorable medically-related events, including abnormal sign, symptom or disease temporarily associated with the subjects participation in the research or clinical trial.

**Agent of the Organization** is a clinician or non-clinician employee, who may also be a principal investigator of research protocol or an Institutional Review Board member, or non-employees who perform institutionally designated activities or who exercise institutionally delegated authority or responsibility such as research or teaching activities. Examples would include community IRB members, Center employee who are conducting research at another institution, an employee performing research while on sabbatical.

**Allegation of Noncompliance** means an unproven assertion of noncompliance.

**Anonymity** means that the identity of a research subject cannot be readily ascertained by anyone, including the Principal Investigator, either directly or through the use of coded data.

**Anonymous Data** pertains to information that is collected or that an individual has disclosed in a study with the expectation that the information has no identifiers linked to the participant and therefore cannot in any way be traced to the participant. An example would be survey research that does not ask for the participants' names or any other form of personal identification. The words "anonymous," "de-identified," and "confidential" do not have the same meaning and are not interchangeable.

**Applicable Clinical Trial** means any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause and effect relationship between the intervention and a health relationship. The definition includes surgical procedures, behavioral treatments, and Uzbek Center for Pharmaceutical Products Safety (UCPPS) regulated studies with drugs, biological products, or devices.

**Approved** means a protocol is approved as written with no explicit conditions or modifications required to secure approval.

**Approved Assurance** means a document that fulfills the requirements of U.S. 45 CFR Part 46 and is approved by the Uzbek Ministry of Health. The Republic Specialized Scientific & Practical Medical Center for Hematology aims at attaining an approved "Federal-wide Assurance" from the U.S. Department of Health and Human Services.

**Approved with Explicit Conditions or Modifications Required to Secure Approval** means the protocol is approved with explicit conditions for minor changes or simple concurrence of the Principal Investigator that will be identified to the Principal Investigator and must be completed and documented prior to beginning the research.

**Assent** means an affirmative agreement to participate in research or clinical investigation. Mere failure to object an absence of affirmative agreement may not be construed as assent. This most often is applicable to children and decisionally impaired adults.

**Authorized deception** means that a Principal Investigator has intentionally not described certain aspects of a research study but subjects are informed that certain information will be withheld until the subject completes the study tasks.

**Basic community partnership research** is a project that involves a relationship with a community partner in which the researcher makes the key decisions in the project, but considers the needs and interests of the community in how the research is conducted and how the outcomes are disseminated.

**Children** are persons who have not attained the legal age for consent to treatments or procedures involved in research or clinical investigations. In Uzbekistan, individuals under the age of 18 are considered to meet the definition of children. For research conducted outside Uzbekistan, children are defined under the applicable law of the jurisdiction in which the research or clinical investigations will occur. Some funding agencies may define children differently.

**Clinical Investigation**, as defined by the Uzbek Ministry of Health, is synonymous with “research” as defined by U.S. DHHS and means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the UCPPS, or the results of which are intended to be later submitted to, or held for inspection by, the UCPPS as part of an application for a research or marketing permit.

**Clinical Trial** means 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 the interventions on biomedical or behavioral health-related outcomes.

**Close community partnership research** is an ongoing collaborative project in which goals are co-defined in ways that balance benefit to the PI and utility of the findings for the community. There is some sharing of decision making between the Principal Investigator and the community, but the research methodology is primarily determined by the Principal Investigator.

**Coded Information/Data** means that identifying information that would enable the Investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

**Coercion** is an overt or implicit threat of harm that is intentionally presented by one person to another in order to obtain compliance. For example, an investigator might tell a prospective subject that his or her grades might suffer if they do not participate in the research.

**Collaborator** is anyone who plays a part in the protocol and has access to study records.

**Common rule** refers to U.S. Department of Health & Human Services 45 CFR Part 46, Subpart A.

**Community** is a group that self-identifies by geography, age, ethnicity, gender, sexual orientation, disability, illness or health condition, common interest or cause, a sense of identification or shared emotional connection, shared values or norms, mutual influence, or commitment to meeting a shared need. Community need not be defined solely by geography. Defining “community” in a community-Center partnership is more about the process of asking questions than about a strict definition of who “is” community or “represents” community: “Are those most affected by the problem at the table? Are community members at the table? Are those who have a stake in the issue being addressed at the

table? Do they play decision making roles?" The purpose of the research partnership drives the definition - each project must define the community of interest.

**Community-based research** is research that takes place in or involves a community. The more precise definitions below reflect the degree of engagement of the community in the research, which can take place along a spectrum of engagement and shared governance.

**Community-placed research** is a researcher-initiated project involving a one time or short-term relationship between the PI and the community, with limited community involvement beyond being a venue for recruiting research subjects or for implementing research procedures.

**Community-based participatory research (CBPR)** is a project defined by co-creation of project ideas and procedures by Principal Investigator and a community, active and substantive participation by the community in all or nearly all stages of the research, and shared power and decision-making responsibilities. There is an expectation that findings will be used to change systems or solve community problems. CBPR sees research subjects as both individuals and as a community comprised of individuals. Issues of confidentiality in CBPR should be viewed differently than with individual subjects and decisions made as to what may or may not be appropriate.

**Confidential** pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission or in ways that are inconsistent with the understanding of the original disclosure. For example, there may be a legal responsibility to divulge information and that should be stated in the consent form. The words "anonymous" and "confidential" do not have the same meaning and are not interchangeable.

**Conflict of Interest** is defined as any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual or group's professional judgment in conducting, reviewing, or reporting research. Members of the Institutional Review Board may not review, deliberate on or approve research if they have a conflict of interest related to the research.

**Continuing Noncompliance** is a pattern of repeated noncompliance that if continued will likely, in the IRB's judgment, materially adversely affect the rights, welfare or safety of research participants, the integrity or validity of the related research, or the work of the IRB. Continuing noncompliance may involve repeated occurrence of the same type of event(s) or a series of different events.

**Dead fetus** means a fetus that does not exhibit heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord.

**Data and Safety Monitoring Plan (DSMP)** is an individualized plan, written by the Principal Investigator (PI) responsible for the study. The DSMP sets forth mechanisms for reviewing and evaluating unanticipated problems and other study-relevant data. The rationale for requiring a DSMP is the need to enhance research subject safety by clearly defining safety related issues prior to subjects being enrolled in a study. These issues include:

1. Monitoring the safety of the environment including the safe handling of drugs, solutions, specimens, physical space, and equipment;
2. Monitoring and protecting the validity and integrity of the data collected for the study; and

3. Documenting, grading, attributing, and reporting unanticipated problems involving risks to subjects or others.

**De-Identified** refers to information or data where direct identifiers such as name and address have been removed. In common use, the term refers to data where it may still be possible to identify individuals by inference or through codes held by the investigator or a third party. Therefore data that is de-identified may not be anonymous because it may still permit at least probabilistic re-identification when analyzed in conjunction with other datasets.

**Deception** (as applies to research) means intentionally giving research subjects false information in order to establish false beliefs during the course of a research study.

**Delivery** means complete separation of the fetus from the woman by expulsion or extraction or any other means.

**Deferred or Tabled** means generally, the protocol or consent form has deficiencies that prevent the IRB from determining that the criteria for approval are met. For example, the IRB is not able to make an accurate determination of risks and benefits or requires significant clarifications, modifications or conditions that, when met or addressed, require full Institutional Review Board (IRB) review and approval of the Principal Investigator's (PI) responses and revisions. The deficiencies will be specified to the PI, and on occasion the PI is asked to attend the full board meeting in order to clarify the points in question. The PI must revise the protocol, consent forms, or other documents as specified by the IRB and re-submit.

**Designated Reviewers** are experienced IRB members, defined in this policy as having been an IRB member for at least one year and having been trained on the expedited process. Designated reviewers may also include IRB staff (named as IRB members) who are experienced (minimum of 1 year experience) with the expedited review process. The IRB Chair has designated the IRB Vice-Chair, and experienced IRB members, including appropriate IRB staff members, as reviewers of protocols requesting and qualifying for expedited review.

**Disapproved** means the protocol describes a research activity that is deemed to have risks which outweigh potential benefits or the protocol is significantly deficient in several major areas. The protocol and/or other documents will need to be completely re-written and re-submitted as a new submission. Principal Investigators may request reconsideration of a determination for disapproval in writing and possibly be invited to attend an Institutional Review Board meeting and present reasons for reconsideration.

**Emergency Use** is the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

**Engaged in human subjects research** as defined by the Department of Health and Human Services guidance document states that in general an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents, for the purposes of the research project, obtain:

1. Data about the subjects of the research through intervention or interaction with them.

2. Identifiable private information about the subjects of the research.
3. Informed consent of human subjects for the research.

**Enrollment** includes all subjects intended to be included in a study, including screen failures and drop outs. (Example: The investigator has a target enrollment of 100 and expects 75 to be screen failures so the study will accrue 25).

**Exculpatory language** in a consent form is language which “has the general effect of freeing or appearing to free an individual or entity from malpractice, negligence, blame, fault, or guilt” according to the [draft guidance](#) released by OHRP and the U.S. FDA on August 19, 2011.

**Food and Drug Administration (FDA)** is an agency within the U.S. Department of Health and Human Services. FDA is responsible for protecting the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products, medical devices, our nation’s food supply, cosmetics, dietary supplements, and products that give off radiation.

**Fetus** means the product of conception from implantation until delivery.

**Financial Interest** in or related to the research means financial interest of any amount in the sponsor, product or service being provided, or a competitor of the sponsor. This can also be referred to as Financial Conflict of Interest.

**Generalizable Knowledge** means information from which one may infer a general conclusion; knowledge brought into general use or that can be applied to a wider or different range of circumstances. For example, publication and presentation are typical methods used to disseminate research findings, thereby contributing to “generalizable knowledge.” However, not all information that is published or presented represents generalizable knowledge. Generalizable knowledge is also interpreted to include data intended for general use, regardless of its eventual distribution or acceptance.

**Guardian** means a person appointed by a court to have full authority to make decisions for and act on behalf of a child or decisionally impaired adult, except as otherwise provided for by law. For research conducted outside Uzbekistan, children are defined under the applicable law of the jurisdiction in which the research or clinical investigations will occur.

**HIPAA** is the acronym for the U.S. Health Insurance Portability and Accountability Act of 1996 and intended to provide standards for protecting the privacy of personally identifiable health information (PHI).

**Human Embryonic Stem Cells** are pluripotent cells that are derived from early stage of embryos, up to and including the blastocyst stage, are cable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers.

**Human Subjects** has reference to two definitions defined by U.S. federal agencies.

1. U.S. Department of Health and Human Services defines human subject as a living individual about whom the investigator conducting research:
  - a. Obtains information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens; or

- b. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
2. U.S. Food and Drug Administration (FDA) defines human subject as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

**Identifiable Private Information** is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

**Identifiable Biospecimen** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

**Incidents of Noncompliance/ Protocol Violations** means that principal investigators did not adhere to Uzbek/U.S. Federal Regulations and/or RSSPMC of Hematology policies, procedures, requirements, or Institutional Review Board determinations for conducting research involving human subjects.

**Incomplete disclosure** means that the principal investigator withholds some information about the real purpose of the study or the nature of the research procedures.

**Individually Identifiable Information** means any information about a living individual that is linked, associated with, or contains the name or any details of the individual that would allow someone to be able to directly or indirectly identify a subject from the information collected.

**Informed Consent** means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. Information conveyed in the informed consent procedure must include all essential elements listed later in this manual.

**Institution** means any public or private institution or agency (including federal, state, and local government agencies).

**Institutional Official (IO)** is the RSSPMC of Hematology official responsible for ensuring that the human research protection program has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. At the RSSPMC of Hematology, the **Vice President for Research** is the IO.

**Interaction** means communication or interpersonal contact between an investigator and participant.

**Intervention** is a physical procedure by which data are gathered, or manipulation of the participant or the participant's environment for research purposes.

**Investigator** is considered to be an individual performing various tasks related to the conduct of human subjects research activities such as:

1. Obtaining information about living individuals by intervening or interacting with them for research purposes.



2. Obtaining identifiable private information about living individuals for research purposes.
3. Obtaining voluntary informed consent of individuals to be subjects in research.
4. Studying, interpreting or analyzing identifiable private information or data for research purposes.

**Lapse of approval** means that, for whatever reason, the Institutional Review Board (IRB) has not received or reviewed required documentation for protocol continuation prior to the protocol's expiration date and all research activities must cease. Continuing review of research activities by the IRB must occur at least annually and a request for continuation must be accompanied by a report and other pertinent documentation. By regulation, no grace period is allowed. The IRB notifies Principal Investigators of lapses in approval and the requirement to cease all research activities until approval for continuation is obtained.

**Legally authorized representative (LAR)** means an individual, judicial or other entity authorized under applicable law to consent on behalf of a prospective subject to such subject's participation in the particular research activity or procedure. For research conducted in Uzbekistan, for healthcare related treatments and procedures and for non-healthcare procedures, individuals in the following order may serve as a LAR: a legal guardian, persons appointed as health care agents under Durable Power of Attorney for Health Care, a spouse, adult child, parent, or an adult sibling. For research conducted outside of Uzbekistan, individuals who meet the definition of an LAR are those who are described under the applicable law of the jurisdiction in which the research will be conducted. Legal counsel may be consulted by the Director of Office of Research Support and Compliance and the Institutional Review Board Chair for assistance in applying laws to research involving human subjects.

**Legally effective informed consent** means that the Principal Investigator obtained consent to participate from a subject or the subject's legally authorized representative (LAR) and documented it in a manner consistent with the human subjects protection regulations and applicable laws of the jurisdiction in which the research is conducted. It is expected that the Principal Investigator will seek consent only under circumstances that provide the prospective subject or LAR sufficient opportunity to consider whether or not to participate and to minimize the possibility of coercion or undue influence. The information provided in the consent process should be understandable to the subject or subject's LAR and may not include any exculpatory language.

**Limited IRB Review** is a type of review process required for certain exemptions. Its purpose is to ensure privacy/confidentiality protections are in place with exempt research that involves the collection or use of sensitive, identifiable data (applicable under exempt categories 2 and 3). Limited IRB review must be conducted by the IRB Chair or designated reviewer.

**Member** includes any individual who serves on the Institutional Review Board as a voting or alternate member.

**Minimal Risk** means that the risks of harm anticipated in the proposed research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. These are risks that reflect background risks that are familiar and part of the routine experience of life for an average person in the general population. For children, the definition means research in which the probability and magnitude of harm or discomfort anticipated in the

research are not greater in and of themselves than those ordinarily encountered in daily life (of a healthy child) or during the performance of routine physical or psychological examinations or tests.

For Prisoners, minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental or psychological examination of healthy persons who are not prisoners.

**Modifications Required to Secure Approval or Approved with Explicit Conditions** means the protocol is approved with explicit conditions for minor changes or simple concurrence of the Principal Investigator that will be identified to the Principal Investigator and must be completed and documented prior to beginning the research.

**Neonate** means a newborn. Per the U.S. FDA, the neonatal period is defined as the day of birth plus 27 days for full-term infants and as the day of birth through the expected date of delivery plus 27 days for preterm infants.

**Noncompliance** means that researchers or individuals other than researchers, such as research staff, Institutional Review Board (IRB) staff, or IRB members, did not adhere to Uzbek, U.S. Federal Regulations and/or The RSSPMC of Hematology policies, procedures, requirements, or IRB determinations for conducting research involving human subjects.

**Nonviable neonate** means a neonate after delivery that, although living is not viable.

**Office for Human Research Protections** is an office in the Office of the U.S. Secretary of Health and Human Services that is responsible for regulatory oversight of human subjects research.

**Parent** means a child's biological or adoptive parent.

**Permission** means the agreement of parent(s) or guardian to the participation of the child in the research or clinical investigation.

**PHI** is the acronym for personal health information which is protected under the U.S. HIPAA regulations.

**Pregnancy** encompasses the period of time from implantation until delivery. A woman shall be assumed pregnant if she exhibits any of the presumptive signs of pregnancy, particularly missed menses, until the results of pregnancy testing are negative or until delivery.

**Principal Investigator** means an individual under whose immediate direction research is conducted or in the event of research conducted by a team of individuals, is the responsible leader of that team. The Principal Investigator is responsible for the oversight of human subjects research including the ethical conduct of the research, minimizing risks to participants, appropriately delegating tasks to qualified individuals on the research team, ensuring full disclosure of conflict of interest (COI) and ensuring objectivity in research. A researcher takes on the following responsibilities when listed as a Principal Investigator on a human subjects research protocol:

- Conducting the research as described in and required by the research protocol.
- Implementing no changes to an expedited or full board approved research protocol or consent form without prior approval of the Institutional Review Board (IRB), unless such changes are necessary to protect the safety of human subjects.
- Conducting the research using only the qualified personnel listed on the approved protocol.

- Obtaining informed consent from all subjects without coercion or undue influence, and provide potential subjects sufficient opportunity to consider whether or not to participate (unless Waiver of Consent is specifically approved or research is exempt).
- Submitting a timely continuing review as required by the IRB.
- Notifying the IRB of any unanticipated problems involving risks to participants or others within 5 business days.
- Promptly reporting and/or responding to all inquiries by the IRB concerning the conduct of the approved research when so requested.
- Immediately notifying the IRB upon termination of the study or departure of the Principal Investigator from this Institution.

**Prisoner** means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Some common examples of the definition are:

1. Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration.
2. Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to criminal prosecution or incarceration.
3. Individuals who have been voluntarily admitted for treatment or who have been civilly committed to non-penal institutions for treatment because their illness makes them a danger to themselves or others are not prisoners.
4. Parolees who are detained in a treatment center as a condition of parole. Parolees living in the community, even with community-supervised monitoring, are not prisoners.
5. Probationers and individuals wearing monitoring devices are generally not considered to be prisoners. However, some situations of this kind may require analysis of circumstances and Office for Human Research Protections should be consulted when questions arise about research involving this population.

**Prisoner Advocate/Representative** is an individual representing the interests of incarcerated persons who may be approached and enrolled as research subjects.

**Privacy** means having control over the extent, timing and circumstances of sharing oneself (physically, behaviorally or intellectually) with others.

**Privacy Board** is a review body that may be established to act upon requests for waiver or alteration of the requirement for a signed “Authorization for Use or Disclosure of Protected Health Information (PHI)” under the U.S. HIPAA Privacy Rule for uses and disclosures of PHI for a particular research study. A Privacy Board may waive or alter all or part of the Authorization requirements for a specified research project or protocol. At the RSSPMC of Hematology, the IRB acts as a privacy board.

**Private Information** includes:

- information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place; and
- information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical record).

**Protocol Deviation** means a deviation from Institutional Review Board-approved activities related to a research study. This means that the principal investigator(s) has performed activities that are different than those described in the protocol, that procedures not previously described in the protocol were performed, or that procedures described in the protocol were not performed.

**Quality Improvement (QI)** projects are defined as those activities that are designed purely to evaluate and improve practice to conform to established or accepted standards. These types of activities are generally not subject to Institutional Review Board (IRB) review and approval. However, if data from the QI activity are used to draw general or widely applicable conclusions beyond evaluating a particular program or activity, the activity probably is research. The distinction is not always clear. The intent to publish, in and of itself, does not require that an activity be reviewed by the IRB. If the activities and data being reported are a result of QI assessment, then no IRB review is required for the activity or for its publication.

**Quorum** is defined as a majority of the voting members. In the case of the Institutional Review Board (IRB), a quorum will consist of at least 51% of the voting IRB members and must include at least one non-scientific member. All members present have equal voting power. At meetings of the IRB, a quorum must be established and maintained throughout the entire meeting. A member with a conflict of interest cannot contribute to a quorum. For U.S. FDA-regulated research, a licensed physician must be present during the review, deliberation and voting to satisfy the quorum requirement under U.S. Code of Federal Regulations Title 21 CFR 56.108(c).

**Research** as defined by the Department of Health and Human Services means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46.102(d)). Research is considered synonymous with Clinical Investigation as defined by the U.S.FDA. The following activities are considered not research by DHHS:

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
- Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance.

- Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
- Including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products.
- Including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

The RSSPMC of Hematology further considers the following activities to not fall within the definition of research, and, as such, does not require IRB review for:

- Classroom research conducted by students as part of required coursework, as long as the results of such research will not be used to support undergraduate research, graduate thesis, or otherwise contribute to generalizable knowledge.
- A single or series of up to 3 medical case studies where there is no intent to conduct a systematic investigation and make generalizations based on case analysis.

**Research** as defined by the U.S. FDA means any experiment that involves a test article and one or more human participants, and that either must meet the requirements for prior submission to the U.S. FDA under section 505 (i) or 520 (g) of the U.S. Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of U.S. FDA regulations. (21 CFR 50.3(c), 21 CFR 56.102(c))

**Research Records** are records consisting of both Institutional Review Board-related records and any data gathered for research purposes.

**Minister/Secretary** means the Uzbek Minister of Health/U.S. Secretary of Department of Health and Human Services (HHS) and/or any other officer or employee of the HHS to whom authority has been delegated.

**Serious Noncompliance** is noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of research participants.

**Sponsor** means any person or entity that takes responsibility for, initiates or funds a study. The sponsor may be an individual, pharmaceutical company, device manufacturer, governmental agency, academic institution, private organization, or other organization.

**Student** means any individual who is enrolled as a student at The RSSPMC of Hematology.

**Staff** means all employees of The RSSPMC of Hematology.

**Suspension** means a temporary cessation of research activities, to include enrollment of new subjects, collection of data from enrolled subjects, and performance of any research activities described in the approved protocol. Suspensions can be administered by the Institutional Review Board (IRB), the IRB Chair, the Director of ORSC, or the principal investigator in order to eliminate an immediate hazard to subjects.

**Systematic Investigation** is a planned activity involving qualitative or quantitative data collection and data analysis that sets forth an objective(s) and a set of procedures intended to reach the objective(s), i.e., to acquire knowledge, develop a theory, or answer a question.

**Tabled or Deferred** means generally, the protocol or consent form has deficiencies that prevent accurate determination of risks and benefits or requires significant clarifications, modifications or conditions that, when met or addressed, require full Institutional Review Board (IRB) review and approval of the Principal Investigator's (PI) responses and revisions. The deficiencies will be specified to the PI, and on occasion the PI is asked to attend the full board meeting in order to clarify the points in question. The PI must revise the protocol, consent forms, or other documents as specified by the IRB and re-submit.

**Termination** means a permanent discontinuance of all research activities described in a research protocol due to withdrawal of Institutional Review Board (IRB) or regulatory agency approval.

**Unaffiliated member** means an IRB member who has no affiliation with the University except as a member of the IRB. Persons retired from the University for less than 3 years or those who have family members (spouse, parent, children) employed by the University are not considered unaffiliated. An unaffiliated member and the member representing the general perspective of research participants may be the same individual. It is expected that unaffiliated members will attend at least 8 meetings per year as documented in the meeting minutes.

**Unanticipated problem per OHRP includes any incident, experience, or outcome that meets all of the following criteria:**

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests 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.

**Undue influence** is an offer or implication, real or perceived, of an excessive or inappropriate reward or other overture in order to obtain compliance. For example, professors recruiting their students or staff may lead to the perception of undue influence to participate.

**Viable** as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. If a neonate is viable then it is a child and the U.S. [45 CFR 46 Subpart D](#) may apply.

**Ward** is defined as a child who is placed in the legal custody of the children protection agency, institution or entity consistent with applicable Uzbek law.

## Section 3: General Policies and Procedures

### 3.1 Applicable Regulations and Laws

The purpose and responsibility of the Institutional Review Board (IRB) is to protect the rights and welfare of human research subjects. The IRB reviews and oversees research activities involving human subjects and requires that the research complies, as applicable, with Uzbek and U.S. Federal regulations at 45 CFR 46, Subparts A, B, C, and D, (or equivalent policies and procedures), the U.S. FDA 21 CFR Parts 50, 56, 312, and 812, and all other pertinent regulations and guidelines. For research that is non-funded, participants are provided the same or equivalent protections.

In addition, the Office of the Vice President for Legal Affairs provides the IRB, ORSC, and other components on the HRPP with counsel on an as needed basis, primarily on matters related to Uzbek laws, cooperative agreements, conflicts of interest, and contractual issues in human subjects research.

### 3.2 Institutional Review Board

#### 3.2.1 Purpose

Safeguarding the rights and welfare of subjects at risk in any research activity, whether financially supported or not, and irrespective of the source of any supporting funds, is primarily the responsibility of the institution. In order to provide for the adequate discharge of the institutional responsibility, no non-exempt research activity involving human subjects may be undertaken by any faculty, staff, employee or student at The RSSPMC of Hematology unless an IRB has reviewed and approved the research prior to commencing the research activity.

#### 3.2.2 Designation and Authority

The RSSPMC of Hematology has designated its IRB as responsible for conducting initial and continuing reviews and providing oversight for all research activities involving the use of human subjects performed by agents or employees of the University. The scope of research reviewed by the IRB is not limited and the IRB reviews all types of research submitted.

The Institutional Official (IO) formally grants the IRB the following authority relative to the protection of human subjects:

1. To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted by the agents of the organization and involving human subjects, based on its consideration of the risks and potential benefits of the research and whether the rights and welfare of the subjects are adequately protected;
2. To require reports for protocol continuing review;
3. To continuously monitor the conduct of research with human subjects;
4. To suspend or terminate approval of research that is not being conducted in accordance with IRB requirements or that has been associated with unexpected serious risk to subjects;
5. To place restrictions on a study, if necessary to protect human research subjects;
6. To observe, or have a third party observe, the consent process;
7. To observe, or have a third party observe, the conduct of the research.



No official within the organization may approve a protocol or human subjects research activity that has not been approved by the IRB. However, the IO or any other RSSPMC of Hematology executive administrative official may disapprove a protocol or research activity that has been approved by the IRB.

### 3.2.3 Composition and Appointment of the IRB

The IRB is a committee formally appointed by the IO, with input and membership nominations coming from the IRB Chair and IRB members, the ORSC Director, department chairs, and self-nominations, and is composed of a minimum of 5 members to assure complete and adequate review of activities commonly conducted at the RSSPMC of Hematology. The composition of the IRB exceeds the minimum regulatory requirements and is sufficiently qualified through the maturity, experience, and expertise of their members and diversity (experience, professional expertise, racial, cultural, and gender) of membership to ensure respect for their advice and counsel specific to safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the IRB is able to ascertain the acceptability of proposals in terms of organizational commitments, regulations, applicable law, standards of professional conduct and practice, and community attitudes and are constituted to meet those requirements.

The IRB will include at least one scientific member, one member whose primary concerns are in nonscientific areas, one member who is not otherwise affiliated with the university and who is not part of the immediate family of a person who is affiliated with the organization, and one member who represents the perspective of research participants. The role of nonscientist and the person representing perspectives of research participants may be fulfilled by a single member. Scientific members of the IRB generally will have had experience in research involving human subjects and will be recruited from among active research members of the RSSPMC of Hematology. Nonscientific members will often be recruited from the faculty at large and will reflect professional expertise in a non-scientific area, such as law, ethics, human or patient rights, etc. The appointment of non-affiliated (community) members and a prisoner representative will also be done by the IO but the ORSC Director is responsible for determining whether or not the nominees are truly unaffiliated and/or have appropriate expertise to serve as prisoner representative.

Alternates are appointed and function in the same manner as the primary IRB members. The alternate's expertise is comparable to those of a primary member. The role of the alternate member is to serve as a voting member of the IRB when a regular member is unable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member received or would have received. The alternate member will not be counted as a voting member unless they are acting in a voting member capacity. The IRB minutes will document when an alternate member acts as a voting member.

At times, the IRB may not have the necessary expertise to judge the scientific soundness of a research protocol and may be unable to make a fair and accurate determination of the risk-benefit ratio. For these protocols the IRB Chair, or the primary reviewer after consultation with the IRB Chair, may call upon an ad hoc consultant for assistance in review for scientific merit or to perform an in-depth review of the study. Ad hoc consultants are not considered to be members of the IRB, are utilized only for expert scientific review, have no voting rights and must disclose whether or not he/she has any conflicts of interest with the protocol. Subject matter experts who are conflicted with a study may not serve as a consultant to the IRB. The consultants will submit a written report and copies of the report will be

distributed to all IRB members. The consultant may also attend a convened IRB meeting and provide a verbal report to the IRB. The report and recommendations will be documented in the IRB minutes for the meeting.

The IO may appoint administrative staff and/or faculty (e.g., legal counsel) at the Center to serve as non-voting members of the IRB should the IO, the IRB Chair, or the ORSC Director decide that such persons would be of assistance to the IRB in conducting its duties. Individuals involved in the business function or in research development do not serve in any capacity on the IRB and have no involvement in the day-to-day operations of the review process. A non-voting member cannot be counted in the quorum and cannot vote, but can participate in discussions. In addition, funding agencies may have additional IRB membership requirements. For example, the U.S. National Institute on Disability and Rehabilitation Research (NIDRR) specifies that when an IRB reviews an NIDRR-funded research project that purposefully includes children with disabilities as research subjects, the IRB must include at least one person whose primary interest is the welfare of children with disabilities. When reviewing these types of research projects, the IRB may use ad hoc reviewers with specific expertise in treating children with disabilities.

ORSC will report changes in IRB membership to OHRP as required.

### 3.3 Term of Appointment

IRB members are appointed to renewable terms, with no term limit. Members may resign at any time by submitting a letter or resignation to the IRB Chair. The IRB leadership may remove members from the committee if the member is unable to complete their responsibilities as an IRB member. The IRB Chair and Vice Chair are expected to hold the positions for several years. Upon appointment and periodically throughout their appointment, each IRB member is queried to determine roster information such as affiliation status, relationship of the member to the Center, indications of experience and other relevant information. The IRB will be evaluated annually via surveys of membership and results are reported back to the committees.

### 3.4 Committee Officers

The IRB will have a Chair and a Vice Chair chosen from IRB members and will typically be members of the faculty of the RSSPMC of Hematology knowledgeable in human subjects research, including the Uzbek and U.S. federal regulations, Center policies, and ethics relevant to such research. The IRB Chair shall preside over and be authorized to speak for the IRB. Whenever the Chair is not available, the Vice Chair will assume the responsibilities of the IRB Chair during the period of their absence.

### 3.5 Committee Meetings

In order to conduct IRB business at a convened meeting, IRB staff determine a quorum (majority) of members are present, including a non-scientist. When studies involving prisoners are reviewed, a prisoner representative must participate to achieve quorum. If quorum is lost, votes are not taken until it is restored. To be approved, a protocol must receive a majority of votes of members present at the meeting. The IRB shall hold regular meetings at a time and place to be determined by the IRB and posted electronically. Researchers are welcome to attend to address specific concerns regarding research protocols but will be asked to leave the meeting during all deliberations and votes. Other members of the University community are permitted to attend meetings but must request to attend through the ORSC Director. Guests may be asked to sign a confidentiality agreement.

Prior to each full board meeting the IRB staff or the IRB Chair will review the agenda of protocols and will assign primary reviewer(s) knowledgeable about or experienced in working with these types of studies. When research involves vulnerable populations, an IRB member or consultant with corresponding expertise is present or has provided feedback to the IRB. The IRB staff ensures that either the Primary or Secondary Reviewer is present at the meeting or available by teleconference during the convened meeting.

### 3.6 IRB Meeting Minutes

Meeting minutes are recorded, may undergo quality assurance review, and are retained. IRB staff members monitor quorum at each meeting and record IRB discussion points for the minutes. Meeting minutes are provided each month to IRB members, the ORSC Director, and the IRB staff via appropriate methods/channels with a request for comments and/or suggested changes regarding the document's accuracy. A vote for approval of the final version of the minutes occurs at the next convened meeting.

Minutes shall include:

1. A record of separate deliberations for each protocol reviewed, resulting IRB actions, and any controverted discussions.
2. The approval period for each initial review, continuing review and amendment.
3. A record of attendance for each protocol including the names of members who left the meeting due to a conflict of interest and a notation of such.
4. The voting record for each protocol and the previous meeting's minutes reflecting the number of members for, against or abstaining from the vote and when alternate members replaced a primary member.
5. The basis for requiring changes to a protocol, tabling/deferring, suspending, or disapproving research.
6. A written summary of the discussion and resolution of controverted issues.
7. Determinations for waiver or alteration of the consent process; research involving pregnant women, fetuses, and neonates; research involving prisoners; research involving children; and research involving participants with diminished capacity.
8. Justification of deletions or substantive modifications of information concerning risks or alternative procedures contained in a previously approved consent form.
9. If applicable, the determination for significant risk/non-significant risk device determinations (rationale for determination documented in IRB submission materials and IRB reviewer checklist).
10. A list of all actions that were taken administratively during the previous month.

Protocol-specific findings for justifying determinations for waiver or alteration of the consent process; research involving pregnant women, fetuses, and neonates; research involving prisoners; research involving children; and research involving participants with diminished capacity are documented in the IRB submission documents (e.g., proposal) and IRB checklists, as appropriate. For committee reviewed actions, only the primary reviewer completes the IRB determination checklists. Checklists are uploaded by the assigned primary reviewer and are retained in the IRB action's "Committee Review Activity."

### 3.7 Confidentiality of the Review Process

During the process of initial, continuing review, or amendment of an activity, material provided to the IRB and ORSC shall be considered privileged information and the IRB shall assure the confidentiality of the data contained therein.

### 3.8 Conflict of Interest

#### 3.8.1 IRB Members – Convened Meeting

The IRB is charged with protecting research subjects from risks in experimental studies. Principles codified in the Nuremberg Code, the Declaration of Helsinki, Belmont Report, and existing Uzbek and U.S. federal regulations are employed to provide a framework for ethical considerations and assessment of risk and benefit in individual studies. The decisions made by the IRB are guided by these principles, but the IRB can only be successful if members are free of conflict of interest (COI).

Prior to discussion of protocols at a convened meeting, the IRB Chair will ask if any member has a COI with any protocol being discussed at that meeting. A conflict of interest may include financial interests of the IRB member or immediate family members (spouse, domestic partner, and dependents) without any de minimus, as well as nonfinancial issues, such as involvement in the design, conduct, or reporting of the research. A financial interest exists when the member has financial relationship with the sponsor, product or service being tested.

Should an IRB member declare involvement in any way in a research protocol under review by the IRB, or state a COI with the research protocol the following is required:

1. IRB member is excluded from discussion and voting except to provide information requested by the IRB.
2. IRB member leaves the meeting room during discussion and voting.
3. IRB member is not counted towards quorum.

IRB members with a conflict are documented in the minutes as being absent with an indication that a conflict of interest was the reason for the absence.

#### 3.8.2 Designated Reviewers for Expedited Review

IRB members (including experienced IRB staff members) who have been designated by the IRB Chair as reviewers for initial or continuing review of research protocols, reports of noncompliance, protocol deviations, unanticipated problems, and amendment requests that qualify for expedited review will self-identify any COI that they may have with the research or PI. In such cases, the review responsibility will be reassigned to another experienced IRB member.

#### 3.8.3 Examples of IRB Member COI

IRB members are considered to have a conflict of interest if they:

1. Are involved in the design, conduct, or reporting of the research study.
2. Have direct administrative powers over the investigators or the study.
3. Have a financial and/or ownership interest of any amount in or related to the research and the value can be readily determined.
4. Have a financial and/or ownership interest in or related to the research but the value cannot be readily determined.

5. Received or will receive compensation and/or have ownership interest of any amount with value that may be affected by the outcome of the study.
6. Have received in the past year, currently are receiving, or will receive from the sponsor of the study, honoraria, payments, or compensation of any amount.
7. Have a proprietary interest in the research, including but not limited to a patent, trademark, copyright, or licensing agreement.
8. Serve as directors, board members, scientific advisors or hold other decision making positions in the entity sponsoring the research.
9. Are not an investigator, co-investigator, or consultant on a study, but are closely associated with the investigators on the study being reviewed, or other studies.
10. Have personal, familial, or intimate relationships with the principal investigator.
11. For any reason, believe they cannot be objective concerning a study.

### 3.8.4 Principal Investigator and Research Staff

PIs and their research staff are required to disclose financial interests in according to the Center's COI policy. The COI Office will review disclosures to determine whether a real or perceived financial interest in research exists (interest in the sponsor, produce or service being tested). Records of disclosures and management plans are maintained according to RSSPMC of Hematology record retention requirements and for a minimum of 3 years from the completion of a related research project.

The IRB will adhere to the following policies regarding conflict of interest requirements for research staff engaged in human subjects research.

**Exempt research:** PIs who have a potential financial conflict of interest relating to the submitted study are required to submit Research Certifications confirming financial disclosures are current.

When reviewing initial exempt submissions or changes to PI on exempt submissions, IRB staff will review the PI's response to the financial conflict of interest prompt in the exempt submission form or provided via feedback and if a potential financial conflict of interest is identified, the IRB staff will initiate the COI certification process. IRB staff will verify COI review is complete prior to issuing an exempt determination letter.

**Non-exempt research** (i.e., expedited and full board research): PIs and research staff identified by the PI as Covered Individuals are required to submit Research Certifications confirming financial disclosures are current.

When reviewing initial submissions and modifications to non-exempt research adding personnel identified as Covered Individuals, IRB staff will identify the PI and research personnel designated as Covered Individuals and initiate the COI Certification process. IRB Staff will verify that PIs and Covered Individuals have completed their Research Certification and that the COI review is complete prior to final IRB approval.

Covered Individuals are defined as individuals who, regardless of title or position, have decision making authority related to the design, conduct, reporting, review, or oversight of research.

An assessment of potential conflicts of interest for each Covered Individual on a study will be completed by the COI Office, as applicable. Disclosed financial interests that might affect the protection of subjects or the objectivity of the research must have a management plan in place. Management plans may include: partial or complete divestment, limiting involvement of the conflicted individual, additional oversight, or disclosure. The COI Office determines if formal COI management strategies are required. The COI Office will work with the researcher to develop and finalize a COI Management Plan. When finalized, the COI Management Plan will be submitted to the IRB for review and final approval. The IRB may impose additional management strategies to further protect research subjects. Under no circumstances will research be approved until the IRB has reviewed and approved the COI Management Plan.

### 3.8.5 Institutional Financial Interests

Institutional COIs are handled according to the RSSPMC of Hematology's Institutional Conflict of Interest in Human Subject Research policy. Management plans pertaining to institutional conflicts of interest will be reviewed by the convened IRB for final approval of elements related to the human subject research being conducted.

Institutional COIs are identified by the ORSC COI program through evaluation of annual personnel disclosures, as well as internal communication and verification processes between all RSSPMC of Hematology departments. The Objectivity in Research Committee (ORC) is responsible for reviewing potential institutional conflicts of interest and for developing management strategies.

## 3.9 Interaction with Other RSSPMC of Hematology Components and Commencement of Research Activities

The successful fulfillment of the Center's intent to protect human research subjects is dependent upon open communication among various institutional components. These committees and offices exchange information, when necessary, to assure that, in addition to IRB review, human subjects research receives all appropriate review prior to implementation of the research activities. Human subjects research is not allowed to commence until all applicable reviews are complete and notification of approval is received by the IRB.

### 3.10 Types of Research Conducted at the RSSPMC of Hematology

The Center supports a broad range of human subjects research including, but not limited to biomedical research and clinical trials, social behavioral and education research, research with vulnerable populations and international research. As a practice, the RSSPMC of Hematology does not currently conduct classified human subject research.

### 3.11 Categories of Research Subjects

Participants in research conducted by faculty, staff, and students at RSSPMC of Hematology include a diverse group of individuals from the local community, throughout the Republic of Uzbekistan. They reflect the communities in which research is conducted and include individuals who represent different racial, ethnic, and cultural backgrounds and who speak languages other than English. Some participants are considered healthy adults, while others are members specifically identified and protected vulnerable populations (such as children, pregnant women, and prisoners) and other groups of individuals entitled to special safeguards (such as those who are decisionally impaired or economically or educationally disadvantaged).

## 3.12 Determining if IRB Review is Required

### 3.12.1 Determination of Human Subjects Research

Most of the time, it will be obvious whether or not the Center and a PI are engaged in human subjects research. However, at times, the IRB staff (consulting with the ORSC Director, Chair, or Vice Chair, if needed) will need to determine if the proposed activity constitutes engagement in human subjects research. The first determination is whether or not the activity proposed is research under each funder's definition for research or clinical trial study. The second determination to be made is whether or not human subjects are involved. The determination is made by using the appropriate definitions found in Section 2 of this manual. The ORSC will accept requests for determinations by phone or email. Information required to make the determination includes a description of the activity, data collection methods and the research setting. Further information may be requested. Determinations of whether or not activities constitute human subjects research will generally be relayed to investigators immediately for phone requests, and within five work days from the date of receipt of the email for written requests. IRB staff will also determine if the proposed research must be reviewed by the IRB. If researchers require an official determination of not human subjects research (NHSR) from the IRB (e.g., sponsor requirement), a submission must through official means. It is strongly recommended that researchers contact IRB staff with any questions.

According to U.S. HHS regulations, the Center becomes engaged in human subjects research when its employees or agents (i) intervene or interact with living individuals for research purposes, or (ii) obtain individually identifiable private information about those individuals for research purposes. Under U.S. FDA regulations, the institution becomes engaged in human subjects research when it undertakes a clinical investigation on individuals who are or become subjects in the investigation, either as recipients of a test article or as controls and may be either patients or healthy non-patients.

PIs are automatically considered to be “engaged” in human subjects research whenever they apply for or receive a direct U.S. federal award to support research that includes human subjects, even if all the activities involving human subjects will be carried out by a subcontractor or collaborator. In all cases the institution to which the grant has been awarded bears the responsibility for protecting human subjects under the award.

### 3.12.2 Class Projects

Class projects typically do not meet the definition of human subjects research. As such, IRB review may not be required.

### 3.12.3 Oral History Projects

The following is based on guidance received from OHRP:

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution's U.S Federal-wide Assurance (FWA) and U.S. HHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the PI and the definition of “research” under U.S. HHS regulations at 45 CFR 46.102(d): “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Specifically, for the purposes of this policy in order to be subject to the Center's human research protections policies, the activity must meet the following standards and general principles for evaluating Oral History type activities:

1. The activity involves a prospective research plan which incorporates data collection,



- including qualitative data, and data analysis to answer a research question; and
2. The activity is designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.
  3. Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) would constitute “research” as defined by 45 CFR 46. For example, an open-ended interview of surviving War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings would require IRB review and approval.
  4. Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Since the intent of the archive is to create a repository of information for other investigators to conduct research as defined by 45 CFR 46, the creation of such an archive would constitute research under 45 CFR 46. For example, open ended interviews are conducted with survivors of a natural disaster in order to create an archive for future research. The creation of such an archive would constitute research under 45 CFR 46 since the intent is to collect data for future research.

Conversely, oral history activities, such as open-ended interviews, that only document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings would not constitute “research” as defined by 45 CFR 46. For example, an oral history video recording of interviews with Genocide survivors is created for viewing in the Genocide Museum. The creation of the video take does not intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Genocide and provide a venue for Genocide survivors to tell their story.

PI’s are advised to consult with the IRB staff regarding whether their oral history project requires IRB review and approval.

### 3.13 Coded Private Information as it Relates to Human Subjects Research

The OHRP does not consider an institution or PI to be engaged in human subjects research if the PI consults or collaborates on human subjects research by obtaining coded private information or human biological specimens from another institution, engaged in the research, which retains the code.

However, one of the following four conditions must be met:

1. The key to decipher the code is destroyed before the investigator receives the coded information.
2. The consulting or collaborating PI and the holder of the key enter into an agreement prohibiting release of the key under any circumstances.
3. The releasing institution has IRB-approved written policies and procedures applicable to



the research project that prohibit release of the key to consultants or collaborators under any circumstances.

4. There are other legal requirements prohibiting release of the key to consultants or collaborators.

For help determining if research involving biospecimens would meet the definition of human subjects research, see the U.S. National Institute for Health Infographic: Research Involving Private Information or Biospecimens: <https://grants.nih.gov/grants/policy/hs/private-information-biospecimens-flowchart.pdf>.

OHRP also does not necessarily consider authorship as a factor in determining whether or not an institution is engaged in human subjects research. It is possible that the authors of a paper or presentation were not involved in obtaining “data about subjects of the research through intervention or interaction with them” or “identifiable private information about the subjects of the research.” If a PI simply receives unidentifiable or coded information about human subjects, OHRP has determined that analysis of the information and/or publication of conclusions based on analysis of the information does not constitute being engaged in human subjects research.

### 3.14 Undue Influence of the IRB of ORSC Staff

It is the policy of the RSSPMC of Hematology that the human subjects research review process and implementation of IRB policies and procedures are conducted objectively and without undue influence over deliberations or processes. Individual members of the IRB whether employed by the institution or community members, as well as HRPP staff, have the right and obligation to report any undue pressure upon them to make decisions that would favor an individual PI over subject protections, during the initial and continuing review processes or when conducting or participating in other IRB related business. The IRB member or HRPP staff person is asked to document the issues related to the case in writing to both the ORSC Director and the IO in order to open a formal report. The IO will formally review the information and may convene a meeting and/or otherwise obtain additional information as necessary. The ORSC Director will then subsequently inform the IRB of the findings. The IO has the authority to take corrective action in consultation with the IRB.

### 3.15 Training Requirements

#### 3.15.1 Researchers and Research Staff

The RSSPMC of Hematology HRPP policy requires training for all faculty, faculty mentors, researchers, and students, including researchers from other institutions who wish to conduct human subjects research at the Center. All personnel, originally listed or later added to a study through an amendment/modification, must complete human subjects research training. In order to comply with the policy, researchers are required to complete the Center’s training requirements. Completion of this training must be accomplished every three years.

In community-engaged research, academic researchers collaborate with different partners from non-academic settings. Community research partners would need to complete human subjects research training if they are engaged in the conduct of research involving human subjects (e.g., interacting with research participants, handling identifiable research data). Please consult the IRB staff to discuss appropriate training options.

Protocol submissions (initial, continuing, amendments) are checked to assure all researchers and research staff have completed training. Protocol actions are not approved until training is completed by all listed on the protocol. Webinars and local conferences are made available to the RSSPMC of Hematology community for additional training.

### 3.15.2 IRB Members and Chairs

IRB members, their alternates, the IRB Chair, and Vice-chair must complete the required human subjects training upon being appointed to the IRB and every three years for the duration of their membership. Initial training consists of completion of modules relating to their service as IRB members. At the time of initial appointment, an ORSC staff member will schedule an in-person meeting to provide orientation information (meeting schedules, locations, etc.), discuss member duties and meeting processes, and provide copies of the following information, as needed:

- IRB Reviewer Checklist templates
- Electronic links to The Belmont Report, U.S. Code 45 CFR 46, and RSSPMC of Hematology Institutional Review Board Policies and Procedures Manual

Continuing education materials may be distributed to members at IRB meetings in the form of relevant periodicals or articles. Staff may also offer presentations or lead discussions with IRB members around relevant topics. Webinars and local conferences are made available to the members to attend.

### 3.15.3 Department Review Committee (DRC) Members

DRCs should review IRB the Policies and Procedures Manual and must complete all required human subjects protection trainings. DRCs may be invited to attend IRB meetings as necessary. Webinars are made available for additional training.

Also, upon request a member of the IRB staff will meet one-on-one with a DRC.

### 3.15.4 ORSC Staff

ORSC staff must document that they have completed all required human subjects protection trainings. Attendance at regional and national meetings is encouraged and supported for ORSC staff. ORSC staff are encouraged to attend any additional training, such as webinars, that are offered by ORSC. IRB staff are highly encouraged to obtain IRB Certification (Certified IRB Professional (CIP)) as they become eligible.

## 3.16 Roles and Responsibilities

### 3.16.1 Principal Investigators

The following are the PI responsibilities and are not all inclusive:

1. Assure that all personnel listed on the research protocol have completed the [human subjects research training](#).
2. Assure that all covered individuals listed as research personnel on non-exempt protocols have submitted a [Financial Interest Disclosure](#).
3. Submit protocols for IRB review and approval of proposed research activities prior to commencing the research activities.
4. Employ sound study design in accordance with standards of the PI's discipline.
5. Assure that adequate time and resources are present before conducting a research study to assure participant protections.
6. Maintain appropriate oversight of each research study, as well as research staff, and

- appropriately delegate research responsibilities and functions.
7. Ensure that the research is conducted according to the protocol, any signed agreements, in compliance with all applicable laws and regulations and organizational policies and procedures with the highest of ethical standards.
  8. Submit for review and approval all proposed protocol and consent form changes prior to implementing the changes in the protocol except where necessary to eliminate apparent immediate hazards to human subjects.
  9. Obtain legally effective informed consent from subjects prior to commencement of research activities, unless the requirement is waived by the IRB.
  10. Ensure the rights, safety and welfare of the research subjects are upheld and protected.
  11. Follow reporting requirements for problems that require prompt reporting (see Section 24).
  12. Submit requested data at specified times for continuing review of ongoing research activities.
  13. Upon completion of a study, honor all commitments that were agreed to as part of the approved research, e.g., providing information about the study results to research subjects or honoring commitments for reimbursements to subjects.
  14. Upon completion of a study, submit a Closure Report to the IRB.
  15. Disclose all conflicts of interest.
  16. Retain records as required by the regulations, the sponsoring entity and local policy for the appropriate time period (See Section 3.21 Record Retention).
  17. When PI is the lead researcher for a multi-site study, applications must include information about the management of information that is relevant to the protection of research participants, e.g., interim results; protocol modifications; how unanticipated problems involving risks to participants or other unanticipated problems will be managed.; how communication of unanticipated problems to all sites will occur; how protocol modifications will be managed; is there a formal agreement in place delineating each site's roles and responsibilities.
  18. If the PI holds an IND/IDE, adhere to sponsor responsibilities in addition to investigator responsibilities.
  19. If appropriate, assure that applicable clinical trials and sponsored clinical trials are registered on the Uzbek governmental database. See section 27.1 for more information.
  20. Resolve research participant's concerns, complaints, or requests for information.

### 3.16.2 Faculty Principal Investigators for Student-led Research

The RSSPMC of Hematology requires all research to be conducted under the guidance of a qualified Principal Investigator. As a teaching institution, students will be engaged in conducting research as an integral part of their educational experience. Faculty who assume PI responsibility for student-led research involving human subjects must be willing to provide oversight to the research activities and assume full responsibility for the conduct of the research. The Faculty PI must be actively involved in the research, from protocol design to data analysis and report preparation. In many cases, it may be the student's first experience with formal research. The success of the student's experience will be measured not only in the outcome of their projects, but also in what they learn from the faculty sponsor. These experiences will help form their perception of scientific research, and in some cases, determine whether a career in academic research is right for them. The following are the Faculty PI responsibilities and are not all inclusive:

1. Advise the student on the selection of a topic, the content and preparation of their research proposal. Understand the research hypothesis, goals and methodology. Guide and interact with the student throughout the research project.
2. Assist the student with the preparation of the IRB application. As the PI on the project, submit the application to the IRB. Ensure the student obtains all necessary approvals (i.e., IRB) before initiating the project, implementing any changes in the research activities and continuing the research activities after the approval period has expired.
3. Assume full oversight of the IRB protocol and ongoing when the student leaves the institution prior to completing the research protocol.
4. Ensure that the student is provided with, or has access to, information on RSSPMC of Hematology policies relating to administration of their protocol.
5. Assure the student understands the underlying ethical principles for conducting research with human subjects and the applicable research regulations and local policies and procedures. Stay abreast of the status of the protocol and ensure on-going compliance with regulations and institutional policies and procedures relating to human subjects research and IRB required reporting.
6. Advise and assist students with the preparation of poster presentations and papers, as applicable.
7. Ensure that all study documents and data are archived at the end of the study in accordance with official policy and regulations.
8. Be available to the student during the active research period.

### 3.16.3 Departmental Review

Review of human subjects research for scientific or scholarly validity is conducted by the IRB on all non-exempt research. However, some departments elect to have a departmental review process for human subjects research conducted within their department. Departmental review occurs outside of the IRB review process per processes set by the individual department.

### 3.16.4 Institutional Official

The IO is designated by the RSSPMC of Hematology Director to have responsibility for the Human Research Protection Program with the authority to delegate activities as may be necessary to fulfill the following responsibilities:

1. Assure compliance with institutional policies and all applicable regulations for the protection of human research subjects.
2. Is legally authorized to represent the institution in matters regarding human subjects research and is the signatory authority for all the Uzbek & U.S. Federal-Wide Assurance to the Office for Human Research Protections.
3. Responsible for review and evaluation of reports on HRPP performance and QI activities.
4. In collaboration with the Director, ORSC, periodically evaluates the resource needs of the HRPP.
5. Responsible for further institutional review and approval or disapproval of research approved by the Center IRB (neither the IO nor any other Center official can approve research that was disapproved by the IRB).

### 3.16.5 Institutional Review Board

IRB main responsibilities in safeguarding the rights and welfare of subjects are as follows and are not all inclusive:

1. Conduct review of initial protocol submissions, continuing reviews, and all revisions to protocols of human subjects research conducted by the Center researchers.
2. Approve, require modifications to secure approval, defer (table), or disapprove research activities overseen and conducted under the auspices of the Center, regardless of location of the research activities.
3. Systematically analyze protocols for benefits to subjects and importance of knowledge to be expected and assess the potential benefits in relation to the potential risks involved in the research.
4. Report in writing the findings and actions of the IRB to the PIs, IO, and, when applicable, to federal regulatory agencies or departments, as necessary.
5. Determine the interval at which ongoing studies need to be reviewed by the IRB.
6. Determine which studies need verification from sources other than the researchers that no material changes have occurred since the previous IRB review.
7. Observe, or have a third party observe, consent processes and/or the conduct of research.
8. Ensure prompt reporting of any changes in research activities to the IRB by researchers.
9. Ensure prompt reporting (within 30 days of the determination), by PIs, to the IRB and/or government agencies or departments (where applicable) of:
  - a. Unanticipated problems involving risks to subjects or others.
  - b. Serious or continuing noncompliance with regulations.
  - c. Suspension or termination of IRB approval.
10. Determine if studies involving drugs need an investigational new drug (IND) number designated by the Uzbek Center for Pharmaceutical Products Safety (UCPPS).
11. Determine if studies involving investigational devices pose significant or non-significant risk and whether an IDE is required.
12. Suspend or terminate approval of research not being conducted in accordance with IRB requirements or that has been associated with unexpected serious harm to subjects.
13. If applicable, act as the Privacy Board for research involving use of PHI.

### 3.16.6 IRB Chair and Vice Chair

IRB Chair and Vice Chair main responsibilities are as follows and are not all inclusive:

1. Serve as public spokesperson for the IRB.
2. Chair convened meetings of the IRB.
3. Ensure adequate expertise for review and determinations.
4. Assure a quorum is present for all meetings.
5. Review protocols, continuing review reports, unanticipated problem and deviation reports, and other documentation submitted to the IRB.
6. Obtain an individual vote on all IRB actions (For, Against, Abstain).
7. Vote on each IRB action
8. Delegate review responsibilities as necessary and applicable.
9. Maintain up-to-date knowledge of human subjects regulations and pertinent events.
10. Consult with investigators as necessary.
11. Suspend the conduct of research when individuals are placed at an unacceptable level

of risk.

12. Collaborate with ORSC staff to provide continuing education for IRB members.
13. Collaborate with the ORSC Director to resolve IRB-related issues with faculty or subjects.
14. Recognize and support partnership with ORSC to assure IRB efficiency and effectiveness.

### 3.16.7 IRB Members

IRB members responsibilities are as follows and are not all inclusive:

1. Be familiar with IRB policies and procedures and national/international regulations policies or guidelines relating to human subjects research.
2. Review submitted proposals as assigned by the Chair or Chair's designee.
3. Review meeting documents in advance of IRB meetings and be prepared for discussion of submitted protocols.
4. Act as a primary or secondary reviewer of protocols when assigned.
5. Maintain confidentiality of IRB proceedings.
6. Disclose conflicts of interest, if applicable.
7. Attend a minimum of 75% of scheduled meetings.
8. Maintain current human subjects training.
9. Actively engage in continuing education related to human subjects research.

### 3.16.8 Medically/Psychologically Responsible Investigator

If research procedures involve clinical elements and the PI is not qualified in the appropriate clinical area, does not hold an applicable license, or does not have privileges to practice where the research will occur, a licensed and institutionally credentialed clinician appropriately qualified by education, training, experience, and background and appropriate privileges must be designated as the Medically/Psychologically Responsible Investigator.

The Medically/Psychologically Responsible Investigator must manage or appropriately delegate all clinical elements of the research such as physical examination, psychological testing, providing counseling services, conducting any drug administrations, follow-up examinations, evaluating lab values, test results and reviewing all adverse events.

Clinical elements of a study are considered any event, procedure, test, or intervention that would require performance by a licensed/credentialed professional in a non-research setting.

During review of human subjects research, the IRB can determine that a Medically/Psychologically Responsible Investigator must be identified. The Medically/Psychologically Responsible Investigator should be noted by name in the research proposal and listed as research personnel. A copy of the Medically/Psychologically Responsible Investigator's CV should be submitted too. The Medically/Psychologically Responsible Investigator's contact information should also be included in the informed consent document(s).

### 3.17 Monitoring/Verification of Compliance from Sources Other than the PI

In accordance with Uzbek and U.S. regulations, it is incumbent upon the IRB to assure itself, by whatever method it deems appropriate, that the rights and welfare of human subjects are being protected. This applies to transnational research and research taking place outside of Tashkent. In doing so, the IRB may determine that it is appropriate to use sources other than reports from the investigator to verify that no material changes in the protocols have occurred since their most recent review, and that investigators are conducting the research in compliance with all regulations, laws (domestic and

international), policies, and guidelines. Also, the IRB may determine that the consent process for some higher risk protocols should be observed.

To assess whether there have been no material changes in the protocols as stated above, the IRB may request that members of the IRB and/or ORSC staff conduct an observational visit for a specific protocol. This review will help ensure that investigators are not implementing protocol changes prior to IRB review and approval, except when necessary to eliminate apparent immediate hazards to subjects.

As a part of an ongoing Quality Improvement (QI) program, monitoring reviews may be initiated in other ways:

1. The QI staff may randomly select protocols from a list of currently approved protocols;
2. The PI or the PI's department may wish to have research protocols reviewed proactively for compliance;
3. The IRB may determine that verification of compliance is required because the protocol is very complex and involves unusual levels or types of risk to subjects;
4. A relatively high risk protocol is being conducted by a PI who is inexperienced in human subjects research;
5. A protocol is being conducted by an investigator who previously failed to comply with regulations, the protocol, local policy, or IRB determination; or
6. Other reasons primarily related to subjects' risk and safety.

Upon completion of the QI visit, the results will be reported to the ORSC Director. The PI will be queried for a response to the findings of the visit, if applicable. The report and if requested by the IRB, the PI's responses will be brought to the IRB at a convened meeting for discussion and action. If the report indicates suspected or observed incidents of noncompliance, procedures outlined in Section 22 of this manual will be followed for investigation of possible noncompliance.

### 3.18 Contacts for Questions, Concerns, Complaints or Input

Faculty, research staff, students, and research subjects or any other person who has a question, concern, complaint, suggestion, or input regarding the HRPP or feels that they have been subjected to coercion or undue influence regarding aspects of human subjects research, or feels that they have observed issues of concern regarding human subjects research, may contact the ORSC:

Office of Research Support and Compliance

The rsspmc of Hematology, Tashkent,

Arnasay 16A

Phone: +998955157572

IRB Helpline: +998909794937

E-mail: [righatm.uz@gmail.com](mailto:righatm.uz@gmail.com)

IRB:

Email: [irbhematology@gmail.com](mailto:irbhematology@gmail.com)

Website: [https://hematology.uz/uz\\_irb.html](https://hematology.uz/uz_irb.html)

Any and all concerns, complaints, input or suggestions regarding the Human Research Protection Program and all allegations of coercion, undue influence or noncompliance are thoroughly investigated and, if applicable, corrective actions taken to rectify the situation. Ultimately, the ORSC Director is



responsible to assure that all concerns, complaints, and allegations have been addressed appropriately and that input and suggestions related to the HRPP are considered when reviewing the program. The ORSC staff will seek to resolve any complaints, in collaboration with the PI as needed. If it appears that the concern/complaint could be an incident of noncompliance, further inquiry will follow procedures delineated in Section 22. If the concern/complaint appears to involve an unanticipated problem involving risks to subjects or others, it will be reviewed according to Section 9 of this manual.

### 3.19 Periodic Review of the HRPP and Community Outreach Programs

#### 3.19.1 HRPP

The ORSC Director, with input from the IRB Chairs will periodically review the composition of the IRB and determine whether it is appropriate for the volume and types of research being reviewed to assure thorough and timely IRB review. Recommendations for the appointment of new members and removal of members will be forwarded to the IO. The ORSC Director will annually consider whether or not the resources and personnel being provided in support of the HRPP are adequate and advise the IO as necessary. Additionally, the ORSC Director will evaluate allocated space, personnel resources to support the HRPP, the availability of legal counsel and the process for assuring that all applicable personnel involved in the HRPP have completed required training and submitted financial interest disclosures.

The ORSC Director will periodically review HRPP policies and procedures and make adjustments as necessary. Comments from research faculty and staff regarding the HRPP will be reviewed as they are received by the IRB Chair, Vice-Chair, ORSC Director, and, if necessary, the IO. If applicable, modifications to the HRPP will be made and implemented and the effectiveness of the implemented changes monitored and discussed at appropriate intervals.

Oversight of the HRPP includes implementation of a quality improvement function to continually assess compliance and effectiveness of the HRPP, and the IRB in particular. The goal of this program is to ensure the HRPP is functioning in full compliance with applicable regulations using processes and procedures that are effective and efficient so that the system facilitates the highest quality of research. This assessment process includes the following components:

- Defining at least one objective for achieving or maintaining compliance and at least one objective for enhancing quality, efficiency, or effectiveness.
- Defining at least one measure of compliance and at least one measure of quality, efficiency, or effectiveness.
- Describing the methods to assess compliance and make improvements, as needed, and methods to assess quality, efficiency, or effectiveness to make improvements.

Examples of assessing compliance might include:

- Evaluating IRB meeting minutes for compliance with quorum requirements, accurate documentation of votes and recusals, and accurate documentation of regulatory findings;
- Assessing IRB reviews and corresponding documentation to ensure the appropriate review category has been determined, regulatory criteria for approval are appropriately met, and appropriate documentation is maintained;
- Assessing IRB reviews of research with additional sponsor requirements or vulnerable



- populations to ensure requirements are met and documented appropriately; and
- Reviewing study documentation and reliance agreements for compliance with policies and procedures.

Examples of assessing quality, efficiency and effectiveness might include:

- Determining whether IRB time to approval is within institutionally identified goals and comparing with AAHRPP accredited peers;
- Evaluating the amount and quality of IRB feedback provided to researchers; and
- Evaluating research community and IRB member needs for training and guidance.

The Director of ORSC, the Director of the HRPP, and the Quality Assurance Manager are responsible for identifying objectives and measures for quality assurance and quality improvement (QA/QI). The outcomes of QA/QI efforts are documented and reviewed via quarterly QA reports and periodic HRPP progress reports.

### 3.19.2 IRB Members and ORSC Staff

The ORSC Director, in consultation with the IRB Chairs, periodically reviews the HRPP, including IRB Members, IRB member feedback, and any input from outside the IRB and provide recommendation(s) to the IO regarding the recruitment, retention, or dismissal of members. This review includes examination of attendance, specialty, expertise, education, affiliation, and diversity. A summary of the evaluations and member comments will be submitted through the ORSC Director to the IO.

The ORSC Director will be evaluated and provided feedback annually by the IO. IRB staff will be evaluated and provided feedback annually by their direct supervisor (e.g., IRB Manager, Assistant Director).

### 3.19.3 Community Outreach

ORSC dedicates a section of its website, entitled “For Research Participants” to current and prospective research participants. This section of the ORSC website includes resources such as “Frequently Asked Questions,” downloadable Center brochures in Uzbek, Russian, and English regarding research participation, and links to relevant source documents and websites relating to volunteering as a participant in research. There are also links to the [OHRP downloadable brochures](#) intended to inform the general public about research participation. Contact information (phone, email, and mailing address) for the IRB office is also included should participants wish to connect with the IRB office. The ORSC Director, HRPP Director, or designee(s) will evaluate, make changes, and implement changes to the outreach program and resources as needed. These individuals may consider any complaints, concerns, suggestions, and other input from participants or others within the research community and consider other departmental outreach efforts on the Center. Periodic assessments of outreach efforts are done at least biannually, and more frequently, if needed, as determined by the ORSC Director, HRPP Director, or designee(s).

### 3.20 Record Retention Policy at The RSSPMC of Hematology

In order to allow a reconstruction of a complete history of IRB actions related to the review and approval of protocols, the IRB records include copies of:

- Protocol applications, research protocols, consent documents, recruitment materials, investigator brochures, and all other documents submitted for review of proposed human subject research
- Scientific evaluations, when provided by an entity other than the IRB
- IRB meeting minutes
- Progress reports submitted by researchers
- Reports of injuries to participants
- Data and safety monitoring reports, if any
- Modifications to previously approved research
- Records of continuing review activities
- Unanticipated problems involving risks to subjects or others
- Documentation of non-compliance
- Significant new findings
- All correspondence between the IRB and researchers
- Records related to IRB reliance, including agreements, local context documents, and documentation of the rationale for not utilizing a single IRB for cooperative research when subject to Uzbek and U.S. federal requirements.

IRB records document all IRB determinations including, but not limited to, those required by laws, regulations, codes, and guidance. IRB records for initial and continuing review of research by the expedited procedure include the justification for using the exempt and expedited procedure and actions taken by the reviewer.

Records are accessible for inspection and copying by authorized representatives of governmental agencies or departments at reasonable times and in a reasonable manner.

Records related to HRPP operations and all research records are retained for at least three years after completion of the research. If a protocol is cancelled without participant enrollment, IRB records are maintained for at least three years after cancellation.



## Section 4: Subject Recruitment and Participation

### 4.1 General Recruitment Guidelines

In some cases, the information in recruiting materials may constitute the earliest components of the informed consent process. In addition to its review for scientific merit and protection of subjects from unnecessary research risks, the IRB will evaluate all protocols for equitable and non-discriminatory subject recruitment. When inclusion is inappropriate with respect to the safety or well-being of the subjects or the purpose of the research justification for exclusion of particular groups will be considered and approved. The IRB will also consider the scientific and ethical justification for exclusion of classes of persons who might benefit from the research and determine if exclusion is justifiable and allowable.

There are several questions in the IRB application in which the Principal Investigator (PI) must describe the proposed study population, the number of subjects to be enrolled, and the procedures to be used for recruitment. In addition, all materials used to recruit subjects must be reviewed and approved by the IRB. These would include written advertisements and the amount of reimbursement (See Section 4.8 Compensation for Research Subjects) to be given to subjects to compensate for their time and inconvenience, parking, travel, etc.

### 4.2 Advertisements

The IRB must review and approve the information contained in all advertisements that will be used to recruit subjects for a specific research study and the mode of their communication. Generally, advertisements used to recruit research subjects should be limited to information that a potential subject would need to determine if they are eligible and interested in participating. More specifically, the advertisements should include information such as:

1. The name and address of the investigator and/or research facility.
2. The condition or disease that will be the focus of the research.
3. The purpose of the research with reference to the fact that the study is investigational.
4. If any, a brief list of potential benefits of participation.
5. A summary of criteria for eligibility to participate.
6. The time and other commitments that will be required of the subject.
7. The location of the study and the office to contact for further information.
8. If any, state that reimbursement for time, travel, etc. will be given.

The advertisement should not contain:

1. Emphasis on the amount of reimbursement that subjects will receive by bolding or using large fonts. The ads may state that reimbursement for time, travel, etc. will be given.
2. Exculpatory language where the subjects would be required to give up some of their rights.
3. A promise for a favorable outcome or benefits.
4. The concept promoting that the subjects will be receiving medical treatment at no cost (free medical treatment) since the reality is that they will not be charged to participate in a research project.
5. Explicit or implicit claims of equivalency or superiority to other standards of treatments or safety and efficacy.
6. Wording that the study involves “new treatment”, “new Medication, or “new drug” without an explanation that the treatment is investigational.

7. Claims, explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with UCPPS/U.S. FDA labeling.

Advertisements conforming to the above guidelines may be approved for any advertising format, e.g., posted flyers, newspapers, internet advertisements, radio/television, slides shown prior to films at movie theaters. However, the IRB must review the final copy of printed advertisements to evaluate the relative size of font type used and other visual effects and must review the script of the final audio or video taped advertisements. To avoid multiple requests for IRB review and approval, investigators should specify in their original request all advertising formats that are anticipated. If a website is to be used to advertise for a research study, the website address must be identified to the IRB.

When following UCPPS/U.S. FDA regulations, the IRB reviews advertising to ensure that advertisements do not allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

#### 4.3 Pre-Screening

Some research may require a pre-screening process in which potential subjects are asked for personal and sensitive health information to determine eligibility for the study. Questions asked during this pre-screening process are subject to IRB review, in particular, to determine if proper procedures are in place for protecting the privacy and confidentiality of the information collected. In addition, if more than the above listed information is present, the IRB must evaluate whether or not the description of potential risks and benefits is presented in a fair and balanced manner. The IRB must also assess the types of incentives, if any, that are offered, whether or not the site clearly states that the trial is voluntary, and other subject protection issues.

#### 4.4 Recruitment of Students and Staff

The RSSPMC of Hematology students/staff have the same rights as any other potential subject to participate in a research project, irrespective of the degree of risk, provided all of the following conditions exist:

1. Recruitment should not be conducted in ways that students may reasonably perceive undue influence.
2. The research must not bestow upon participating Center subjects any competitive academic or occupational advantage over other students or staff who do not volunteer. The researchers must not impose any academic or occupational penalty on those not volunteering.
3. Due to the potential for perceived or undue influence to participate, Center students and staff who desire to participate in the research must not be under the direct supervision of anyone who has access to identified data (e.g., researchers, those collecting data).
4. If incentives for participation are offered (e.g., extra course credit), the incentives should not be so large as to cause undue influence. Typically, this means that any credit or extra credit must be only a small portion of the total grade. When extra course credit is offered, an alternative method requiring similar time and effort instead of research participation must be offered.

## 4.5 Researchers Recruiting from Their Own Courses

One particular circumstance that raised special ethical concerns involves researchers recruiting students from courses that they are teaching. The primary issue with gathering data from one's own course is the potential for undue influence.

### 4.5.1 Potential for Undue Influence

Instructors have inherent power over students (e.g., through their responsibility for assigning grades). Because of this power relationship, it is likely that some students will feel pressure to comply with requests made by their instructors. This is true independent of whether the instructors actually try to pressure the students. For example, when instructors ask students to participate in research projects, some students may worry that not participating could influence the instructor's opinion of them or that their grade might be affected. Such potential concerns are problematic regardless of whether the instructor actually should think negatively of nonparticipation or whether the students' grades actually would be affected. Students' perceptions that such negative consequences could happen are enough to make them feel pressure to participate.

### 4.5.2 Reducing the Potential for Undue Influence

In the rare instances in which recruiting from one's own class is permissible, researchers are expected to minimize the potential for students to feel pressured to participate. There are various strategies for minimizing the potential pressure to participate. One way that researchers have reduced the potential to cause undue influence is to design the study so that the instructor is blind to the identity of the participants (at least until after the final grades have been assigned). For example, a researcher can run the study and keep any identifying information from the instructor. If a researcher designs a study in this way these points are crucial:

1. Before being asked to participate, potential subjects should be informed that the instructor will not know who did and who did not participate (at least until after the final grades have been assigned).
2. The research should be designed so that the instructor cannot infer who participated through indirect means (e.g., by seeing who walks into the laboratory, by getting a list of who earned extra credit for participating in the study).

In short, due to the potential for undue influence, researchers generally should avoid recruiting subjects from their own classes. When recruiting from their own class is the only feasible way to do a study, researchers are expected to design the research in such a way that the potential for students to feel pressure is minimized.

### 4.5.3 Exceptions

There are cases in which the research cannot be feasibly completed without recruiting students from a particular course. For example, if the research project concerns a teaching method that will be implemented in the course, then the only possible subject pool comes from the students enrolled in that course. If a research project has a reasonable chance of yielding benefits, and the only feasible way to complete the study is to recruit in the researcher's course, the reach may be permissible if the researcher is able to sufficiently reduce the potential for students to feel pressure to participate.

## 4.6 Subject Pools

A subject pool is a research resource used by some departments and schools in academic settings as a registry of individuals who are interested in participating in research and agree to be contacted for potential participation in a study. These volunteers are used in studies for that school or department. The IRB provides guidance and oversight of departmental subject pools, and reviews all research requesting subject pool participation.

Student subject pools serve to not only provide researchers a pool from which to recruit primarily student participants for their studies, but also serve to familiarize students with the research process as subjects and researchers. Student subject pools are composed of undergraduate students enrolled in particular departmental courses that provide credit for participation in one or more research projects. All student participation in subject pool research must be completely voluntary. Departments may provide students with incentives (usually extra credit) to participate in the subject pool. However, reimbursement for participation must not jeopardize the subject confidentiality or anonymity and subject pools offering extra credit to participating students must provide alternative opportunities to earn the same extra credit for those not wishing to participate in the research. Alternatives to the research subjects should require an equivalent amount of time and effort to complete for extra credit. Subject pools including subjects under 18 years-of age are required to obtain parental permission prior to their involvement in research unless those individuals are emancipated. It is up to the student to decide whether to participate in any study; instructors cannot mandate or require student participation. As stated above, instructors are strongly discouraged from recruiting subjects they directly supervise or selecting subjects on such basis. Subject pool requirements and procedures vary by department so it is best to consult with your individual departments for specific guidelines and additional requirements.

## 4.7 Equitable Subject Recruitment

The IRB will only approve studies demonstrating equitable subject recruitment, taking into account:

- The purposes of the research,
- The setting in which it will be conducted,
- Whether prospective participants will be vulnerable to coercion or undue influence,
- The selection (inclusion/exclusion) criteria,
- Participant recruitment and enrollment procedures, and
- The influence of payments to participants.

The IRB evaluates all research applications to verify that investigators have demonstrated equitable selection and recruitment (distributive justice) of all research subjects and have made every effort to ensure diversity of subject selection. In particular, the IRB evaluates any special problems that may occur with proposed research involving vulnerable populations, such as children, prisoners, pregnant women, and decisionally impaired adults. For greater than minimal risk studies, the IRB ensures that proposed sampling efforts do not favor some classes of subjects solely due to ease of availability, compromised positions, or manipulability. IRB reviewers also require researchers to make every effort to include women and members of minority groups, if appropriate to the research purpose.

## 4.8 Compensation for Research Subjects

### 4.8.1 General Guidelines

The amount and schedule of all participant payments must be presented to the IRB for review. The IRB reviews both the amount of payment and the proposed method and timing of disbursement to assure that they are neither coercive nor present undue influence outlined in U.S. [45 CFR 46.116, 21 CFR 50.20]. Compensation can be in the form of money, course credit, or other incentives.

The IRB proposal submission should fully describe the plan for compensation of subjects as well as rationale behind amount, method, and terms of compensation, as appropriate. The informed consent document should disclose all information concerning payment, including the total amount, schedule/form of payment, and any plans for prorating payment if a subject withdraws. It should be noted that compensation is not considered a benefit to participants; therefore, this information should be stated separately from the discussion of benefits in both the protocol and consent document.

It is also appropriate to disclose possible compensation in recruitment materials. In general, payment information should not be any more prominent than other elements (see Section 4.2).

Investigators should consider the following guidelines:

- Compensation should be appropriate for the time and effort subjects devote to participation. The level of payment should not be so high as to compromise a subject's evaluation of the risks or affect the voluntariness of their choice to participate in the research.
- Similarly, if it is proposed to compensate subjects at a rate that is substantially lower than average local compensation for such activity, or to compensate subjects in one group less than another, the investigator should provide justification in the proposal. The IRB will consider individual circumstances for such situations.
- To not exert undue influence, it is often acceptable for investigators to base payment amount on the average wage in the location where the research is conducted or for the specific study population.
- In general, all subjects completing the same tasks in a single research project should be compensated at equivalent rates. In some cases, distinct subject populations may be compensated at different rates, but clear justification for this is required in the study proposal.
- Payment should be prorated for the time of participation in the study rather than delayed until study completion. Making payment conditional on completing a multi-session study could unduly influence a subject's decision to exercise their right to withdraw at any time. For studies that require extended time or multiple interactions/interventions, it is recommended that payment be prorated for the time of participation in the study rather than delayed until study completion.
- While compensation should not be contingent on completion of the entire study, may be acceptable to offer additional incentive or completion bonus to subjects that remain for the duration of the study. If offered, these amounts should be reasonable so as to not unduly influence subjects to stay in the study when they otherwise would have withdrawn. The IRB is responsible for determining that the amount is not so large as to be coercive or represent undue influence.



- Alternative forms of compensation (gift cards, certificates, other tangible gifts, class credit, online compensation can be acceptable forms of compensation and are considered by the IRB. Investigators should ensure that these methods of payment are appropriate to the target population.
- For clinical trials, UCPPS/U.S. FDA guidance prohibits payment in the form of coupons good for a discount on the purchase price of a test article (drug or device) once it has been approved for marketing.

#### 4.8.2 Use of Lotteries

The key question for researchers who want to use drawings as incentives for research participation is whether the subject's participation requires a substantial amount of time and effort. Researchers should ensure that no conditions are imposed for enrollment. This means that everyone is eligible for the drawing upon providing consent to participate in the study. If the researcher wants to impose a condition (e.g., completion of the survey) before entry is granted to the subject, then the IRB (with legal counsel if needed) will need to make the determination as to whether or not the condition(s) involve a "substantial expenditure of time and effort" on behalf of the subject.

The determination of "substantial time and effort" is made on a case by case basis and considers various factors such as the time involvement of the subject, if return visits are required, what is asked of the subject (e.g., survey completion, blood draw), etc.

#### 4.9 Finder's Fees and Bonus Payments

Finder's fees (payments to professionals in exchange for referrals or potential subjects) and bonus payments (payments designed to accelerate recruitment that were tied to the rate or timing of enrollment) are generally associated with clinical trials and are offered by the sponsor of the research as an incentive to enhance recruitment. The IRB does not permit the payment of finder's fees and/or bonus payments (monetary or in kind) in any form, due to the potential that such a practice could be perceived as causing undue influence and bordering on unethical research subject recruitment. In addition, several professional associations and groups, such as the American Medical Association have stated that this practice is unethical.

#### 4.10 Costs to Research Participants

When appropriate, a statement should be included in the informed consent document alerting the potential subject to any additional costs that may result from participation in the research, specifically if a research subject may have to bear any costs which would be unnecessary if the subject had declined to participate in the research. All potential subjects should be fully informed of the nature and estimated extent of these costs when obtaining consent.

## 4.11 Protection of Privacy for Subjects and Confidentiality of Subject Data

### 4.11.1 General

The possibility that research activities may invade the privacy of individuals or result in loss of confidentiality of their private information should always be of concern to researchers involved in human subjects research. In some cases, the risks of serious harm resulting from loss of privacy or confidentiality may exceed the physical or other risks associated with the research activity. In addition, loss of privacy or confidentiality associated with a research activity can be considered a moral wrong and can provide cause for legal actions against the investigator and/or the institution. In this regard, as part of its review of research proposals and protocols, the Center IRB considers several issues related to procedures to protect research subject's privacy and confidentiality.

### 4.11.2 Considerations and Provisions to Protect Human Subjects Privacy

When the IRB considers whether or not subject's privacy is adequately and appropriately protected in a particular study, members might consider, but not be limited to, the following:

1. The methods used to identify and contact potential subjects, the nature of the information being sought, and whether or not an invasion of privacy is involved.
2. The setting in which subjects will be interacting with the investigator.
3. The methods used to obtain information about and from subjects.
4. The nature of the information being obtained from individuals other than the "target subjects" that might result in an invasion of subject privacy (e.g., survey information about a family member).
5. Whether or not the information is publicly available.
6. Whether or not information about the subject is recorded in such a manner as to prevent identification.
7. The methods used to limit access to subject logs and signed consent forms.
8. Whether subject consent will be sought and obtained or the requirement to obtain consent meets criteria for waiver.
9. Whether signed consent forms will be kept in locked cabinets or other secure location separate from subjects' data.
10. For observational studies, chart reviews, or discarded materials studies, the subjects will not be identified.

### 4.11.3 Confidentiality Data Security Considerations

Whenever researchers promise subjects that their responses and data will be maintained in confidence, all researchers (investigators, directors, transcribers, students, and staff) are required to prevent accidental and intentional breaches of confidentiality. However, all measures used to assure confidentiality of data need to be understood by all research staff before research is initiated, and followed once research is initiated. Confidentiality procedures must be described in research applications that come before the IRB. Researchers proposing projects that will address sensitive, stigmatizing, or illegal subject matter must explicitly outline the steps they will take to assure any information linking participants to the study is maintained in confidence. The requirement of signed consent forms is often waived in sensitive studies, if the consent document is the only written record linking participants to the project and a breach of confidentiality presents the principal risk of harm anticipated in that research. When the IRB considers whether or not subject confidentiality is

adequately and appropriately protected in a particular study, members might consider, but not be limited to, the following:

1. The methods used by the investigator to ensure that information obtained is not improperly divulged.
2. The nature and adequacy of the safeguards that will be used to ensure protection of sensitive data.
3. The methods used to de-identify data.
4. Substituting codes for subject identifiers.
5. Removing names from survey instruments containing data.
6. Proper disposal of identified data at the earliest possible time.
7. Limiting access to data in locked file cabinets or password protected computer files.

#### 4.11.4 Protecting Subjects' Health Information

Use or disclosure of subjects' Protected Health Information (PHI) is generally required to have the subject's signed authorization (See Section 6.8). Even in circumstances where a waiver of the requirement for written documentation of informed consent has to be approved by the IRB, a signed authorization from the research subject permitting the use and disclosure of their Protected Health Information (PHI), may still be required. The requirement for written documentation authorizing use or disclosure of PHI may also be waived by the IRB under certain circumstances (See Section 6.9). Confidentiality is best maintained by anonymous data collection. In the event that the Privacy rule is more restrictive than the procedures described in the consent requirements, the more restrictive rule must be followed.

#### 4.11.5 Certificates of Confidentiality

In accordance with Public Health laws, the Minister of Health "may authorize persons engaged in biomedical, behavioral, clinical, or other research ... to protect the privacy of individuals who are the subject of such research by withholding, from all persons not connected with the conduct of such research, the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any national or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

Protection can be granted only to research activities, i.e., systematic investigations designed to develop or contribute to generalizable knowledge. The protection will be granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives. Research can be considered sensitive in any of the following categories if it involves the collection of information (including but not limited to):

1. Relating to sexual attitudes, preferences, or practices.
2. Relating to the use of alcohol, drugs or other addictive products.
3. Pertaining to illegal conduct.
4. That, if released, could be reasonably damaging to an individual's financial standing, employability, or reputation within the community.
5. Would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination.
6. Pertaining to an individual's psychological well-being or mental health.
7. Pertaining to qualified genetics.

Certificates of Confidentiality are issued by the U.S. NIH. Information regarding Certificates of Confidentiality is available on the NIH website at: <http://grants.nih.gov/grants/policy/coc/index.htm>.

For NIH funded research, Certificates of Confidentiality (CoC) will automatically be issued to individuals engaged in biomedical, behavioral, clinical, or other research, in which identifiable sensitive information is collected. The Notice of Award and the Grants Policy Statement will serve as documentation of the CoC. This policy is effective as of October 1, 2017 and retroactively applies to research that began on or after 12/13/2016.

NIH considers research in which identifiable, sensitive information is collected or used to include:

- All human subjects research as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46), except research that meets an Exemption and information obtained is recorded without identifiers or the identity of participants cannot be readily ascertained;
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Any research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data regardless of identifiability;
- Any other research that involves information about an individual 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.

Research Supported by U.S. CDC, HRSA, or SAMHSA, or under the authority of FDA: These agencies issue their own certificates of confidentiality. Contact the [Certificate Coordinator](#) at the funding agency to determine how to obtain a CoC.

Other Non-U.S. DHHS, Federally Funded Research and Non-Federally Funded Research: Health-related research that is not federally funded may request a CoC using the [online application system](#) hosted by NIH. The proposed informed consent form must be submitted as part of the CoC application. Direct a CoC request to the NIH Institute or Center (IC) that supports similar research. NIH recommends verifying this with the appropriate IC coordinator before submitting an application. If unsure about which IC is most appropriate for the research topic, contact the NIH Central Coordinator at [NIH-COCCoordinator@mail.nih.gov](mailto:NIH-COCCoordinator@mail.nih.gov). For additional information and guidance on CoCs including informed consent implications, see IRB guidance on [Certificates of Confidentiality](#).

It should be noted that the protection offered by a Certificate of Confidentiality is not absolute. It does not restrict voluntary disclosures. For example, it does not prevent PIs from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject threatening violence to self or others, or from reporting a communicable disease. However, if PIs intend to make such disclosure it should be clearly stated in the consent form. In addition, a Certificate of Confidentiality does not authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if:

1. The subject or the subject's legally authorized representative consents to the disclosure in writing.

2. Authorized personnel of the Department of Health and Human Services (HHS) request the information for audit or program evaluation or for investigation of HHS grants or contractors and their employees.
3. Release of such information is required by the Federal Food, Drug and Cosmetic Act or regulations implementing that act.

#### 4.12 Use of Collected Data if a Subject Withdraws from a Study

Current regulatory agencies generally agree that when a subject withdraws from a study or participation of a subject in a study is terminated by the PI, the PI is allowed to retain and analyze already collected data pertaining to the subject. The use and/or analysis of the data must fall within the scope described in the IRB approved protocol and may include identifiable private information relating to the subject.

However, PIs can choose to honor a subject's request to destroy data relating to the participant or exclude the data from further analysis. PIs are encouraged to consult with the funding agency, if applicable, to assure that requirements of the funding agency are met.

Additionally, PIs are encouraged to consider discussing during the enrollment process, verbally or in the consent form, the use or analysis of collected data if a subject chooses to withdraw from a research study. In deception research, subjects should be permitted to withdraw their data at the time of the debriefing.

For more detail information on U.S. HHS and FDA information see:

<http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html>  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126489.pdf>

#### 4.13 Specimen Collection for Research Purposes

At RSSPMC of Hematology, the IRB oversees all human subjects research, including use of human specimens for research purposes. All prospective collection of human specimens for research requires IRB approval. The secondary use of existing human specimens for research purposes can be permitted under certain circumstances. Some types of secondary use require prior review (approval or confirmation of exempt status) by the IRB. Investigators are encouraged to contact the IRB staff for guidance regarding research involving human specimens.

## Section 5: Initial IRB Review of Research Activities

### 5.1 Governing Principles/Regulations

The IRB will evaluate each proposed human subjects research project on an individual basis to assess whether or not the investigator is adequately protecting the rights and well-being of the subjects. The governing principles for the IRB derive from those described and discussed in the Belmont Report.

#### Initial IRB Review at a Convened IRB Meeting

Generally, protocols that must be reviewed at a convened meeting are considered to be more than minimal risk studies. The IRB will evaluate each project on an individual basis in order to assess whether the PI is providing adequate protection for the subjects. The assessment will be based on the initial IRB application, which includes the applicable documents listed in Section 5.2.1.

Submission deadlines are listed on the Center's ORSC website.

All meeting documents will be made accessible to all members including alternates who will be attending in place of primary members. Members may bring laptop computers to access meeting documents. In the event that a member cannot attend in person, teleconference capability is present and members may participate through teleconference.

#### 5.1.1 Submission and Review Schedule

If the proposal meets requirements for full board review, the following is required to be electronically submitted:

1. A completed original IRB application.
2. A research proposal describing the rationale for the study, research questions to be answered, information that allows the IRB to assess the benefits and risks of the study and to determine whether selection of participants will be equitable, methods, procedures, data analysis plan, and other required information that will allow the IRB reviewer(s) to conduct an analysis of the risks and potential benefits. The research proposal must be formatted in one of the required proposal templates depending on the nature of the research performed. Required proposal templates can be found on Center's ORSC website.
3. An informed consent document.
4. Complete human subjects research training. (See 3.17 Training Requirements).
5. Recruitment materials; i.e., flyers, posters, web-pages, email messages, etc.
6. Data and Safety Monitoring Plan (DSMP) (See 21 below), as applicable.
7. Copies of all instruments if the study involves the use of questionnaires, surveys, or similar instruments.

If applicable:

8. Review/confirmation of Environmental Health and Safety (EHS), Institutional Animal Care and Use Committee (IACUC), and/or Institutional Biosafety Committee (IBC) approval.
9. Sponsor protocol (and the Investigator's Brochure, when one exists).
10. A multicenter research protocol.

11. U.S. DHHS-approved sample consent document (when one exists)
12. Complete U.S. DHHS-approved protocol (when one exists)

#### 5.1.2 Assignment of Primary and Secondary Reviewers

IRB staff will assign each protocol to IRB members who, as primary and secondary reviewers, will review the protocol in detail and act as a liaison between the IRB and the PI. Primary and secondary reviewers are assigned, as closely as possible, according to their expertise with the research being proposed and/or the subject population(s) being enrolled and their appropriate scientific or scholarly expertise to review the protocol. The primary and secondary reviewers may contact the investigator, co-investigators, other IRB members, or outside sources as necessary to ensure a thorough evaluation of risks and benefits of the proposed research. Members who have a conflict of interest with a protocol will recuse themselves from a review assignment.

At times, the IRB may not have the appropriate expertise to review the study for scientific or scholarly validity. In those cases, the IRB Chair will consider who in the Center faculty or community has the appropriate scientific expertise to serve as an expert consultant to perform an in-depth review of the study. Consultants will disclose any COI prior to performing the review and those with a COI will not be used for protocol review.

#### 5.1.3 Distribution of Submitted Materials to IRB Members

All submitted study materials will be accessible to the IRB members 3-4 weeks prior to the scheduled meeting. The primary and secondary reviewers are expected to review all materials for their assigned protocol(s) as appropriate. IRB members who are not assigned as primary or secondary reviewers are expected to review at least the application, protocol and consent forms for research studies being considered at the meeting.

#### 5.1.4 IRB Meeting Schedule

Schedules may be adjusted as necessary to accommodate member schedules, semester breaks, and other factors that affect member availability. The schedule may be viewed on the Center's ORSC website.

#### 5.1.5 Presentation and Discussion of Protocols

Protocols undergoing initial and continuing review at the convened meeting are presented individually to the IRB by the Primary and Secondary Reviewers. IRB staff will assure members with appropriate scientific expertise, local knowledge and other expertise specific to the protocols are present at the IRB meeting, along with at least one member who is knowledgeable about or experienced in working with vulnerable subjects, when research involving subjects who are vulnerable to coercion are reviewed. If a member with the appropriate expertise, knowledge, or experience in that given subject cannot be present, the IRB staff will notify the IRB Chair to defer the review to another meeting or obtain a consultant, if needed, to provide a written report of their evaluation of the protocol.

To be properly presented and discussed, a quorum of the members, which must include a non-scientist and a prisoner representative (if research including prisoners is discussed) must be present for the entire presentation, discussion, and deliberation. The IRB staff will determine if a quorum of members in

present and inform the Chair when quorum is met. Members not present for a substantial part of the discussion and deliberations should abstain from voting. The presence of a quorum of members is documented in the meeting minutes. For those protocols undergoing initial review, the following are discussed in detail (list is not all-inclusive):

1. The regulatory criteria for approval at Uzbek laws/U.S.45 CFR 46.111 or 21 CFR 56.111 are met.
2. The setting in which the research occurs; i.e. investigators have adequate time, staff and facilities to safely conduct and complete the research.
3. The scientific and ethical justification for including vulnerable populations (children, prisoners, pregnant women, fetuses, decisionally impaired adults), if applicable.
4. Analysis of the procedures to minimize risk that includes PI access to a population that will allow recruitment of the necessary number of participants and the availability of medical or psychosocial resources that participants might need as a consequence of the research.
5. The procedures to be used to ensure protection of subject privacy and data confidentiality.
6. The scientific qualifications and experience of the investigators and their research staff.
7. The human subjects protection training of the investigators and their research staff.

If applicable:

8. Potential or disclosed investigator conflict of interest.
9. The scientific and ethical justification for excluding classes of persons from the research.
10. DSMP.
11. Written consultant reports. (If the protocol was reviewed by a consultant, the consultant will not be present for deliberation and the voting on the protocol.)

#### 5.1.6 Criteria for IRB Approval of Research

In order to approve research, the IRB will provide ethical and scientific review of all human subjects research to the extent necessary to determine that all of the requirements of Uzbek laws/U.S. 45 CFR 46.111 Criteria for IRB approval of research are satisfied. Criteria for approval include:

1. Risks to subjects are minimized:
  - a. By using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
  - b. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects continue to be reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result from the research. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapy the subjects would receive even if not participating in the research.
3. Selection of subjects is equitable and takes into account the purpose of the research and the setting in which the research will be conducted. Special attention is paid to problems of research involving vulnerable populations such as, children, prisoners, pregnant women, fetuses, and decisionally impaired adults.



4. Unless waived by the IRB, informed consent will be appropriately sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by appropriate local, state, and federal laws or regulations. The IRB is responsible for the review and approval of the informed consent form submitted by the PI.
5. Informed consent will be appropriately documented according to local, state, and federal laws or regulations.
6. Where appropriate, there are adequate provisions to protect the privacy of the subjects and to maintain the confidentiality of their identifiable data.
7. When appropriate, the research plan continues to make adequate provision for monitoring the data collected to ensure the safety of subjects.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study and in the IRB review process, to protect the rights and welfare of the subjects.

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111>

To ensure that all regulatory requirements for review have been met, reviewer checklists may be utilized.

#### 5.1.7 Scientific/Scholarly Review

The IRB is ultimately responsible for the scientific/scholarly and ethical review of the research as it relates to determining that the risk-benefit ratio of a study is acceptable and the IRB criteria for approval are met.

#### 5.1.8 Length of Approval Period

The IRB will determine the interval for the continuing review of the research, appropriate to the degree of risks that will be experienced by subjects. The interval for continuing review will be at least once per year (not to exceed 365 days; 366 days during a leap year) for studies requiring a continuing review, but may be shorter. Protocols that have not undergone continuing review will expire at midnight on the expiration date. Research activities may not continue after midnight of the expiration date. The following conditions are likely to require review more often than annually:

- There is a high degree of risk to subjects.
- The stage of research is such that many of the risks are unknown.
- The proposed procedures have not been used in humans.
- There have been confirmed instances of serious or continuing noncompliance.
- An IRB member believes more frequent review is required.
- Other reasons for which the IRB requests closer monitoring.

## 5.2 Research Appropriate for Expedited Review

If a protocol has been determined to be minimal risk it may be considered for expedited review provided that it fits one of the categories authorized by U.S. [45 CFR 46.110](#) for expedited review, listed below:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

- a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
  - b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
  - a. from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
  - b. from other adults and children [2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
3. Prospective collection of biological specimens for research purposes by noninvasive means.  
 Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)  
 Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the U.S. HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)
8. Continuing review of research previously approved by the convened IRB as follows:
  - a. Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
  - b. Where no subjects have been enrolled and no additional risks have been identified; or
  - c. Where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The expedited review proposal may be reviewed and approved by the IRB Chair, Vice Chair, or other IRB member designated reviewer.

#### 5.2.1 Submission and Review Schedule

Protocols submitted for expedited review may be submitted at any time and will be processed within the timeframe listed on the RSSPMC of Hematology ORSC website.

One IRB member is assigned as the designated reviewer and is provided with and reviews the complete submission to determine criteria for approval are met. The designated reviewer will complete checklists to document IRB determinations, as applicable.

#### 5.2.2 Submission Requirements/Materials Reviewed

If the protocol meets all requirements for expedited review, the following must be electronically submitted:

- A completed IRB application submitted to the RSSPMC of Hematology IRB.
- A research proposal describing the rationale for the study, research questions to be answered, information that allows the IRB to assess the benefits and risks of the study and to determine whether selection of participants will be equitable, methods, procedures, data analysis plan, and other required information that will allow the IRB reviewer(s) to conduct an analysis of the risks and potential benefits. The research proposal must be submitted using IRB Proposal Standard Submission Template. Or IRB Proposal Secondary Submission Template if the research only involves secondary use of

- existing data or biospecimens and does not meet the criteria for an exemption).
- Informed consent documents, parental permission forms, minor assent forms, as appropriate.
- Recruitment materials; i.e., flyers, posters, web-pages, email messages, etc.

If applicable:

- Copies of all measures/instruments if the study involves the use of questionnaires, surveys, or similar instruments.
- Intervention materials
- Site letters for extramural research.
- EHS, IACUC, IBC approval documentation.
- Sponsor protocol.

### 5.2.3 Assignment of Expedited Reviewer

Upon processing, the IRB staff will verify the protocol is appropriate for expedited review. They will work with the PI to assure that all required documentation has been uploaded and the application is complete. The research protocols are then sent to the IRB Chair, Vice Chair, or other IRB member designated reviewer. Designated reviewers will be experienced IRB members, defined as having served on an IRB for at least one year or demonstrated competency via mentoring with an experienced member, Chair, or staff person. Reviewers who have a conflict of interest with an assigned study should notify the IRB staff who will reassign the study to a non-conflicted reviewer.

### 5.2.4 Reviewer Considerations

Protocols undergoing expedited review are reviewed to assure:

1. The research meets all applicability criteria (See Section 5.3.5) and falls into **one or more categories** of research eligible for review using the expedited procedure. [45 CFR 46.110](#)
2. The regulatory criteria for approval are met. (See Section 5.3.6 Criteria for IRB Approval of Research)
3. Investigators and their research staff have appropriate and sufficient qualifications, expertise, and training. (See 3.17 Training Requirements).
4. Any real or perceived conflicts of interest are adequately managed.

### 5.2.5 Applicability Criteria

The following criteria should be considered for research undergoing expedited review:

1. The research procedures present no more than minimal risk to subjects.
2. The identification of subjects or their responses will not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation or be stigmatizing, unless reasonable and appropriate protections will be implemented so that the risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
3. The research is not classified.

### 5.2.6 Criteria for IRB Approval of Research

In order to approve research, the IRB will provide ethical and scientific/scholarly review of all human subjects research to determine that all of the **requirements** of [45 CFR 46.111](#) criteria for IRB approval of research are satisfied.

Protocols that may be minimal risk but are not included on the list of activities that may undergo expedited review are reviewed at a convened meeting of the IRB. The IRB may then designate that a protocol is minimal risk and determine that the protocol may undergo an expedited review process under [Category 9](#) during its subsequent reviews for continuation.

### 5.2.7 Scientific/Scholarly Review

As stated in Section 3.15.3, the IRB may rely upon departmental review to assure that submissions contain appropriate information to facilitate IRB review. The IRB is ultimately responsible for the scientific/scholarly and ethical review of the research.

### 5.2.8 Length of Approval Period

Effective January 21, 2019, a continuing review is no longer required for most studies that qualify for the expedited review process. For new studies approved via the expedited review process on or after January 21, 2019 or for studies that have been transitioned to the Revised Common Rule, the expedited reviewer will determine the need for continuing review. Most expedited studies will not require a continuing review, however, the Principal Investigator is still responsible for submitting any modifications and/or unanticipated problems for IRB review as well as a closure report when the study meets criteria for closure.

If a continuing review is required, the interval for continuing review will be at least once per year (not to exceed 365 days; 366 days during a leap year) but may be shorter. When a continuing review is required on a study that qualifies for expedited review, the rationale for requiring the continuing review will be documented in the study file. Protocols that have not undergone continuing review will expire at midnight on the expiration date. Research activities may not continue after midnight of the expiration date.

### 5.2.9 Reporting of Expedited Review to the IRB

The protocol number, title, PI name, and the category of research for which each protocol that was approved using an expedited review procedure is reported to the IRB at the next scheduled meeting.

## 5.3 Exempt Research

For U.S. HHS-funded research, the following exemptions do not apply if research includes prisoners as research subjects or if the research is FDA regulated. If the research is not U.S. HHS-funded, the exemptions will apply for research including prisoners as research subjects unless the research involves interaction with prisoners (including obtaining informed consent).

Research qualifying for exempt status must be in accordance with the RSSPMC of Hematology's ethical standards and training requirements.

The U.S. HHS and FDA regulations define some research as exempt from IRB review. The IRB recognizes the exempt categories described in Section 5.4.1. However, depending on the potential risks subjects may experience, the IRB may require a higher level of review either through the expedited process or by the IRB at a convened meeting. PIs who feel their research exactly fits one of the categories for exemption may request such a determination by submitting an application to Center IRB and completing

IRB Proposal Exempt Submission Template or the IRB Proposal Secondary Use Submission Template. Upon receipt, the IRB staff, in consultation with an IRB member designated reviewer as necessary, will evaluate all requests for exemption and determine whether or not the research is eligible for exemption. PIs are not allowed to make the final determination of exemption. PIs will be informed of the results of the evaluation by letter. PIs are not authorized to begin until this letter is received.

Modifications that involve a change in PI, increase risk, or otherwise affect the exempt category or the criteria for exempt determination must be submitted as a modification to the Center's IRB. Investigators are strongly encouraged to contact the IRB staff to describe any changes prior to submitting a modification. The IRB staff can help investigators determine if a formal application is necessary or if the modification does not require a formal application process.

Continuing review will not be required for research determined to be exempt.

### 5.3.1 Exempt Research (Not U.S. FDA Regulated)

The categories for exemption are as follows:

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
  - a. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
  - b. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
  - c. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
3. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

- a. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- b. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
- c. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

**Note:** For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

If the research involves deceiving subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subjects is informed that they will be unaware of or misled regarding the nature or purpose of the research.

- 4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
  - a. The identifiable private information or identifiable biospecimens are publicly available;
  - b. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
  - c. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
  - d. The research is conducted by, or on behalf of, a government department or agency using government-generated or government-collected information obtained for non-research activities.
- 5. Research and demonstration projects that are conducted or supported by a government department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies

that have been delegated the authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including 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. Such projects include, but are not limited to, internal studies by government employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities.

- a. Each government department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Governmental Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the government department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.
6. Taste and food quality evaluation and consumer acceptance studies:
  - a. If wholesome foods without additives are consumed, or
  - b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Uzbek UCPPS.
7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).
8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:
  - a. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
  - b. Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;
  - c. An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent; and the investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.



### 5.3.2 Exempt Research (U.S. FDA regulated)

The categories of research qualifying for exemption are as follows:

1. Any investigation that commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB that meets the FDA requirements in effect before July 27, 1981;
2. Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date;
3. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review;
4. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical or environmental contaminant at or below the level found to be safe by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

### 5.3.3 Criteria to Determine that Subjects of Exempt Research are Protected

Although exempt research is not covered by the federal regulations, it is not exempt from institutional ethical considerations. The IRB staff member making the exempt determination will assure the research meets the criteria of one of the categories for exemption listed in Section 5.4.2 and that ethical standards are met regarding risks, equitable selection of subjects, privacy and confidentiality, and informed consent. The Principal Investigator is responsible for assuring the following during the conduct of the research:

1. Ensure that all research personnel are trained in ethical principles, relevant Uzbek regulations, and institutional policies governing human subjects research.
2. Ensure that all subjects are provided pertinent information (e.g., risks and benefits, contact information for investigators and the ORSC), are selected equitably, and voluntarily agree to participate.
3. Promptly report to the IRB any instances of noncompliance or unanticipated problems that may increase the risk to the subjects.
4. Promptly report complaints from subjects regarding their risks and benefits. If a researcher is unsure whether a complaint involves risks or benefits, contact the IRB staff for assistance.
5. Ensure that the privacy of the subjects and confidentiality of the research data will be maintained appropriately to ensure minimal risks to subjects.
6. Submit a modification to the RSPMC of Hematology IRB:
  - a. If proposed changes increase the risk or if the study no longer qualifies as exempt
  - b. Change in PI.

#### 5.3.4 Submission Requirements/Materials Reviewed

The following materials should be submitted with an application for an exempt determination, as applicable:

1. A completed IRB application.
2. A research proposal describing the rationale for the study, research questions to be answered, methods, procedures, and other required information. The research proposal must follow one of the following templates: Template IRB Proposal Exempt Submission or Template IRB Proposal Secondary Use Submission.
3. Unless the study involves only the use of secondary data, an informed consent document or information sheet containing the following:
  - a. disclosing to participants that the activity involves research,
  - b. a description of the research procedures,
  - c. who to contact with questions, and
  - d. notice that participation is voluntary.
4. Recruitment materials
5. Copies of all measures/instruments if the study involves the use of questionnaires, surveys, or similar instruments.

#### 5.3.5 Limited IRB Review

Research eligible for limited IRB review is deemed to be no more than minimal risk and meets exemption categories 2 or 3. If a designated reviewer finds that research is greater than minimal risk, the reviewer must document the rationale for this determination and the rationale for review by the convened IRB.

Investigators should submit materials as outlined in Section 5.4.4 in RSSPMC of Hematology IRB for review.

A designated reviewer will review the submission and assure the research meets the criteria of exempt category 2 or 3 and that ethical standards are met regarding risks, equitable selection of subjects, privacy and confidentiality, and informed consent. The designated reviewer will assure there are adequate protections for the privacy interests of participants and the confidentiality of identifiable data. The designated reviewer may not disapprove research.

Continuing review is not required for research approved under limited IRB review. RSSPMC of Hematology retains the authority to suspend or terminate IRB approval of research approved with a limited IRB review.

#### 5.3.6 Length of Approval Period

Since protocols that are exempt from IRB review are not approved by the IRB, there is no approval period. Investigators are requested to notify the IRB of the study's closure by submitting a closure application to RSSPMC of Hematology IRB.

## 5.4 Possible IRB Protocol Determinations

Either the IRB at a convened meeting or a designated reviewer (expedited protocols) will render one of the following determinations for each protocol:

1. **Approved:** Made when all criteria for approval are met. Approved by the IRB as written with no explicit conditions.
2. **Approved with Explicit Conditions or Modifications Required to Secure Approval:** Approved with requirements for minor changes or simple concurrence of the PI. These will be identified to the PI and must be completed and documented prior to beginning the research. Minor or prescriptive changes or requirements will be reviewed for approval by the IRB chair or a designated IRB member, typically the IRB staff person assigned to the study. Substantive changes or requirements, requests for more information for IRB consideration, and other issues related to the criteria for approval require review and approval by the convened IRB.
3. **Deferred or Tabled:** Generally, the protocol or consent form has deficiencies that prevent accurate determination of risks and benefits or requires significant clarifications, modifications, or conditions that, when met or addressed, require full IRB review and approval of the PI's responses and revisions. The deficiencies will be specified to the PI, and on occasion the PI is asked to attend the full board meeting in order to clarify the points in question. The PI must revise the protocol, consent forms, or other documents as specified by the IRB and re-submit the entire protocol for full review at a convened meeting. The PI may request reconsideration of determination by submitting a written response to the IRB. The IRB will invite the PI to the IRB meeting if the IRB has additional questions. The IRB will reconsider its original decision in light of new information presented by the PI.
4. **Disapproved:** This determination may only be made at a convened IRB meeting. The protocol describes a research activity that is deemed to have risks which outweigh potential benefits or the protocol is significantly deficient in several major areas. The protocol and/or other documents will need to be completely re-written and re-submitted as a new submission. PIs may request reconsideration of disapproved studies by submitting a written response to the IRB. The IRB will invite the PI to the IRB meeting if the IRB has additional questions. The IRB will reconsider its original decision in light of new information presented by the PI. The second decision is final.

For those protocols reviewed using the expedited review process, the designated reviewer may render decisions of approved, modifications required to secure approval, or refer for review to the full committee/board for consideration. The designated reviewer may not render a decision of disapproved. A decision of protocol disapproval may only be rendered by the IRB at a convened meeting.

Due to the high volume of protocols reviewed by the IRB, any protocol for which no PI response to modifications required to secure approval, approved with explicit conditions, or tabled is received in 60 days may be withdrawn from IRB consideration. Reconsideration of the protocol may require complete re-submission.

## 5.5 Notification of Determination

### 5.5.1 Full Board Review

After each IRB meeting a letter is prepared and sent to the PI of each protocol notifying them of the IRB determination for the protocol. An approval letter requires no further action and the PI can begin research.

Letters requiring modification(s) to secure approval will contain a list of required conditions and PIs will not receive final approval until all required conditions have been met. Along with the determination, the IRB will determine whether the PI's responses to the conditions will need to be reviewed for appropriateness and completeness at another IRB convened meeting or by the IRB Chair or designated reviewer. Responses to clarifications that are directly relevant to regulatory criteria must be reviewed by the convened IRB. When the PI has responded to all conditions appropriately and completely then final approval is granted. The PI will be notified by an approval letter that research can begin and when the protocol will require continuing review.

For deferred/tabled protocols, the PI will be notified by letter the reasons the protocol was deferred/tabled. In order to have the protocol reviewed again, the PI must respond to all the tabled reasons by adjusting the protocol and supporting submission documents or attaching additional supportive documentation.

Due to the high volume of protocols reviewed by the IRB, any protocol for which no PI response to modifications required to secure approval or tabled items is received in 60 days may be withdrawn from IRB consideration. Reconsideration of the protocol may require a complete re-submission.

The PI of protocols that are disapproved will receive a letter that delineates the reasons for disapproval.

### 5.5.2 Expedited Review

After the protocol is reviewed by a designated reviewer, the PI will receive a letter of the IRB determination. An approval letter requires no further action and the PI can begin research. Letters requiring modification(s) to secure approval will contain a list of required conditions and PIs will not receive final approval until all conditions have been met. When the PI has responded appropriately and completely in a letter to the IRB office addressing all conditions, then final approval is granted. The PI will be notified by an approval letter that research can begin and when the protocol will require continuing review.

### 5.5.3 Exempt and Limited IRB Review Research

If the research study is determined to meet the criteria for exempt status, the IRB staff will send an Exempt Determination letter to the PI.

The investigator assures that all investigators and co-investigators are trained in the ethical principles, relevant Uzbek laws and U.S. Federal Regulations and institutional policies governing human subjects research. The investigator assures that:

1. Human subjects will voluntarily consent to participate in the research when appropriate (e.g., surveys, interviews) and will provide subjects with pertinent information such as risks and benefits of participation, contact information for investigators and the IRB office, etc.
2. Human subjects will be selected equitably, so that the risks and benefits of the research are justly distributed.
3. The IRB will be immediately informed of any information, unanticipated problems that would increase the risk to the human subjects and cause the category of review to be upgraded to Expedited or Full Board Review.
4. The IRB will be immediately informed of any complaints from participants regarding their risks and benefits.
5. Confidentiality and privacy of the subjects and the research data will be maintained appropriately to ensure minimal risk to subjects.

### 5.6 Final Approval and Expiration Dates

Approval dates:

- Full board reviews:
  - For submissions that gain approval at a convened meeting, the approval date will be the date of the convened meeting.
  - For submissions that require modification(s) to secure approval, the approval date will be the date a designated reviewer confirms that the condition(s) have been met.
- Expedited reviews: Approval dates are set as the date the reviewer approves the research study.
- Exempt research: Approval dates are set as the date the reviewer approves the research study.

In RSSPMC of Hematology-IRB, the effective date is present. The effective date is the date the IRB decision takes effect. For initial submissions, this is typically the start day of the approval period. The effective date is most significant when modifications are required before approval because the research cannot start immediately when the IRB decision is made (the approval date). The effective date is set to the day the modifications are reviewed and accepted.

Expiration dates:

- The expiration date means the last day that the review is approved, up until midnight.

- The RSSPMC of Hematology IRB has the authority to set approval date or other limitations it deems necessary in order to ensure adequate monitoring of the research, so long as the approval period does not exceed one year.
- Research approved at a convened meeting for an annual review cycle: Expiration dates will be set at 364 days from the approval date.
- Research reviewed at a convened meeting and require modifications to secure approval for an annual review cycle: Upon subsequent confirmation by the designated reviewer that conditions have been met, the expiration date will be set at 364 days from the date of the designated reviewer approved the study.
- Research approved by the expedited process for an annual review cycle: Expiration date will be set at 364 days from the approval date.

If a study is approved with no conditions or required modifications, the final approval is effective the day the study is approved, i.e., the date of the convened IRB meeting for full board protocols and the date of reviewer's approval for expedited protocols.

If a study is determined to require modifications to secure approval, the approval date is the date a designated reviewer confirms that the condition(s) have been met. This determination will be documented in the IRB meeting minutes. The expiration date for the approval is based on the date it was approved at a convened meeting or approved by a designated reviewer and will be no longer than 365 days (366 days if during a leap year) from the approval date but may be sooner if more frequent review is stipulated by the IRB.

## Section 6: Informed Consent

### 6.1 General Policy

Researchers must describe in the research protocol how the informed consent process will be conducted, the setting in which it will occur, a description of the waiting period between informing the prospective participant and obtaining consent and methods in place to prevent undue influence on a potential participant to enroll in a study. The following are points to consider when conducting the consent process.

Researchers should consider obtaining informed consent as a process, not just a consent form, by which the research study is thoroughly explained to the potential subject. The requirement to obtain informed consent should be seen as not only a legal obligation, but also as an ethical obligation. Documentation of informed consent is accomplished through the use of a consent form. Prior to enrolling subjects in a research activity, researchers are required to obtain legally effective informed consent from a potential subject or their LAR and, if the research involves children, a parent's permission or child's consent. (See Section 6.6 Parental Permission/Child Assent).

As part of the informed consent process, researchers are responsible for ensuring subjects (or LARs) are given sufficient opportunity to consider whether or not to participate in the study and must seek to avoid coercion or undue influence. Information given to potential subjects (or LAR) must be in language that is understandable to the subject or representative. The potential subjects (or LAR) must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate and an opportunity to discuss that information. Non-native speaking subjects must have information presented in a language they understand (Section 6.4.1 Non-native Language Informed Consent and other Study Documents).

No process or consent form used to obtain and document consent may include exculpatory language through which the subject waives any of their legal rights or releases, or appears to release, the researcher, sponsor, or institution or its agents from liability for negligence. Any consent form used to enroll subjects in a research protocol must be reviewed and approved by an IRB prior to enrollment. In addition, the IRB may request to observe the informed consent process to ensure adequate consent when the research involves particularly vulnerable populations.

Researchers should be aware that the setting in which consent is sought may introduce a feeling of undue influence. For example, students in an educational setting may feel that refusal to participate will affect their grades. Prevention of these sorts of pressures should be addressed in the research design as the process must always preserve the right to refuse participation.

The informed consent document must begin with a concise and focused presentation of the key information that is most likely to assist a potential subject (or LAR) in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. A key information section will be required for all non-exempt research studies using a consent form longer than 4 pages.

In all cases, consent forms must be consistent with Uzbek laws and governmental regulations regarding content. The informed consent requirements stated in this manual are not intended to preempt any applicable local laws that require additional information to be disclosed in order for informed consent to be legally effective.

Procedures for requesting a waiver of the requirements for obtaining and/or documenting informed consent are delineated in Section 6.7.

## 6.2 Elements of Informed Consent

The IRB will determine that the required disclosures will be provided to each subject or a legally authorized representative in accordance with legal and regulatory requirements listed below as required elements of informed consent. The IRB will also consider whether additional disclosures are required for inclusion in the consent process.

It is expected that researchers will use one of the consent templates provided by the IRB with required sections and verbiage for preparing consent forms. Other formats may be considered providing that all required elements and applicable additional elements are present.

Research-related consent forms must contain all the basic elements of informed consent regardless of the risk level of the study unless a request for waiver or alteration of some or all of the elements is requested by the researcher and the waiver is approved by the IRB. The consent form template contains all the required elements of consent. In addition, the IRB requires that all consent forms be written in the second person, e.g., “You will be required to ...” The following are the basic required elements (extracted from U.S. 45 CFR Part 46.116):

1. A statement that the study involves research.
2. An explanation of the purpose of the proposed research.
3. The expected duration of the subject’s participation.
4. A description of the procedures to be followed.
5. Identification of which procedures are experimental. For studies that are not greater than minimal risk and are not Government funded, this element may be omitted.
6. A description of reasonably foreseeable risks or discomforts that the subjects may encounter, and, if appropriate, a statement that some risks are currently unforeseeable.
7. A description of possible benefits, if any, to the subject and others which may be reasonably expected. It should be stated that if it is an experimental treatment or procedure, no benefits can be guaranteed.
8. A disclosure of appropriate alternative procedures or treatments, if any, which are available and might be advantageous to the subject. One alternative might be to choose not to participate in the research. For studies that are not greater than minimal risk and are not Government funded, this element may be omitted.
9. A statement describing the manner and extent, if any, to which confidentiality of records identifying the subject will be maintained, a statement that the IRB and other entities may inspect the records, and, if the research is Uzbek UCPS or U.S. Food and Drug Administration (FDA)-regulated, FDA may inspect the records.
10. For research involving more than minimal risk, an explanation as to whether any compensation or any medical treatments are available if injury occurs and if so, what they consist of or where further information may be obtained. For studies that are not greater than minimal risk and are not Government-funded, this element may be omitted.



11. A description of whether or not reimbursement for time, inconvenience, etc. will be given, including the schedule of payments.
12. Information regarding who to contact for answers about the research and in the event there is a research-related injury (this is generally the principal investigator (PI) or another staff member closely associated with the study). A separate contact, typically this is the Office of Research Support and Compliance, must be named for questions concerning the subject's rights to provide input, comments, or complaints.
13. A statement that the subjects' participation is voluntary, that refusal to participate will not involve penalty or loss of benefits to which the subject is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is entitled.
14. If the research involves collection of identifiable private information or identifiable biospecimens, one of the following statements must be included as appropriate:
  - a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or LAR, if this might be a possibility; or
  - b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Note: for Uzbek UCPS/U.S. FDA regulated *applicable clinical trials* (See definition in Section 2), U.S. NIH funded clinical trials, or studies meeting the definition of a clinical trial that will be posted on ClinicalTrials.gov, the following statement must be included:

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

The following additional elements of informed consent must be added to the consent form when appropriate:

1. A statement that the particular treatment and/or procedure may involve risks to the subject (or to the embryo or fetus, if the subject becomes pregnant) that are currently unforeseeable. This element should be included when the research involves an investigational drug or device or involves procedures for which the risk profile is not well known.
2. Anticipated circumstances under which the subject's participation may be terminated by the PI, with or without the subject's consent. Include when there are known circumstances under which the subject's participation may be terminated by the PI or sponsor.
3. A description of additional costs for which the subject will be responsible, that may result from participation in the research study. Include when there are additional costs to subjects, over and above standard of care, e.g., additional MRIs, radiographs, DEXA scans, additional visits that may not be covered by Uzbek National Health insurance.

4. A description of the consequences of a subject's decision to withdraw from the research and procedures for orderly and safe termination of participation by the subject. This element should be included when there is a likelihood that abrupt termination from the research is likely to result in adverse events to the subject.
5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject. Include when there is likelihood that interim findings might indicate increased risk and a reasonable person would wish to reconsider participation.
6. The approximate number of subjects that will be involved with the study, totally and at the RSSPMC of Hematology.
7. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subjects will or will not share in this commercial profit.
8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).
10. Other additional information may be required by the IRB.

### 6.3 Other Requirements for Obtaining Informed Consent

1. The IRB must be made aware of the person(s) who will be conducting the informed consent process. These faculty/staff members should be listed in the application and are the only personnel allowed to obtain consent. The IRB requires that the person obtaining consent be appropriately trained in human subjects research (See Section 3.16 Training Requirements) and fully knowledgeable about the project and be able to answer questions that potential subjects may ask regarding the project and/or procedures performed as a part of the project.
2. If potential subjects are deemed as decisionally impaired, informed consent must be obtained from a LAR (See Section 6.5: Third Party/Surrogate Consent). They should be told that their obligation is to try to determine what the subject would do if they were competent, or if the subject's wishes cannot be determined, what they think is in the best interest of the decisionally impaired subject. The IRB must approve the inclusion of decisionally impaired subjects.
3. The consent form is only part of the total consent process in which the researcher conducting the informed consent process, perhaps using the written consent form as an outline, describes all facets of the study and answers the subject's questions. The person obtaining consent is responsible for ensuring that research subjects understand the research procedures and risks. Each subject (or LAR) must be provided adequate time to read and review the consent form, in addition to being advised of the procedures, risks, potential benefit, alternatives to participation, etc. Failure of the subjects to ask questions should not be construed as understanding on the part of the subject.
4. The IRB has the authority to observe the consent process at any time. Depending on the perceived risk of the research procedures, the IRB may wish to observe the consent

process for that protocol. In these cases, the PI will be contacted and the time and place for observing the process will be scheduled.

5. Obtaining informed consent from subjects must be accomplished prior to performing the research activity and using only an IRB-approved and stamped consent form. Modifications/amendments to an existing consent form must be submitted to the IRB and approved prior to implementation, at which time the revised consent form will be stamped and dated by the IRB system.
6. Upon receipt of an IRB approved consent form, copies of all old versions should be discarded to prevent inadvertent use of an outdated consent form. Copies of the most recently approved consent form may be made and should be used until superseded by an amended consent form. New approval dates will not be stamped on consent forms unless the documents have been amended. If consent forms are amended, it is advised the researchers retain a copy of the original, expired consent form(s) for their records.
7. For long-term studies, researchers are reminded that the informed consent process is an ongoing process and that does not end with the signing of the consent form. Subjects should be kept apprised of events that might affect their willingness to participate.
8. Subjects who reach the age of majority while continuing participation in a study must be consented as adults before participating in any further study activities.
9. Researchers are reminded that the informed consent process and form must be in a language understandable to the subject. Therefore, if it is anticipated or known that there will be non-native speaking potential subjects who might be interested in enrolling in a study, the consent form must be translated. It will then have to be reviewed and approved by the IRB. Translation of the consent form should be conducted by a certified translator or if performed by someone who is not a certified translator but is fluent in the translated language the PI must certify that it is an accurate translation.

#### 6.4 Documenting Informed Consent

Uzbek and U.S. federal regulations governing the use of human subjects in research activities require written documentation of informed consent (written signature of the subject) unless the research meets the criteria for waiver of documentation.

After completing the consent process and assuring that the subject (or LAR) has no further questions and agrees to participate in the research activity, the person obtaining informed consent should instruct the subject (or LAR) to sign and date the consent form in the appropriate spaces.

If the research is subject to ICH Good Clinical Practice (GCP), the researcher or designee conducting the consent interview must then sign and date the consent form in the appropriate spaces. It is assumed that in most cases, all persons signing the consent form will do so at the conclusion of the consent process.

Each subject (or LAR) must be given a copy of the signed consent form. The original consent form should be filed in such a manner as to ensure immediate retrieval when required by auditing entities or the IRB.

#### 6.4.1 Non-Native Language Informed Consent and other Study Documents

It is neither ethically justifiable to exclude potential subjects in a research study that offers the potential for direct benefit solely on the basis of language spoken nor ethically justifiable to obtain consent of subjects who do not have a clear understanding of the consent document or who do not have the opportunity to freely ask and receive answers to their questions. Without this understanding and opportunity, consent may not be truly informed and may not be legally effective. In order to address these considerations, when enrolling subjects who do not speak Uzbek in research, the subject must be provided with:

1. A written consent document in a language understandable to them.
2. An interpreter fluent in both Uzbek and the subject's spoken language.

A consent form translated into the appropriate language should be submitted the IRB. If the informed consent and other documents are not professionally translated to the non-English language version, other translation procedures may be considered by the IRB. Be sure to describe the proposed translation procedures in the study protocol.

#### 6.4.2 Use of a Short Form Written Consent Document

A short form is a written document stating that the elements of informed consent required by 45 CFR 46.116 have been presented orally to and understood by the subject or the subject's legally authorized representative. A short form may be used when the majority of subjects in a study are Uzbek speakers, but there are a small portion of the subjects who will not be able to understand the consent form written in Uzbek.

However, if the majority of the anticipated subjects to be enrolled do not speak Uzbek or will be unable to understand the consent form written in Uzbek, the consent form must be translated into a language understandable to the subjects.

##### *6.4.2.1 When following Uzbek/U.S. DHHS regulations the IRB must determine:*

1. The consent document states that the elements of disclosure required by regulations have been presented orally to the participant or the participant's legally authorized representative.
2. A written summary embodies the basic and required additional elements of disclosure.
3. There will be a witness to the oral presentation.
4. For participants who do not speak Uzbek, the witness is conversant in both Uzbek and the language of the participant.
5. The participant or the participant's legally authorized representative will sign the consent document.
6. The witness will sign both the short form and a copy of the summary.
7. The person actually obtaining consent will sign a copy of the summary.
8. A copy of the signed short form will be given to the participant or the legally authorized representative.
9. A copy of the signed summary will be given to the participant or the legally authorized representative.

#### 6.4.2.2 When following Uzbek UCPS/U.S. FDA regulations the IRB must determine:

1. The consent document states that the elements of disclosure required by regulations have been presented orally to the participant or the participant's legally authorized representative.
2. There is a statement noting the possibility that a governmental agency may inspect the records that will be provided to each participant.
3. There is a statement that the results of the research will be posted on [clinicaltrials.gov](http://www.ClinicalTrials.gov): "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."
4. A written summary embodies the basic and required additional elements of disclosure.
5. There will be a witness to the oral presentation.
6. For participants who do not speak English, the witness is conversant in both English and the language of the participant.
7. The participant or the participant's legally authorized representative will sign the consent document.
8. The witness will sign both the short form and a copy of the summary.
9. The person actually obtaining consent will sign a copy of the summary.
10. A copy of the signed short form will be given to the participant or the legally authorized representative.
11. A copy of the signed summary will be given to the participant or the legally authorized representative.

#### 6.4.3 Informed Consent Process for Online Survey-Based Research

Internet consent documents should include all the elements of a regular signed [consent form](#). Researchers should maintain the format of the template consent document, with study specific information added, as much as possible.

### 6.5 Third Party/Surrogate Consent

The regulations are clear that written documentation of informed consent (or permission of the parents if the subject is a child) of the subject (or LAR) is required.

When a PI proposes to conduct a research project utilizing adult subjects who by virtue of age, physical impairment, mental impairment, or any other reason may not be able to personally execute legally effective informed consent, the IRB shall review the project on the basis of risk and benefit. This policy is not meant to imply that the requirement for written documentation of consent is waived. Rather, it applies to those studies in which third party/surrogate consent is obtained from a LAR.

### 6.6 Parental Permission/Child Assent

If the research involves minors under the age of 18 years the federal regulations require the assent of the child or minor and the permission of the parent(s) (45 CFR 46.408). While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent. The assent process should involve taking the time to explain to a child, at whatever age they can begin to understand, what is going on in the proposed study, why the study is being done, what will be done to

them, and that if they object, their participation in the research will be terminated. *Assent* means the potential subject's affirmative agreement to participate in the research. Mere failure to object should not, in the absence of affirmative agreement, be construed as assent.

To obtain informed consent for children under the age of 18 years it is recommended that researchers use the [Parent Consent for Child Participation and Child Assent](#) form templates.

For more information, see Section 12.4 Research Involving Children.

## 6.7 Waiver of Informed Consent and Waiver of Documentation of Consent

Obtaining informed consent from research participants or their legally authorized representatives is required for all expedited and full board research unless the IRB determines that the regulatory criteria for a waiver or alteration of consent or a waiver of documentation of consent is justified based on study specific criteria. The IRB will document its determination to approve a consent waiver in meeting minutes or reviewer checklists.

### 6.7.1 Waiver of Informed Consent

Federal regulations include provisions for approval of a waiver or alteration of part or all of the consent process. There are two general instances when an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in 45 CFR 46.116, or waives the requirement to obtain informed consent. In the first general instance (45 CFR 46.116(c)) when research is not Uzbek UCPPS/U.S. FDA regulated, the IRB must find and document that:

1. The research is to be conducted by or subject to approval of government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) Possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not be practicably carried out without the waiver or alteration.

In the second general instance an IRB may approve a consent procedure that does not include, or that alters some or all of the elements of informed consent or that waives the requirement to obtain informed consent provided that the IRB finds and documents that:

1. The research/clinical investigation involves no more than minimal risk to the subjects;
2. The research/clinical investigation could not practicably be carried out without the waiver or alteration;
3. If the research/clinical investigation involves using identifiable private information or identifiable biospecimens, the research/clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects, and;
5. Whenever appropriate, the subjects or LAR will be provided with additional pertinent information after participation.

#### 6.7.1.1 Screening, recruiting, or determining eligibility

An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining eligibility of prospective subjects without the informed consent of the prospective subject or LAR, if either of the following conditions are met:

- The investigator will obtain information through oral or written communication with the prospective subject or LAR, or
- The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

#### 6.7.2 Waiver of Documentation of Consent

The IRB has the authority to waive the requirement for written documentation of informed consent. When waiving the requirement for a consent form, the IRB must review a written description of the information that will be provided to subjects and consider whether to require the researcher to provide subjects with a written statement regarding the research. If required, the IRB encourages researchers to use the consent template, or a reformatted version, with the signature sections removed. The IRB may waive the requirement for the researcher to obtain a signed consent form for some or all subjects if it finds and documents any of the following (45 CFR 46.117 (c)):

1. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. Research approved for this waiver of documentation of consent may not be U.S. FDA regulated.
2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (45 CFR 46.117(c) and 21 CFR 50.109(c)).
3. If the subjects or LAR are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. Research approved for this waiver of documentation of consent may not be U.S. FDA regulated.

### 6.8 Broad Consent

In the revised Common Rule, broad consent is an alternative consent process for use only for the storage, maintenance, and secondary use of identifiable private information or identifiable biospecimens for future, yet-to-be specified research. In order to utilize broad consent, the study team and/or the department/biorepository responsible for the storage of the identifiable information/biospecimens are required to identify the types of research that may be conducted with the data/biospecimens, record and track who has agreed to or refused consent, and to track the terms of consent to determine whether proposed future research use falls within the scope of the identified types of research.



**Important:** At this time, the RSSPMC of Hematology IRB will not mandate nor implement the institutional use of broad consent, as the tracking requirements may be burdensome. Exempt categories 7 and 8, which rely on broad consent, will not be utilized. RSSPMC of Hematology IRB will continue to support investigators seeking subject permission for the collection and storage of identifiable private information/biospecimens for future secondary use research through other processes including comprehensive IRB review and consent procedures as appropriate.

## 6.9 Posting of Clinical Trial Consent Forms

For each clinical trial supported by a government department or agency, one IRB-approved informed consent form used to enroll subjects has to be posted by the PI on a publicly available Federal website that will be established as a repository for such forms. The form must be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject.

## 6.10 Authorization to Use or Disclose Protected Health Information

Researchers may perform research activities in which they collect or have access to Protected Health Information (PHI). To use or disclose PHI, researchers must obtain an authorization signed by the subjects.

### 6.10.1 Required Elements

1. A description of the information to be used or disclosed presented in a specific and meaningful fashion.
2. The name or other specific identification of the person(s), or class of persons, to whom the use or disclosure will be made.
3. A description of each purpose of the requested use or disclosure.
4. An expiration date or event that relates to the individual or the purpose of the use or disclosure.
5. A statement of the individual's right to revoke the authorization in writing and the exceptions to the right to revoke, together with a description of how the individual may revoke the authorization.
6. A statement indicating when the authorization for use and disclosure occurs; e.g., at the end of the research.
7. Signature of the individual and date. If the authorization is signed by a personal representative of the individual, a description of such representative's authority to act for the individual must also be provided.

In addition to the core elements, the authorization is required to contain statements adequate to place the individual on notice of all of the following:

1. The individual's right to revoke the authorization in writing, and either:
  - a. The exceptions to the right to revoke and a description of how the individual may revoke the authorization; or
  - b. To the extent that the information in Section 6.7.1 is included in the notice required by 45 CFR 164.520, a reference to the covered entity's notice.
2. The ability or inability to condition treatment, payment, enrollment, or eligibility for benefits on the authorization, by stating either:



- a. The covered entity may not condition treatment, payment, enrollment, or eligibility for benefits on whether the individual signs the authorization when the prohibition on conditioning of authorizations applies; or
  - b. The consequences to the individual of a refusal to sign the authorization, the covered entity can condition treatment, enrollment in the health plan, or eligibility for benefits on failure to obtain such authorization.
3. The potential for information disclosed pursuant to the authorization to be subject to redisclosure by the recipient and no longer be protected.
4. The authorization must be written in plain language.
5. The individual must be provided with a copy of the signed authorization.

### 6.11 Waiver of Authorization for Use and Disclosure of PHI

In order to use or disclose PHI without an authorization signed by the research subject, the researcher must obtain one of the following:

1. Documentation that an amendment or waiver of the research subjects' authorizations, for use/disclosure of PHI has been approved by the IRB. This provision of the rule might be used, for example, to conduct records research when researchers are unable to use de-identified information; or
2. Where researchers represent:
  - a. That the research is only for purposes of preparing a research protocol or similar uses preparatory to research.
  - b. That he or she will not remove any PHI from the covered entity and
  - c. That PHI is necessary for the research purpose; or
3. To disclose PHI of decedents, where the researcher represents that the use or disclosure of PHI is:
  - a. Solely for research on the PHI of decedents,
  - b. Necessary for the research, and
  - c. Documentation of the death of the individuals about whom PHI is sought and provided.

### 6.12 Re-Consenting Subjects

Researchers have the responsibility to inform subjects of any new information that might affect subjects' willingness to continue participation in the research. In these cases, an amended consent form, delineating the findings and the changes to research risks/benefits, must be reviewed and approved by the IRB. Subjects should then be briefed on the changes, asked if they wish to continue participation and signify their willingness to continue participation by signing the amended consent form. For minor changes to the consent form that will not change risk/benefit, re-consenting is generally not required.

### 6.13 Record Retention Requirements for Subject Consent Forms

The PI shall maintain, in a designated location, the original copy of all executed subject consent forms. The signed consent forms, along with all research-related files, are to be available for inspection by authorized officials of the University administration, the IRB, regulatory agencies, sponsors and, if applicable, the Uzbek UCPPS/U.S. FDA or HHS. For non-FDA regulated studies, forms should be retained for at least three years after completion of the study. For FDA-regulated studies, all signed subject consent forms shall be retained by the PI for the appropriate period(s) specified below:

1. Drugs: 2 years following the date a marketing application is approved or the study is discontinued.
2. Devices: 2 years after a study is terminated or completed and the records are needed to support FDA approval.

Should a PI or project director depart the University prior to the completion of an activity or less than the time specified above, the PI is responsible for initiating mutually satisfactory arrangements with their department and the University administration as to the disposition of executed subject consent documents.

#### 6.14 IRB Approval of Consent Forms

The IRB issues approved consent forms as a .pdf with an IRB stamp that includes the following language, “RSSPMC of Hematology IRB Approved, Submission ID, Date Approved.” The approved date represents the date the consent form was approved, but may vary from the study approval date, depending on whether modifications to the consent form have been made subsequent to initial approval via a modification.

IRB approved consent forms do not include an expiration date. The approval of the consent form is valid until the study is closed or until the consent form is modified via a modification. Therefore, the IRB issues approved consent forms only when changes to the consent form are made. The revised consent form IRB stamp will include the date the revised consent form was approved. The PI/research support staff is responsible for including or updating any other versioning they include on the consent forms. The IRB will not re-stamp consent forms at time of continuing review.

IRB approved consent forms are available in RSSPMC of Hematology RB.

## Section 7: Continuing Review of Human Subjects Research Activities

Effective January 21, 2019, the Revised Common Rule removes the requirement to conduct continuing review of ongoing research for minimal risk studies approved via the expedited review process and for full board research that is in long-term follow-up or data analysis only, unless the research is UCPS/FDA regulated. Most minimal risk studies approved via the expedited review process on or after January 21, 2019 will not automatically undergo continuing review by the IRB. The IRB may require continuing review for special circumstances, to be determined on a study-by-study basis and documented as part of the review. The research team will be notified at time of initial approval whether or not a continuing review will be required.

When a continuing review is required, study approval end dates will be posted on the parent study workspace in RSSPMC of Hematology-IRB. Investigators will receive automatic reminders from RSSPMC of Hematology-IRB when a continuing review is required.

### 7.1 Requirement for Continuing Review

Research approved via convened IRB review will be subject to continuing review unless the study intervention(s) have been completed and the remaining research activities consist of data analysis and/or involve only observational follow up in conjunction with standard clinical care. Additionally, all non-exempt research regulated by the UCPS/FDA will be subject to continuing review. Time intervals for such reviews shall be made at the discretion of the IRB based on the anticipated risks to subjects but shall occur no less than once per year. The principal investigator (PI) must seek approval of continuation unless all of the following are true:

1. The research is permanently closed to the enrollment of new subjects.
2. All subjects have completed all research-related interventions.
3. Collection and analysis of private identifiable information has been completed.

As a courtesy, the IRB office will send a reminder to PIs approximately two months before the study expires. If no response is received a second notice will be sent approximately a month later. However, it is ultimately the PI's responsibility to complete and submit the IRB Continuing Review Application in time for IRB review prior to the study's expiration of approval.

Generally, if a protocol was approved at a convened meeting of the IRB at initial review, it must be reviewed at a convened meeting of the IRB for its continuing review. However, if the research initially did not qualify for expedited review the IRB may designate the protocol as minimal risk and determine that the protocol may undergo an expedited review process under [Category 9](#). This determination can be made at the time of initial review or at a subsequent continuing review.

No research protocol may continue after approval has expired until final approval for continuation is granted.

### 7.2 Submission Requirements

Continuing reviews must be submitted through RSSPMC of Hematology-IRB. Full board and expedited studies require the following be submitted for continuing review:

1. Completed IRB continuing review application (Status report) which includes the following information:

- a. Number of participants accrued.
- b. A summary since the last IRB review of:
  - i. Adverse events, untoward events, and adverse outcomes experienced by participants.
  - ii. Unanticipated problems involving risks to participants or others.
  - iii. Participant withdrawals.
  - iv. The reasons for withdrawals.
  - v. Complaints about the research.
  - vi. Amendments or modifications.
  - vii. Any relevant recent literature.
  - viii. Any interim or significant findings that might affect participants' willingness to continue.
  - ix. Any relevant multi-center trial reports.
  - x. The researcher's current risk-potential benefit assessment based on study results.
2. Data and Safety Monitoring Board reports or Monitoring Plan updates (if applicable).

### 7.3 Continuing Review of Research Appropriate for Expedited Review

Continuing review will be required for research approved via expedited review if the research is regulated by the UCPPS/FDA. Additionally, the IRB may require continuing review in certain situations as appropriate. When the IRB requires continuing review when it is not otherwise required by regulation, IRB records will document the rationale for requiring the continuing review. Study approval end dates will be posted on the parent study workspace in RSSPMC of Hematology-IRB. Investigators will receive automatic reminders from RSSPMC of Hematology-IRB when a continuing review is required.

When research approved under expedited review does not require a continuing review, modifications and reportable events (e.g., unanticipated problems, noncompliance) must still be submitted to the IRB as they occur throughout the life of the study such that the IRB can provide ongoing review and oversight to research that does not require continuing review. Expedited research requiring a continuing review must also continue to report unanticipated problems and noncompliance as directed in this manual.

#### 7.3.1 Review of Protocol

Continuing reviews for expedited studies are reviewed by IRB staff for completeness and congruence with the currently approved protocol. In addition, the IRB staff determine if the continuing review of studies previously reviewed at a convened meeting qualify for expedited review because:

1. The protocol was initially reviewed using the expedited review process.
2. The protocol meets the criteria for expedited review under expedited [Category 8a, 8b or 8c](#).
3. The protocol was designated by the IRB at a convened meeting as meeting the criteria for expedited review under [Category 9](#).

### 7.3.2 Review of Materials

The materials that will be reviewed as part of an expedited continuing review application include but are not limited to study documents such as the protocol and consent forms, and the information listed in Section 7.2.

### 7.3.3 Reviewer Considerations

IRB reviewers will consider the following when conducting a continuing review:

1. The research falls into one or more of the categories of research eligible for review using the expedited procedure and meets applicability criteria for expedited review:
  - a. The research procedures present no more than minimal risk to subjects. For continuing review, this applies to current and future procedures and does not include procedures no longer being performed. These criteria do not apply to Category 8(b).
  - b. The identification of subjects or their responses will not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that the risks related to invasion of privacy and breach of confidentiality are no greater than minimal. For continuing review, this applies to current and future procedures and does not include procedures no longer being performed. These criteria do not apply to Category 8(b).
  - c. The research is not classified.
2. The regulatory criteria for approval are met (See Section 5.6.3)
3. Whether the protocol needs verification from sources other than the researchers that no material changes have occurred since previous IRB review. When UCPS/FDA regulated, the IRB should consider:
  - a. The nature of and any risks posed by the clinical investigation.
  - b. The degree of uncertainty regarding the risks involved.
  - c. The vulnerability of subjects.
  - d. The experience of the clinical investigator in conducting clinical research.
  - e. The IRB's previous experience with the investigator.
  - f. The projected rate of enrollment.
  - g. Whether the study involves novel therapies.
4. The current consent document is still accurate and complete.
5. Any significant new findings that arise from the review process and that might relate to participants' willingness to continue participation will be provided to participants.

### 7.3.4 Possible IRB Protocol Determinations

Either the IRB Chair or a designated reviewer will render one of the following determinations for each protocol:

1. **Approved:** It is approved as written with no explicit conditions.
2. **Approved with Explicit Conditions/Modifications Required to Secure Approval:** The protocol was approved with explicit conditions requiring minor changes or simple concurrence of the PI. These will be identified to the PI and must be completed and documented prior to continuing the research.

3. **Referred to full board for review:** The study does not meet the requirements for review at an expedited level or additional input from the committee is appropriate prior to final approval.

A designated reviewer may not render a decision of disapproval. Protocol disapprovals may only be rendered by the IRB at a convened meeting.

#### 7.3.5 Length of Approval Period

The interval for continuing review will be at least once per year (not to exceed 365 days; 366 days during a leap year) but may be shorter. The expiration date is calculated from the date of review by the IRB Chair or designated reviewer. Protocols that have not undergone continuing review will expire at midnight on the expiration date. Research activities may not continue after midnight of the expiration date.

#### 7.3.6 Notification of the IRB Expedited Review

A list of protocols approved for continuation through the expedited review process since the previous IRB meeting is provided to IRB members at each meeting.

### 7.4 Continuing Review at an IRB Convened Meeting

#### 7.4.1 Assignment of Primary and Secondary Reviewers

Upon receipt, IRB staff will assign each protocol to IRB members who, as primary and secondary reviewers will review the protocol in detail. Primary and secondary reviewers are assigned, as closely as possible, according to their expertise with the research being proposed and/or the subject population(s) being enrolled and their appropriate scientific or scholarly expertise to review the protocol. Protocols are not assigned to reviewers who have a conflict of interest. The primary and secondary reviewers may contact the investigator, co-investigators, other IRB members, or outside sources as necessary to insure a thorough evaluation of risks and benefits of the proposed research.

At times, the IRB may not have the appropriate expertise to review the study for scientific or scholarly validity. In those cases, the IRB Chair will consider who in the University faculty or community has the appropriate scientific expertise to serve as an expert consultant to perform an in-depth review of the study. Consultants will disclose any conflict of interest (COI) prior to performing the review and those with a COI will not be used for protocol review.

#### 7.4.2 Distribution of Submitted Documents

All materials submitted by an investigator in support of a continuing review application (described in 7.2) are available in the RSSPMC of Hematology-IRB system for all IRB committee members to review.

#### 7.4.3 Presentation and Discussion of Protocols

Protocols undergoing continuing review are presented individually to the IRB by the assigned Primary and Secondary Reviewers. IRB staff will assure that appropriate scientific expertise, local knowledge, and other expertise specific to the protocol(s) is present at the IRB meeting and at least one member who is knowledgeable about or experienced in working with such subjects, when research involving subjects who are vulnerable to coercion are reviewed, will be present at the IRB meeting. If a member with the appropriate expertise, knowledge, or experience in working with the specific vulnerable population cannot be present, the IRB staff will notify the IRB Chair to obtain a consultant if needed. To be properly

presented and discussed, a quorum of the members must be present for the presentation, discussion, and deliberations of the protocol. Members not present for a substantial part of the discussion and deliberations should abstain from voting. For those protocols undergoing continuing review, the following are discussed in detail (list is not all-inclusive):

1. The regulatory criteria for approval at 45 CFR 46.111 are met.
2. Verification that the consent form(s) being used and the consent process remain adequate.
3. Demographics of recruited/enrolled subjects.
4. Reports of protocol deviations, unanticipated problems, amendments/modifications, multi-center/ Data and Safety Monitoring Board reports, and audits reports.

#### 7.4.4 Possible IRB Determinations

After presentation by the primary and secondary reviewers and complete discussion by the IRB, each protocol is voted upon for one of four possible dispositions:

1. **Approved:** It is approved as written with no explicit conditions.
2. **Approved with Explicit Conditions/Modifications Required to Secure Approval:** Approval with explicit conditions is not a final approval. The protocol was approved with minor changes or simple concurrence of the PI. These will be identified to the PI and must be completed and documented prior to beginning the research. For these conditions, the IRB Chair or a designated reviewer, upon reviewing the PI's response(s) to the conditions, may approve the research on behalf of the IRB. PI responses to conditions deemed to be significant or that are directly relevant to regulatory criteria must be reviewed at a convened meeting.
3. **Tabled/Deferred:** The information in the submitted documents has deficiencies that prevent accurate determination of risks and benefits or requires significant clarifications, modifications, or conditions that, when met or addressed, require full IRB review and approval of the PI's responses and revisions. The deficiencies will be specified to the PI, who must address all IRB concerns in a written response. On occasion the PI is asked to attend the full board meeting in order to clarify the points in question. PIs may respond to a "tabled/deferred" decision with a written request. The IRB will review the appeal and invite the PI to the IRB meeting if the IRB has additional questions. The IRB will reconsider its original decision in light of new information presented by the PI. The second decision is final.
4. **Disapproved:** The submitted materials describe events or situations that indicate that research risks now outweigh potential benefits. PIs may appeal a determination for disapproval in writing or by attending an IRB meeting and presenting reasons for reconsideration. Upon appeal, the IRB will reconsider its original decision in light of new information presented by the PI. The second decision is final.

#### 7.4.5 Length of Approval Period

The IRB will determine the interval for the continuing review of the research, appropriate to the degree of risks that will be experienced by subjects. The interval for continuing review will be at least once per year (not to exceed 365 days; 366 days during a leap year) but may be shorter. When the IRB grants approval for one year at the time of continuing review and performs the continuing review and re-approval (with or without explicit conditions) of the research within 30 days prior to the IRB approval

period expiration, the IRB will retain the anniversary of the expiration date of the initial IRB approval as the expiration date of the subsequent one-year approval period. Protocols that have not undergone continuing review will expire at midnight on the expiration date. Research activities may not continue after midnight of the expiration date.

The IRB may require certain protocols be reviewed more than once a year. Reasons for the IRB to require more than annual review include but are not limited to the following:

1. Increase in risks over what was originally anticipated.
2. Noncompliance history.
3. As necessitated by protocol Quality Assurance recommendation.

#### 7.4.6 Third Party Observation

The IRB has the authority to observe or appoint a third-party to observe research conduct, including consent procedures. It may also consider whether a study requires independent verification from sources other than the PI to ensure that no material changes have occurred since the last IRB approval. The IRB will require verification of the information provided for continuing review when:

1. Continuing review materials appear inconsistent or inaccurate compared to prior applications or records and discrepancies cannot be resolved via communication with the PI; or
2. The IRB determines that such actions are useful as part of a corrective action plan for any unanticipated problem or event.

If the findings of such investigations during the continuing review process warrant corrective actions, the IRB may suspend or terminate a research project to ensure the quality of research and protection of research subjects.

#### 7.5 Criteria for IRB Approval of Research Continuation

In order to approve research for continuation, the IRB must consider the PI's continuing review report and assure that the criteria for approval are still met. See section 5.3.6.

The IRB also determines:

1. Whether the protocol needs verification from sources other than the researchers that no material changes have occurred since previous IRB review.
2. The current consent document is still accurate and complete.
3. That any significant new findings arising from the review process that might relate to participants' willingness to continue participation will be provided to participants.

#### 7.6 Notification of IRB Determinations

After the IRB meeting at which the protocol was reviewed for continuation or after expedited review by an IRB Chair or designated reviewer, the PI will be notified of the IRB determination for their protocol. Approved protocols require no further action.

Protocols that are approved with explicit conditions/modifications required to secure approval will have a list of conditions provided and PIs are notified that final approval will not be granted until all conditions have been met. For protocols reviewed at a convened meeting, the IRB will determine, at the



convened meeting, whether the PI's responses to explicit conditions must be reviewed by the entire IRB or may be reviewed for appropriateness and completeness by the Chair or designated reviewer. Responses to clarifications that are directly relevant to regulatory criteria must be reviewed by the convened IRB. When the PI has responded appropriately and completely to all conditions a final approval is granted. The PI will be notified by an approval letter that research can resume.

For tabled/deferred protocols the PI will be notified, by letter, of the reasons the protocol was tabled. The PI is required to respond to the tabled/deferred items and upload revised study documents/new study materials as appropriate to respond to the requirements of the IRB. The entire submission, with all required documents, will need to be resubmitted after revision for IRB review.

For protocols that are disapproved for continuation, the PI will receive a letter that delineates the reasons for disapproval. PIs may appeal the determination in writing to the IRB Chair.

### 7.7 Failure to Comply with Continuing Review Requirements – Lapsed Protocols

IRB approval for non-exempt research requiring a continuing review can be for no longer than a one-year period of time and there is no grace period beyond the expiration date of IRB approval. Extensions of approval beyond the expiration date cannot be granted. Failure to submit the required documents and receive IRB continuing approval for the protocol before the end of the approval period will result in a status of "Lapsed." This will occur even if the PI has provided the required documents but IRB review and approval is not completed before the expiration date. If a protocol is placed in this status, the PI will be notified that they must cease all research activities (recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection and analysis of private identifiable information) until the required documents are submitted, reviewed, and approved by the IRB. However, subjects who are currently enrolled and for which continuation would be in the best interest of their health or well-being, may continue to participate if the PI requests and justifies, in writing, the need for continuation. The request will be considered by the IRB Chair. If the IRB Chair is of the opinion that stopping participation could result in increased risk or potential injury or hardship to subjects, the IRB Chair may approve continued participation for a reasonable time beyond the expiration date. Therefore, to prevent expiration of IRB approval and stopping of research, it is of vital importance to ensure timely completion and submission of the continuing review submission to allow sufficient time for IRB review prior to the expiration date. No research protocol may continue activities after the expiration date of the protocol until final approval for continuation is granted.

## Section 8: Modification/Amendment of Human Subjects Research Activities

### 8.1 Requirements for Modifications

Modifications to consent forms or process, protocols, or procedures/study-related activity must be reviewed and approved by the IRB prior to making any changes in study procedures except when necessary to eliminate apparent immediate hazards to subjects. If modifications are made prior to IRB approval to remove immediate hazards to subjects, the modification must be promptly (within 5 days of learning of the event) reported to the IRB and the modification(s) will be reviewed by the IRB to determine whether the change was consistent with ensuring participants' continued welfare.

### 8.2 Submission Requirements

Modifications to non-exempt research must be submitted to RSSPMC of Hematology-IRB. The requirements for modifications/amendments are:

1. Completed modification application.
2. Summary of proposed modification(s) (including why changes are required and if changes pose any additional risks to the subjects, as applicable).
3. Submit revised study documents as applicable.
4. Submit new study documents, as applicable.

### 8.3 Assignment of Expedited Reviewer

Upon receipt, the IRB staff will verify the modification/amendment is appropriate for expedited review. They will work with the PI to assure that all required documentation has been uploaded and the application is complete. The modification/amendment is then reviewed by the IRB Chair or a designated reviewer.

### 8.4 Review of Modification/Amendment Requests to Research Originally Reviewed by the Convened IRB

Minor changes to studies initially approved by the convened IRB may be reviewed by the expedited procedure when the changes involve minimal risk procedures and/or do not increase the risk or decrease the potential benefit to subjects. Typical changes considered to be minor include changes in personnel, non-significant changes in sample size, an addition of a questionnaire that does not include sensitive or controversial questions, a change in the compensation schedule, an addition of a site, etc. Reviewers using the expedited review process must consider the following:

1. The modification/amendment is a minor modification to previously approved research,
2. The regulatory criteria for approval are met.

At the reviewer's discretion the modification may be referred to the convened IRB. All modifications reviewed through an expedited process are reported, as a list included with the minutes of the previous convened meeting, to the IRB at a convened meeting.

Changes considered as more than minor must be reviewed at a convened meeting of the IRB. When modifications are reviewed by the convened IRB, all IRB members can access copies of all documents

submitted by the PI. Each modification to be considered will be assigned and presented by the assigned Primary and Secondary Reviewers. IRB staff will assure that appropriate scientific expertise, local knowledge, and other expertise specific to the protocol(s) is present at the IRB meeting and at least one member who is knowledgeable about or experienced in working with such subjects, when research involving subjects who are vulnerable to coercion are reviewed, will be present at the IRB meeting. If a member with the appropriate expertise, knowledge, or experience in working with the specific vulnerable population cannot be present, the IRB staff will notify the IRB Chair to obtain a consultant, if needed. To be properly presented and discussed, a quorum of the members must be present for the entire presentation, discussion, and deliberation of the amendment request. Members not present for a substantial part of the discussion and deliberations should abstain from voting.

### 8.5 Possible IRB Modification Determinations

Either the IRB Chair, a designated reviewer, or the IRB committee will render one of the following determinations for each submission:

1. **Approved:** It is approved as written with no explicit conditions.
2. **Approved with Explicit Conditions/Modifications Required to Secure Approval:** The protocol was approved with explicit conditions requiring minor changes or simple concurrence of the PI. These will be identified to the PI and must be completed and documented prior to continuing the research.
3. **Tabled/Deferred:** The information in the submitted documents has deficiencies that prevent accurate determination of risks and benefits. The deficiencies will be identified to the PI, who must address all concerns in a written response.

A designated reviewer may not render a decision of disapproval. Protocol disapprovals may only be rendered by the IRB at a convened meeting.

### 8.6 Criteria for Approval of Modifications

In order to approve a modification to research activities, the IRB will provide ethical and scientific scholarly review of all human subjects research to determine that all requirements are satisfied according to [45 CFR 46.111](#) Criteria for IRB approval of research. Additionally, the IRB determines that any significant new findings that arise from the review process and that might relate to participants' willingness to continue participation are provided to participants.

### 8.7 Length of Approval Period

Modification approvals do not change the approval period of the protocol. Therefore, the expiration date will remain the same as was determined for the protocol at the time of initial or continuing review as appropriate.

### 8.8 Notification to Investigators of IRB Determination

After each IRB determination, a letter is prepared and sent to the PI notifying them of the IRB determinations for their protocols. An approval letter requires no further action and the PI can begin research.

Letters giving approval with explicit conditions/modifications required to secure approval will contain a list of required conditions and PIs will not receive final approval until all required conditions have been met. Along with the determination the IRB will determine whether the PI's responses to the explicit

conditions will need to be reviewed for appropriateness and completeness by another IRB convened meeting, the IRB Chair or designated reviewer. When the PI has responded appropriately and completely to all conditions then final approval is granted. The PI will be notified by an approval letter that research can begin and when the protocol will require continuing review, as applicable.

For tabled/deferred protocols the PI will be notified by letter the reasons the protocol was tabled. The PI is required to respond to the tabled/deferred items and upload revised study documents/new study materials as appropriate to respond to the requirements of the IRB.

For disapproved modifications, the PI will be notified by letter the modification was disapproved and the reason(s) for the disapproval.

## Section 9: Reporting Unanticipated Problems

### 9.1 Principal Investigator Reporting Requirements

The Institutional Review Board (IRB) requires principal investigators (PI) to promptly report (within 5 days) a summary of each unanticipated problem involving risks to subjects and others to the IRB.

Unanticipated problems are defined as events that meet all of the following three criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (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. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Examples of events that require reporting to the IRB include but are not limited to the following:

1. Adverse or other events that meet the 3 criteria above.
2. External events that are determined to be unanticipated problems (i.e., by another IRB for a multicenter study).
3. New information about a research study (e.g., a publication in the literature, interim findings, safety information released by the sponsor or regulatory agency, or safety monitoring report) that indicates a possible increase in the risks of the research.
4. Changes in approved research initiated without IRB review and approval to eliminate apparent immediate hazards to the subject.
5. Incarceration of a subject.
6. A sponsor-imposed suspension of a protocol due to possible increased risk.
7. A complaint from a subject when the complaint indicates potential increased risk or when the complaint cannot be resolved by the PI.
8. A protocol deviation (Section 22: Protocol Deviation and Noncompliance) that places one or more subjects at increased risk or has the potential to occur again.

### 9.2 Review of Unanticipated Problem Reports

#### 9.2.1 Initial Review

Upon receipt of the RNI submission, the IRB staff will make an initial assessment to determine whether the report likely represents an unanticipated problem, and, if so, refer the report for review by the IRB Chair or designated IRB member. If the IRB Chair or designated IRB member concludes that the report likely meets the criteria for an unanticipated problem, the report will be referred for review at a convened meeting of the IRB where the final determination will be made. If the reported problem clearly does not meet the unanticipated problem criteria, the report will be acknowledged. All reports will be reviewed to determine if possible noncompliance has occurred.

### 9.2.2 Convened Meeting Review

If initial review indicates that the report is likely an unanticipated problem involving risks to subjects or others, a copy of the report, the protocol, and informed consent will be provided to the IRB members for review prior to the convened meeting. The IRB will consider whether the event meets all three criteria for an unanticipated problem involving risks to subjects or others.

Upon discussion, the IRB will determine whether the event does in fact represent an unanticipated problem involving risks to subjects or others. However, if after reviewing the information, the IRB determines that the event was not an unanticipated problem, the issue will be returned to the ORSC to be handled administratively.

Deliberations and determinations of the IRB will be fully documented in the minutes.

### 9.3 Possible IRB Actions

Any unanticipated problem or an event that is determined by the IRB to be unanticipated and indicates that subjects or others are at increased risk will warrant consideration of substantive changes in the research protocol and/or consent document/process or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Some of the corrective actions that might need to be considered in response to an unanticipated problem include:

1. Changes to the protocol initiated by the PI prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects may need to be made a permanent part of the protocol.
2. Modification of inclusion/exclusion criteria to mitigate the newly identified risks.
3. Implementation of additional procedures for monitoring subjects, the consent process, and/or the research.
4. Halt to enrollment of new subjects.
5. Suspension of research procedures on currently-enrolled subjects.
6. Modification of the protocol.
7. Modification of the continuing review schedule.
8. Modification of informed consent documents to include a description of newly recognized risks or any other information that should be disclosed during the consent process.
9. Notification of current subjects when such information may relate to subjects' willingness to continue.
10. Provision of additional information about newly recognized risks to previously enrolled subjects.
11. Require the investigator to re-consent current participants.
12. Termination of the protocol with consideration for health and well-being of currently enrolled subjects; and
13. Referral to other organizational entities.
14. Monitoring of the research or the consent process.

### 9.4 University Reporting Requirements

Any event that meets the criteria for an unanticipated problem involving risks to subjects as determined by the convened IRB and is Uzbek/U.S. government funded must be reported to the appropriate agencies (OHRP, FDA) and sponsoring entities within 30 days of finalizing a determination. For government funded and non-federally funded research, unanticipated problems may be reported to the PI's department and/or other university leadership, as appropriate.

## 9.5 Notification of Principal Investigators

Upon completion of the review, the PI will be notified by letter. If the problem/event does not meet the criteria of unanticipated and indicates that subjects or others are not at increased risk, the letter will acknowledge the report. If the problem/event meets the criteria of being unanticipated and indicates that subjects or others are at increased risk, the letter will inform the PI that the IRB determined the problem/event to be an unanticipated problem involving risks to subjects or others, that the problem/event will be reported to the appropriate government agency, and provide a list of required actions and/or changes to the protocol or consent form.

## Section 10: Research with Investigational Drugs

### 10.1 General

If a proposed research activity involves evaluation of an investigational drug or biological material in humans or before a UCPPS/FDA-approved drug can be used for unapproved indications, the sponsor or researcher may need to obtain an FDA Investigational New Drug Exemption (IND). Whenever possible, the IND should be obtained prior to review by the IRB.

It is critical that the Principal Investigators (PI) understand that by obtaining and holding an IND they assume sponsor and investigator responsibilities for the conduct of the research as described in 21 CFR 312.

If research involves the use of a food, nutritional or food supplement that might fit the FDA definition of a “drug,” the IRB staff will review the protocol to determine whether the research involves the use of a drug as defined by Uzbek UCPPS/U.S. FDA. Generally, bioavailability and bioequivalence studies are exempt from the IND requirements.

The U.S. FDA defines a drug as:

1. An article recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
2. An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
3. An article (other than food) intended to affect the structure or any function of the body of man or other animals; and
4. An article intended for use as a component of any article specified in the numbered statements 1, 2 and 3 above.

If required, IND numbers are usually obtained by the study sponsor and can usually be found on the sponsor protocol. PIs should confirm that the number is either on the protocol, in some form of communication from the sponsor or in a letter from the FDA to the sponsor. The IRB primary reviewer for the study will expect to find and will verify existence of an IND from one of these sources. The investigator’s brochure may not be used to verify the IND. If the PI of the study holds the IND then a copy of the communication from the FDA noting the IND number should accompany the protocol submission.

When completing the application, the PI will be asked to provide a copy of the research and informational materials generated by the drug company, if applicable. The storage, preparation and dispensing of investigational drugs should be described in the protocol.

Biological products subject to licensure may also be considered drugs within the definition. A dietary supplement may also fit the definition of a drug, in which case research activities with dietary supplements should be considered under the numbered statements 1 and 2 above. If the intended research with a dietary supplement is to evaluate its use under statement 3 above, it is not considered a drug, and the study is not FDA-regulated and will not require an IND.

An FDA-regulated study is a study in which a PI uses a drug in one or more persons and the drug is not



an approved drug in the course of medical practice and/or the data collected in the study is intended to be submitted to or held for inspection by the FDA. During initial review of a drug study, the IRB primary reviewer will determine whether the study has a valid IND by reviewing the sponsor protocol, communication from the sponsor or a letter from the FDA to the sponsor. If there is no IND, the primary reviewer will determine if the study meets one of the exemptions from the requirement to have an IND. A study requiring an IND will not be approved until the IRB verifies a valid IND is in place.

## 10.2 Exemptions

While IND numbers are generally required for drug studies there are several possible FDA exemptions from this requirement listed in 21 CFR 312.2(b). PIs should submit documentation to support an exemption and may contact an FDA consumer safety officer for confirmation that the investigation fits one of the exemptions.

### 10.2.1 For Exemption under 21 CFR 312.2(b)(1)

To qualify for this exemption, the study must meet all of the following:

1. The drug is lawfully marketed in the United States. (Sponsors or sponsor-investigators are allowed to make low-risk modifications to the lawfully marketed dosage form, i.e., changing the color, scoring or capsule, or the size of the dosage.)
2. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor is it intended to be used in support of any other significant change in the labeling for the drug.
3. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in advertising for the product
4. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks or decreases the acceptability of the risks associated with use of the drug product.
5. The investigation will be conducted in compliance with the requirements for institutional review as set forth in 21 CFR Part 56 and with the requirements for informed consent as set forth in 21 CFR Part 50.
6. The investigation will be conducted in compliance with 21 CFR 312.7 which restricts promotion, commercial distribution or charging for the drug or undue prolongation of the study.

### 10.2.2 For Exemption under 21 CFR 312.2(b)(2)

To qualify for this exemption, the study must meet all of the following:

1. The clinical investigation will involve an in vitro diagnostic biologic product that involves blood grouping serum, reagent red blood cells and/or anti-human globulin.
2. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
3. The diagnostic test will be shipped in compliance with 21 CFR 312.160 that delineates investigational labeling, assurance of shipment to an authorized user, record keeping and disposition of unused drugs.

### 10.2.3 For Exemption under 21 CFR 312.2(b)(3)

To qualify for this exemption, the study must meet the following:

1. The drug is intended solely for tests *in vitro* or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

#### 10.2.4 For Exemption under 21 CFR 312.2(b)(5)

To qualify for this exemption, the study must meet the following:

1. The clinical investigation involves use of a placebo and the investigation does not otherwise require submission of an IND.

#### 10.2.5 Exemption for Bioavailability (BA) or Bioequivalence (BE) Studies

FDA regulations describe criteria under which BA/BE studies using unapproved versions of approved drug products can be conducted without submission of an IND. A BA/BE study in humans does not require an IND if all of the following are met:

1. The drug product does not contain a new chemical entity (21 CFR 314.108), is not radioactively labeled, and is not cytotoxic.
2. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.
3. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and the requirements for informed consent (21 CFR part 50).
4. The sponsor meets the requirements for retention of test article samples (21 CFR 320.3(d)(1)).

#### 10.2.6 Exemption for Studies using Stable Isotopes

When used for basic research purposes, cold (or stable) isotopes ordinarily present fewer safety concerns than radioactive isotopes. FDA does not intend to object to clinical investigations using cold isotopes of unapproved drugs being conducted without an IND, provided the following conditions were met:

1. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding physiology, pathophysiology, or biochemistry.
2. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject.
3. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies.
4. The quality of the cold isotope meets relevant quality standards.

#### 10.2.7 Dietary Supplements

For studies with dietary supplements, if the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required.

However, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, or prevent a disease, an IND is required under part 312.

### 10.3 Applying for and/or Filing an IND

An IND application should include the facts that satisfy the FDA that the article may be justifiably administered to a human as proposed. If the PI wishes to apply for and hold an IND, they must give the FDA the information specified in "Notice of Claimed Investigational Exemption for a New Drug (IND)," Form FD-1571. Visit the FDA website for instructions for completing and submitting an IND:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571>

The IND goes into effect 30 days after the FDA receives the IND unless the sponsor receives earlier notice from the FDA. The 30-day period can be extended if the FDA requires additional time for the sponsor to correct deficiencies.

### 10.4 Investigator Responsibilities for use of Investigational Drugs and Biologics

#### 10.4.1 General

1. Ensure that the clinical research is conducted according to the signed investigator statement for clinical investigations, the investigational plan and applicable regulations.
2. Inform the subjects, or any persons used as controls, that the drugs/biologics are being used for investigational purposes. Include a statement in the consent form.
3. Administer the study drug or biologic only to subjects under the investigator's personal supervision or the supervision of a sub-investigator.
4. Follow reporting requirements in Section 9 for problems that require prompt reporting.
5. Do not supply the study drug or biologic to any person not authorized to receive it (patient or another investigator).
6. Comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements of 21 CFR 312.
7. Investigational drugs used in research conducted in Ascension Seton Health facilities must be stored and distributed according to the Ascension Seton Investigational Drug-Use and Control Policy. For all other research involving investigational drugs, the principal investigator is responsible for providing for control of drugs or biologics in accordance with 21 CFR 312.60.
8. Maintain adequate records of the disposition of the study drug or biologic to include dates, quantity and use by subjects.
9. Return any unused supply of study drug to the sponsor upon completion, suspension, termination or discontinuation of the clinical investigation. (21 CFR 312.59 and 312.62)
10. Permit the FDA to have access to and copy and verify records or reports (generally not required to divulge subject names) made during the study. (21 CFR 312.68)
11. If the investigational drug is subject to the Controlled Substances Act, take adequate precautions, including storage of the drug in a securely locked, substantially constructed cabinet or enclosure to which access is limited to prevent inappropriate distribution. (21 CFR 312.69)
12. Read and understand information in the Investigator's Brochure, including potential risks and side effects of the drug.
13. As noted in Section 10.1 above, researchers who apply for and hold an IND are also subject to sponsor responsibilities.
14. Comply with Section 21: Data and Safety Monitoring in Clinical Research.

#### 10.4.2 Additional Reporting Requirements

If the PI does not hold the IND and an external sponsor funds or supports the study, then the PI is responsible for notifying the sponsor of any serious adverse events or unanticipated problems. For any studies under FDA jurisdiction, it is the PI and/or sponsor's responsibility to notify the FDA within 24 hours of any serious adverse events or unanticipated problems.

Similarly, if the study is a multi-site project and the unanticipated problem occurs at a site other than the University, then the sponsor (PI if they hold the IND) is required to inform researchers of unanticipated problems or reactions that occur at other sites. When PIs are informed of unanticipated problem(s) in sponsor safety memos or other correspondence, then the PI must notify the IRB as promptly as possible after receipt of the report from the sponsor

Note that notifying the IRB does not relieve the PI from their responsibility to notify the sponsor and/or FDA, as applicable.

## Section 11: Research with Investigational Devices

### 11.1 General

If a research activity appears to use a device for an indication for which it has not been cleared, the IRB staff will review UCPS/FDA regulations to verify that the research meets the definition of a device investigation. Device studies must satisfy one of the following:

1. Have an Investigational Device Exemption (IDE) approved by the FDA under 21 CFR 812.30;
2. Be categorized as fitting abbreviated requirements under 21 CFR 812.2(b) or;
3. Be deemed by the FDA as being exempt from the requirement to have an IDE under 21 CFR 812.2(c).

By reviewing the protocol, some form of communication from the sponsor or a letter from the FDA to the sponsor, the IRB primary reviewer will determine whether or not the study has a valid FDA-approved and issued IDE. The investigator's brochure may not be used to verify the IDE. If an IDE is not required, the primary reviewer will determine whether or not the study meets the requirements for an abbreviated IDE or exemption from the requirement for an IDE. A study requiring an IDE will not be approved until the IRB verifies a valid IDE is in place.

### 11.2 Abbreviated Requirements

The following categories of investigations are considered to have applications for IDEs, unless FDA has notified a sponsor under 21 CFR 812.20(a) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:
  - a. Labels the device in accordance with 21 CFR 812.5;
  - b. 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 (See section 11.4 below);
  - c. Ensures that each PI participating in an investigation of the device obtains from each subject under the PI's care, informed consent under 21 CFR Part 50 and documents it, unless documentation is waived by an IRB under 56.109(c);
  - d. Complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
  - e. Maintains the records required under 21 CFR 812.140(b)(4) & (5) and makes the reports required under 21 CFR 812.150(b) (1)-(3) and (5)-(10);
  - f. Ensures that participating PIs 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) & (7); and
  - g. Complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.
2. An investigation of a device other than one subject to 21 CFR 812.2(e), if the investigation was begun on or before July 16, 1980 and to be completed, and is completed on or before January 19, 1981.

### 11.3 Applying for and/or Filing an IDE

An IDE application should include the facts that satisfy the FDA that the device may be justifiably administered to a human as proposed. If the PI wishes to apply for and hold an IDE, they must give the FDA the information required per the FDA website for instructions for completing and submitting an IDE:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm>

### 11.4 Exemptions

The regulations at 21 CFR 812.2 do not apply to investigations that fit one of the following categories:

1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling that the FDA reviewed under Subpart E of part 807 in determining substantial equivalence;
3. A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing is i) non-invasive, ii) does not require an invasive sampling procedure that presents significant risk, iii) does not by design or intention introduce energy into a subject, and iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. A device undergoing consumer preference testing, testing of a modification or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. A device intended solely for veterinary use;
6. A device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

### 11.5 Significant/Non-Significant Risk Determinations

If a PI or sponsor claims a device is not a significant risk, then the IRB will review research involving the investigational device at a convened meeting. The IRB will determine whether the study using the device is significant risk, within the context of the overall study, by reviewing the criteria in [21 CFR 812.3\(m\)](#). A significant risk device means that the device:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is 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;
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A non-significant risk device study is one that does not meet the definition for a significant risk device study.

If the IRB determines that the study using the device is not “significant risk,” it will document that determination in the primary and secondary reviewer checklist and the minutes, along with the IRB’s rationale for that decision. The IRB will notify the PI of its determination and the study may begin without submission of an IDE application to the FDA.

If the IRB disagrees with the sponsor’s or PI’s assessment that a device study is “non-significant risk” and determines that the study using the device is “significant risk,” it will notify the PI, and where applicable, the sponsor (21 CFR 812.66) and document its determination in the IRB minutes. The study will be tabled, the sponsor or PI must apply for an IDE, and the study may not begin until the FDA approves the IDE application and the IRB approves the study. Upon receipt of FDA approval, the sponsor or PI must provide the IRB with the FDA’s approval letter or conditional approval letter as part of the re-submission process.

### 11.6 Principal Investigator (PI) Responsibilities

1. Must not begin the study or obtain informed consent of any subject prior to IRB and FDA approval.
2. Ensure that the clinical investigation is conducted according to the signed PI agreement for clinical investigations, the investigational plan, applicable regulations (21 CFR 812), and any conditions of approval imposed by the reviewing IRB or FDA.
3. Supervise all testing of the device involving human subjects in accordance with 21 CFR 812.43(c)(4)(ii) and 812.110(b).
4. Permit use of an investigational device only with subjects under the supervision of the PI and to supply the investigational device only to persons authorized to receive it.
5. Provide for control or take adequate precautions, including storage of the device in a securely locked area to which access is limited to prevent inappropriate use of the device in accordance with 21 CFR 812.100, and return any remaining supply of the device (or otherwise dispose of it as directed by the sponsor) upon completion or termination of the clinical investigation or the PI’s part of an investigation.
6. Permit the FDA to inspect and copy any records pertaining to the investigation, including those which may identify subjects (21 CFR 812.145).
7. Prepare and submit to the sponsor:
  - a. Progress reports,
  - b. Final report,
  - c. Financial disclosure reports and;
  - d. Any other information requested by the FDA (21 CFR 812.110).

### 11.7 In Vitro Diagnostic Devices

In vitro diagnostic devices (IVDs) are products (reagents, instruments, and systems) intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent a disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body (21 CFR 809.3). IVDs are considered to be devices under the regulations and are therefore subject to FDA regulation. In many cases, the research usually involves the comparison of the IVD under investigation to the “gold standard” using data generated from samples analyzed on both instruments. The comparison data and

subsequent statistical analysis are submitted to the FDA for consideration of clearance or approval for marketing.

Technically, within the FDA regulations there is no distinction between an IVD and a device that may be implanted regarding informed consent of subjects in the study. However, the samples used in IVD studies typically are laboratory samples that have already been analyzed for clinical and/or diagnostic reasons and obtaining informed consent to use the samples for IVD analyses would be cumbersome. In a recent [guidance document](#) the FDA informed IRBs and others that it does not object to the use of “leftover specimens” in IVD studies without the consent of the specimen donors, providing that:

1. The investigation meets the IDE exemption criteria at 21 CFR 812(c)(3);
2. The study uses leftover specimens collected for routine clinical care or analysis and/or leftover specimens that were previously collected for research purposes;
3. The specimens are not individually identifiable;
4. The specimens may be accompanied by clinical information as long as the information does not make the specimen source identifiable to the PI or any other person associated with the investigation;
5. The individuals caring for the patients are different from and do not share information about the patient with those conducting the study;
6. The specimens are provided to the PI without identifiers and the supplier has established procedures to prevent the release of personal information;
7. The study has been reviewed and approved by an IRB.

The FDA has a guidance document entitled “[In Vitro Diagnostic \(IVD\) Device Studies – Frequently Asked Questions](#)” which should be considered when proposing IVD studies.

Proposed research on IVDs may be reviewed using an expedited review process providing that the research meets all applicability criteria as listed in Section 5.3.5 of this manual and one of the categories of research that qualify for expedited review <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html>

### **11.8 Principal Investigator Responsibilities in Storage and Use of Investigational Devices**

Storage and use of investigational devices are the responsibility of the PI. Investigational devices must be stored in a locked room designated for research or in a locked cabinet within a room designated for research that is under the direct control of the PI and accessible only to the PI and his/her authorized and IRB-approved staff. If applicable, the storage area for investigational devices must be separate from storage areas for approved devices. An investigational device or its packaging must be labeled with the following information:

1. The name and place of business of the manufacturer;
2. Packer or distributor;
3. The quantity of contents, if appropriate; and
4. The following statement: "CAUTION - Investigational device. Limited by Federal law to investigational use." The label or other labeling must describe all relevant contraindications, hazards, adverse effects, interfering substances, or devices, warnings, and precautions.



An investigational device is to be used only on subjects under the PI's supervision or under the supervision of a Co-I on the study. A PI will not supply an investigational device to any person not authorized to receive it. The PI is responsible for records of receipt, use, or disposition of a device that:

1. Relate to the type and quantity of the device;
2. The dates of its receipt;
3. The batch number or code mark;
4. The names of all persons who received, used, or disposed of each device; and
5. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

Upon completion or termination of a clinical investigation or the PI's part in an investigation, or at the sponsor's request, the PI must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

## Section 12: Vulnerable Populations

### 12.1 Inclusion of Vulnerable Populations in Research Activities

When some or all of the subjects that will be enrolled in a research study are likely to be vulnerable to coercion or undue influence, such as pregnant women, prisoners, children, and decisionally impaired adults, additional safeguards must be included in the study to protect the rights and welfare of these subjects. Plans for implementing additional safeguards must be described in the application to the IRB.

In addition to the responsibilities prescribed for the IRB under 45 CFR Part 46, Subpart A, the IRB shall follow special procedures with respect to pregnant women, fetuses, neonates of uncertain viability, prisoners, and children as specified in Subparts B, C, and D. Inclusion of other vulnerable populations as research subjects is considered by the IRB and is discussed in further detail in this section.

### 12.2 Pregnant Women, Fetuses, and Neonates

#### 12.2.1 Research Involving Neonates

When research involves neonates of uncertain viability, the IRB determines and documents:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provided data for assessing potential risks to neonates.
- Individuals engaged in the research have no part in determining the viability of a neonate.
- One of the following is true:
  - 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.
  - The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there is no added risk to the neonate resulting from the research.
- The consent of either parent of the neonate is required or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective consent of either parent's legally authorized representative is required, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

When research involves nonviable neonates, the IRB determines and documents:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provided data for assessing potential risks to neonates.
- Individuals engaged in the research have no part in determining the viability of a neonate.
- Vital functions of the neonate are not artificially maintained.
- The research will not terminate the heartbeat or respiration of the neonate.
- There is 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 consent of both parents is required, except:
  - If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the consent of one parent is required.
  - If the pregnancy resulted from rape or incest the consent of the father need not be obtained.
- When the research involves non-viable neonates, the IRB is not allowed to approve the consent of a legally authorized representative.

### 12.2.2 IRB Review of Non-Uzbek/Non-U.S. HHS Funded Research Involving Pregnant Women and Fetuses

For studies not greater than minimal risk and not funded by HHS, 45 CFR Part 46, Subpart B may be used as a guide, but determinations of approval for inclusion of pregnant women will predominantly be made by assuring that risks to the fetus are minimal and all criteria for approval under 45 CFR 46.111 are met. However, additional protocol-specific safeguards may be required by the IRB on a case-by-case basis depending on risks to the woman and fetus.

Note: Recruitment and enrollment of women of child bearing potential does not necessarily require compliance with these policies.

### 12.2.3 IRB Review of Government-Funded Research Involving Pregnant Women and Fetuses

For those studies that are funded by governmental sources, including but not limited to U.S. HHS and other Common Rule agencies, 45 CFR 46.204, in addition to the responsibilities prescribed in Subpart A, will be followed. The IRB chair will assure that the IRB determines and documents that Subpart B is followed.

Government-funded research activities requesting inclusion of pregnant women may be undertaken if all the following conditions, 45 CFR 46.204, are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means;
3. Any risk is the least possible risk for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the pregnant woman or the fetus when the risk is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, the consent of the mother will be obtained in accordance with the regulations (45 CFR 46, Subpart A), unless altered or waived in accordance with 45 CFR 46.116(d);
5. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accordance with the informed consent provisions of 45 CFR 46, Subpart A, except that the father's consent

- need not be obtained if he is unable to consent because of non-availability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
6. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
  7. For children as defined in 45 CFR 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of 45 CFR Part 46, Subpart D. Generally, in the State of Texas, if the research is related to the pregnancy, only the child's assent/consent is needed. If the research is on the pregnant minor and is not related to the pregnancy, parental permission and child assent/consent is required;
  8. No inducements, monetary or otherwise, may be offered to terminate pregnancy for the purposes of the activity;
  9. Individuals engaged in the research will have no part in any decisions as to timing, method, and procedures used to terminate a pregnancy; and
  10. Individuals engaged in the research will have no part in determining viability of the neonate.
  11. If the research is greater than minimal risk, a Data and Safety Management Plan (DSMP) to monitor participants must be established.

Research activities that are approved for inclusion of pregnant women must be documented in the IRB minutes.

#### 12.2.4 Research Not Otherwise Approvable that Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women (45 CFR 46.207)

For Government funded research, the U.S. Secretary of HHS will conduct or fund research that the IRB does not believe meets the requirements of 45 CFR 46.204 only if:

1. The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
2. The Secretary of HHS, after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment, including a public meeting announced in the Federal Register, determines either:
  - a. That the research in fact satisfies the conditions of 45 CFR 46.204, or
  - b. The research:
    - i. Presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates,
    - ii. Will be conducted in accordance with sound ethical principles, and
    - iii. Informed consent will be obtained in accordance with 45 CFR 46, Subpart A.

### 12.3 Research Involving Prisoners

The IRB determines whether the criteria for approval of research are met when research involves prisoners.

Since prisoners (See definition of prisoner and minimal risk in Section 2) may be influenced by their incarceration to participate in research and in order to assure that their decision to participate is not

coerced, for research funded by HHS, the IRB will adhere to Subpart C of 45 CFR Part 46.

The RSSPMC of Hematology is considered “engaged” in research involving prisoners when an agent or employee of the RSSPMC of Hematology, for the purposes of the research obtains:

1. Data about the prisoner subjects through intervention or interaction with them; or
2. Identifiable private information about the prisoner subjects.

In addition, the RSSPMC of Hematology would become engaged in research involving prisoners if agent or employee are the primary awardee of funds to conduct such research, even when all activities involving prisoner subjects are carried out by agents or employees of another institution.

#### 12.3.1 IRB Review of Non-Federally-Funded Research Involving Prisoners

For research that is not government-funded, the additional safeguards under 45 CFR 46.305(a)(2-7) will generally be followed but the overall determination of whether or not to approve research for inclusion of prisoners (See definition of prisoner in Section 2) will be based on the criteria for approval specified in 45 CFR 46.111. Research will not have to meet one of the categories listed in 46 CFR 46.306. When research involves the Bureau of Prisons, additional safeguards are provided as set forth in Section 25. If an enrolled subject becomes incarcerated and the research was not initially approved for inclusion of prisoners the following determination must be made:

1. The IRB Chair will determine whether it is in the best interests of the subject to remain in the study or to terminate enrollment and will decide whether it is feasible for the subject to remain in the study.
2. If it is determined that it is in the best interests of the subject to remain in the study, keep the subject in the study and review the research at the next convened IRB meeting.

When reviewing research that involves prisoners, the IRB will review and approve an appropriate consent process that includes a determination that:

1. The information will be presented in a language that is understandable to prisoners.
2. Each prisoner will be informed in advance that participation in the research will have no effect on his or her parole.

In addition, research requesting inclusion of prisoners as subjects may be reviewed by an expedited review process and may be considered for exemption (if an exemption is appropriate for the prison population being studied) under the categories listed in Sections 5.4.1 and 5.4.2. An exemption may not be granted if the research involves interaction with prisoners (including obtaining informed consent).

For research involving interaction with prisoners reviewed by expedited procedure:

1. Research involving interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied.

Note: The prisoner representative must concur with the determination that the research involves no greater than minimal risk.

2. The prisoner representative must review the research as a reviewer, designated by the IRB Chair. This may be as the sole reviewer or in addition to another reviewer, as appropriate.
3. Review of modifications and continuing review must use the same procedure for initial review using this expedited procedure including the responsibility of the prisoner representative.

For research that does not involve interaction with prisoners (e.g., existing data, record review) reviewed by expedited procedure:

1. Research that does not involve interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied.
2. Review by the prisoner representative is not required.
3. The prisoner representative may review the research as a reviewer or consultant if designated by the IRB Chair.
4. Review of modification and continuing review must use the same procedures as the initial review.

#### 12.3.2 IRB Review of Government-Funded Research Involving Prisoners

For those studies that are funded by government sources, including but not limited to HHS and other Common Rule agencies, none of the exemption categories listed in Sections 5.4.1 and 5.4.2 applies for research involving prisoners. The IRB determines and documents that for Federally-funded research, all requirements for 45 CFR Part 46, Subpart C are followed. All such protocols will be reviewed at a convened meeting with a prisoner representative present.

For government-funded research desiring to include prisoners as subjects, a majority of the IRB members (exclusive of the prisoner advocate) must have no affiliation with the prison system, apart from membership on the IRB and at least one member who is a prisoner representative, with appropriate background and experience to serve in that capacity, must be present at any meeting at which protocols including prisoners will be discussed. In addition, the prisoner representative will be a voting member of the IRB, will be a primary or secondary reviewer, will receive all submitted protocol documents (initial review, modifications, continuing review) and will present their review orally or in writing at the IRB meeting either in person or via remote, live connection to the meeting. If no prisoner representative is present, review of proposals requesting inclusion of prisoners must be postponed and no determinations on approval of protocols for inclusion of prisoners as research subjects may take place.

Minor modifications to research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.

- Modifications involving more than a minor change reviewed by the convened IRB – must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).
- Continuing review – must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

- If no participants have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8.

In addition to all other responsibilities prescribed under 45 CFR Part 46 Subpart A, the IRB shall review and approve Federally-funded research for inclusion of prisoners only if it finds the research under review represents one of the categories of research permissible in 45 CFR 46.306 (a)(2) (See Section 12.3.3) and meets all criteria under 45 CFR 46.305(a) as follows.

1. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
2. The risks involved in the research are commensurate with the risks that would be accepted by non-prisoner volunteers.
3. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator (PI) provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
4. The information is presented in language that is understandable to the subject population.
5. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
6. Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examinations or care, taking into account the varying lengths of individual prisoner's sentences, and for informing participants of this fact.

### 12.3.3 Requirements by Categories in Research Involving Prisoners

1. 45 CFR 46.306(a)(2)(A)  
The study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
2. 45 CFR 46.306(a)(2)(B)  
The study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
3. 46.306(a)(2)(C)  
Research on conditions particularly affecting prisoners as a class (e.g., vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults), provided that the study may proceed only after the Secretary of HHS has consulted with appropriate experts including experts in penology, medicine,

and ethics, and published notice, in the Federal Register, of his/her intent to approve such research. Note: HHS Secretary consultation does not apply if research is not funded by HHS.

4. 45CFR 46.306(a)(2)(D)

Research on practices, both innovative and accepted, that have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners, in a manner consistent with the protocols approved by the IRB, to control groups that may not benefit from the research, the study may proceed only after the Secretary of HHS has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his/her intent to approve such research.

Note: HHS Secretary consultation does not apply if research is not funded by HHS.

In accordance with the federal regulations, the IRB has the authority to waive the requirement that research activities fit Categories 1-4 listed above if the proposed research meets the following specific criteria:

1. The research involves epidemiologic studies in which the sole purposes are:
  - a. To describe the prevalence or incidence of a disease by identifying all cases, or
  - b. To study potential risk factor associations for a disease, and
2. The IRB has determined that items in Section 12.3.2 have been appropriately addressed and has also determined that:
  - a. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
  - b. Prisoners are not a particular focus of the research.

#### 12.3.4 Subjects that Become Incarcerated During Government-Funded Research

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to the requirements in Sections 12.3.2 and 12.3.3 above:

1. Confirm the subject meets the definition of a prisoner.
2. Terminate enrollment or review the research study under Subpart C if it is feasible for the subject to remain in the study.
3. Before terminating the enrollment of the incarcerated subject the IRB should consider the risks associated with terminating participation in the study.
4. If the enrollment of the subject cannot be terminated for health and safety reasons:
  - a. Keep the subject enrolled in the study and review the research under Subpart C.  
Note: If some of the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, keep the subject enrolled and inform OHRP of the decision along with the justification.
  - b. Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

#### 12.3.5 Documentation and Certification of Research Involving Prisoners

Research activities that are approved for inclusion of prisoners as subjects must be documented in the IRB minutes that the research has been reviewed and meets the criteria for approval.



In addition, for research that is funded by the HHS, the HRPP Director must also send a certification letter to the OHRP stating that:

1. The IRB has been constituted according to the regulations,
2. That the IRB has considered and made the seven findings set forth in 45 CFR 46.305, and
3. That the IRB finds that category A, B, C, and/or D of 46.306 permits the research to go forward with prisoners as human subjects. The certification letter should also provide a brief description of the research sufficient to allow OHRP to determine whether or not to concur with the IRB's findings or whether to consult with appropriate experts and publish a notice. This requirement does not apply if not funded by HHS.

#### 12.3.6 Expedited Review of Research Involving Prisoners

Research including prisoners and involving direct interaction with the prisoners may be reviewed by the expedited review process if a determination is made that the research is minimal risk for the prison population being studied or included, and a prisoner representative must review the research as either a primary or secondary reviewer.

Research that does not involve interaction (e.g., existing data, record review) with prisoners may be reviewed by the expedited review process if a determination is made that the research is minimal risk for the prison population being studied or included. A prisoner representative may review the research but review by a prisoner representative is not required.

### 12.4 Research Involving Children

Note: Studies involving children in schools will require approval of the school district(s) and parental permission. So as not to unnecessarily delay review and approval of a study, IRB applications and requests for district permission to conduct the study should, when allowed by the school district(s), be submitted simultaneously.

#### 12.4.1 IRB Review of Government-Funded Research Involving Children

In reviewing government-funded research requesting the inclusion of children as research subjects, it is necessary to apply special safeguards as prescribed in 45 CFR 46, Subpart D in addition to the responsibilities prescribed in other Subpart A. Special risk/benefit determinations must be discussed and documented by the IRB in the minutes as to the specific paragraph and subparagraph(s) under which the research is approved.

In addition, some funding agencies may have additional IRB membership requirements. For example, the U.S. National Institute on Disability and Rehabilitation Research (NIDRR) specifies that when an IRB reviews a NIDRR-funded research project that purposefully includes children with disabilities as research subjects, the IRB must include at least one person whose primary interest is the welfare of children with disabilities. When reviewing these types of research projects, the IRB will use ad hoc reviewers (consultants) with specific expertise in treating children with disabilities, as appropriate.

#### 12.4.2 Requirements by Category in Research Involving Children

Research involving Children as subjects must meet one of the following categories:

1. 45 CFR 46.404  
Minimal Risk with or without a potential for direct benefit.
  - a. Adequate provisions need to be made for obtaining assent of the children.
  - b. Adequate provisions must be made to obtain permission of parents or guardians (Permission Form).
2. 45 CFR 46.405  
Greater than Minimal Risk with a potential for direct benefit (to each individual subject).
  - a. IRB must find that the risk is justified by the anticipated benefits.
  - b. The relation of the anticipated benefit to risk is at least as favorable as alternative approaches.
  - c. Adequate provisions must be made for obtaining assent of the children.
  - d. Adequate provisions must be made to obtain permission of parents or guardians (Permission Form).
3. 45 CFR 406  
Greater than Minimal Risks with no prospect of direct benefit, but likely to provide generalizable knowledge about the subject's disorder or condition and:
  - a. The risk represents a minor increase over minimal risk.
  - b. The intervention or procedure presents experiences commensurate with those inherent in the subjects' actual or expected medical, dental, psychological, social, or educational experience.
  - c. The intervention or procedure yields generalizable knowledge about the subjects' disorder or condition that is vital to understanding or ameliorating the subjects' disorder or condition.
  - d. Adequate provisions must be made for obtaining assent of the children.
  - e. Adequate provisions must be made to obtain permission of parents or guardians (Permission Form).
4. 45 CFR 46.407  
Greater than Minimal Risks with no prospect of direct benefit and cannot meet the conditions specified in the category of 45 CFR 406 (Number 3 above a-e). The research is not otherwise locally approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research in this category must meet the following requirements:
  - a. The IRB must find that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children.
  - b. A request must be made by the PI, through the IRB, to the Minister of Health or the Commissioner of UCPPS to approve the research. The Minister or Commissioner, after consultation with a panel of experts in pertinent disciplines and following opportunity for public comment, may approve the research.

#### 12.4.3 IRB Review of Non-Government-Funded Research Involving Children

Research that involves children and is not Government-funded must meet one of the approvable categories described in Section 12.4.2 (1-3). However, for research falling under category 45 CFR 46.407 (See Section 12.4.2 (4)) and not UCPPS/U.S. FDA regulated, the PI must request that the IRB establish an expert panel to review the research. Based on recommendations of the panel, the IRB will consider the research for approval.

#### 12.4.4 Assent/Permission Requirements for Research Involving Children

1. Requirements for documentation of assent depend on the age, maturity, and psychological state of the child:
  - a. For children under the age of 7, assent is waived or verbal assent is obtained as determined by the IRB.
  - b. For children ages 7-12, a simple assent form is used and verbal assent is obtained. The child does not have to sign the assent form.
  - c. For children ages 13-17, a simple assent form is used, verbal assent is obtained, and the child must sign the assent form.
2. If the research is approvable under 45 CFR 46.404 46.405, the IRB will determine that the permission of one parent is sufficient or whether the permission of both parents is required unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
3. If the research is approvable under 45 CFR 46, 406, 46.407, both parents must sign the parental permission form, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
4. For research approved under 45 CFR 46.404, 46.405, the parents can override a child's decision not to participate. Parents cannot override a child's decision not to participate if the research is approvable under 45 CFR 46.406, 46.407. The IRB could waive the requirement for the child's assent, in which case the parents could override the child's decision to participate for all research activities.
5. A legal guardian could only give permission for inclusion of a child as a research subject if the document granting guardianship authorizes the person to give permission for "medical care including research."

#### 12.4.5 Exceptions to Assent Requirements for Research Involving Children

When the IRB determines that assent is not a requirement for some or all children in a study, the IRB determines and documents one or more of the following:

1. The children are not capable of providing assent based on their age, maturity or psychological state.
2. The intervention or procedure holds the prospect of direct benefit that is important to the health or well-being of the child and is available only within the context of the research and the capability of the children is so limited that they cannot reasonably be consulted.
3. Assent can be waived using the criteria for waiver of the consent process.

#### 12.4.6 Waiver of Permission Requirements for Research Involving Children

Generally, written documentation of parental permission is required when recruiting and enrolling subjects who are children. The documentation must signify "active" permission in which the parent specifically signs the document granting permission for the child to participate in the research. "Passive" permission, in which the researcher assumes that if the permission form is not returned the parent has granted implied permission, is not allowable.

However, the IRB will consider requests for a waiver of the requirement for parental permission and/or

a waiver of the requirement to obtain written documentation of consent on a case-by-case basis, determine if a waiver is appropriate and/or permissible under 45 CFR 46.408(c), and document its findings and determination. The IRB may determine that the research protocol is designed for conditions or for a subject population for which parental permission is not a reasonable requirement to protect the subjects and may approve a waiver, provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted and the waiver is consistent with federal, state, and local law.

If the research will be conducted in a school setting, a waiver of the requirement for parental permission and/or the requirement for written documentation of parental permission may not be allowable under the requirements of the [Protection of Pupil Rights Amendment](#).

#### 12.4.7 Compensation to Children and/or Parents

For many studies, especially those conducted in schools, reimbursement is generally not appropriate. However, if a researcher believes that reimbursement is appropriate, the following general guidelines, as described in Section 4.8, should be adhered to:

1. Any compensation should not be contingent upon the subject completing the study, but should accrue as the study progresses.
2. Unless it creates undue inconvenience or a coercive practice, compensation to subjects who withdraw from the study should be made at the time they would have completed the study, had they not withdrawn.
3. Compensation given as a “bonus” or incentive for completing the study is technically acceptable to the UCPPS/U.S. FDA, provided that the amount is not coercive. However, this sort of compensation is usually viewed by the IRB as coercive. The IRB is responsible for determining if the amount is not so large as to be coercive or represent undue influence.
4. The amount of compensation should be clearly set forth in the assent and parental permission forms.

When considering the amount of compensation to be given to a child and/or the child’s parents, special consideration must be given to ensure that the child does not simply assent to participate based on the amount or type of compensation. In addition, the amount of compensation should not be so large that the parents would provide undue pressure on the child to assent to participate. The PI should consider that the type or amount of compensation may be coercive in some situations and not coercive in others and make every effort to establish a compensation amount and schedule that will not be a factor in the child’s decision whether to participate or the parent’s decision to give permission for a child’s participation.

#### 12.4.8 When a Child Reaches the Age of Consent While Enrolled in a Study

Informed consent should be viewed as an ongoing process throughout the duration of a research project. When a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent (18 years old in Uzbekistan) to the procedures involved in ongoing research, the subject’s participation in the research is no longer regulated by the requirements of 45 CFR Part 46, Subpart D regarding parental or guardian permission and subject assent.

Unless the IRB determines that the requirements for obtaining informed consent can be waived, the PIs

should seek and obtain legally effective informed consent as described in Section 6 for the now-adult subject for any ongoing interactions or interventions with the subject. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent, if it finds and documents that the criteria for waiver are met.

Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of “human subjects research” (e.g., continued analysis of specimens or data for which the subject’s identity is readily available to the PI), it would be necessary for the PI(s) to seek and obtain legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver of the requirements for obtaining informed consent in order for the subjects to continue to participate in the research.

#### 12.4.9 Wards

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 or 45 CFR 46.407 only if such research is:

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

Research approved for inclusion of wards under 45 CFR 46.406 or 45 CFR 46.407 shall 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 a guardian or *in loco parentis*. One individual may serve as advocate for more than one child. The advocate shall 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 and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the PI(s), or the guardian organization.

### 12.5 Other Vulnerable Populations

Although there are no specific regulations governing the inclusion of other groups of vulnerable persons in research, there are other vulnerable populations that may be approached for enrollment in research protocols. A vulnerable population is one in which there is potential for real or perceived coercion or undue influence for subjects to enroll in the study or the subjects may be incapable of fully understanding the potential risks of the research. In all cases, the IRB must consider the possibility and justification for including these subjects in the proposed research and safeguards to protect their rights and welfare. The reference for vulnerable populations in 12.5.1 and 12.5.2 are not all inclusive.

#### 12.5.1 Research Involving Decisionally Impaired Adults

Special procedures for IRB review and approval apply to research activities involving potential research subjects who, for a wide variety of reasons, are incapacitated to the extent that their decision-making capabilities are diminished or absent. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems. Conversely, individuals with these problems should not be presumed to be cognitively impaired.

The following guidelines are taken from a document produced by the OHRP as “Points to Consider”. The OHRP intends that these points be considered by IRBs and PIs in their effort to protect research subjects.

Initially, the PI must assess whether or not the study could be performed utilizing competent subjects (those without impaired decision making capacity) and determine that competent persons are not suitable for the proposed research. PIs must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision making capacity as subjects by considering the following:

1. Incompetent persons or persons with impaired decision making capacity are not being proposed as subjects simply because they were readily available;
2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there is at least a greater probability of direct benefit to the subject;
3. The research does not impose a risk of injury, unless the research is intended to benefit each subject and the probability of benefit is greater than the probability of harm;
4. Procedures are devised to ensure that subjects' legally authorized representative (LAR) are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity;
5. LARs will be told that their obligation is to try to determine what the prospective subject would do if competent, or if the prospective subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

Potential or actual research subjects who are decisionally-impaired may not understand the difference between research and treatment or the PI's role as both clinician and PI. Therefore, it is essential that the consent process clearly indicate the differences between individualized treatment and research and between the roles of clinician and PI. Mental or decisional impairment may include, but is not necessarily limited to, psychiatric disorders, organic impairments, developmental disorders, persons under the influence of drugs or alcohol, persons with traumatic injuries, and women in labor.

The following are a list of general guidelines to be considered:

1. Each IRB includes at least one voting member, independent of the research and with appropriate professional background, knowledge, and experience in working with individuals with questionable decision-making capacity. The IRB will also consider including additional voting members from the community, perhaps representatives of patient advocacy groups.
2. PIs should be sensitive to differing levels of capacity and use assessment methods tailored to the specific situation. Also important is the PI's timing of the assessment in order to avoid periods of heightened vulnerability. Both the IRB and PIs must recognize that decision-making capacity may fluctuate and require ongoing assessment throughout the course of the research.
3. Responsibilities of the IRB are significant and will reflect heightened vigilance in reviewing protocols proposing to include this vulnerable population. As such, not all projects proposing to include decisionally-impaired persons should or will be approved by the IRB.
4. As the level of impairment increases, along with an increase in risks and discomforts, safeguards should also increase proportionate to the severity of the impairment. Provisions for additional safeguards should be in place prior to involving subjects in more than minimal risk research when the subjects' decision-making capacity is

- impaired. PIs should provide ongoing efforts to enhance the subjects' understanding and appreciation of their role in the research.
5. IRBs and PIs should be creative in choosing appropriate protections. Other options that may be used to provide additional protections may include:
    - a. Use of an independent monitor to assess the potential subject's decision-making capacity or to be present during subject recruitment and the consent process. If the impairment in decision-making capacity is based on a diagnosis of mental illness, the PI should obtain consultation with a psychiatrist or licensed psychologist.
    - b. Use of a family member or other LAR as a surrogate for research decisions. This must be approved by the IRB and should be documented on the consent form. The representative should be authorized to give permission for "medical care including research."
  6. The autonomy of the individual with impaired decision-making capacity should be respected. Their assent to participate in the research should be obtained, whenever possible, and their decision to withdraw from a study at any time should be honored.
  7. Use of an advance directive for research may be considered.
  8. Since informed consent is an ongoing process throughout the course of the research, a written summary of important information about the research may be useful when provided on a regular basis. Communication between PIs and their staff and the participants and their families is critical.
  9. Individuals with impaired decision-making capacity may need more time to consider the information they are given regarding the research. Information should be provided incrementally to facilitate understanding. Planned waiting periods to allow potential participants to consult with family members about whether to participate or not may be useful.
  10. IRBs and PIs must strive for a balance that maximizes potential benefits, recognizes individual autonomy, and minimizes risks associated with the research.

#### 12.5.2 Educationally/Economically Disadvantaged

According to the U.S. Federal regulations at 45 CFR 46.111(b), when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as the educationally or economically disadvantaged, additional safeguards must be included in the study to protect the rights and welfare of these subjects. The IRB will review protocols that are likely to include educationally/economically disadvantaged subjects for special risks that may be present for this group, i.e., the potential for undue influence/coercion in recruitment or enrollment, the potential for enrolling more subjects from this group than from other groups because of their vulnerability, etc.

## Section 13: Community-Based Research

### 13.1 Purpose

With increased focus of funding agencies and researchers on approaches to public health research and the influence of social and political systems on behavioral and health outcomes, there is increased potential for more faculty to become involved in community-based research. Due to this increased interest and focus, it is important for the RSSPMC of Hematology, researchers, and the IRB to understand the distinctions along a continuum of community-based research. As with research involving individuals, all parties to the research, especially the IRB, must consider both individual and community interests, risks, and potential benefits.

### 13.2 Principles for Community-Based Research

The RSSPMC of Hematology recognizes the importance of research conducted within communities. When conducting or participating in these research activities, the RSSPMC of Hematology desires to engage the community, strengthen community linkages, and respect community values. Human research has historically been guided by principles relating to risk and benefits to the individual research subject. Community-based research has interaction with the community that goes beyond interactions with individual potential research subjects and, therefore, requires consideration of the risks and benefits to the stakeholder community.

Because there is a continuum of involvement between RSSPMC of Hematology researchers and communities, a single set of guidelines is not appropriate. However, all research involving communities should follow best practices for respectful and productive relationships. The following principles, in addition to those principles for human subjects research, then guide the research:

1. Principles of community-based research necessitate that the researcher:
  - a. Should be aware and respectful of community interests that go beyond those of individual potential research subjects
  - b. Identify potential community stakeholders as well as individual research subjects.
  - c. Inform the community stakeholders and potential research subjects about the research.
  - d. Invite feedback regarding concerns about the research from community stakeholders and individual potential research subjects.
2. Principles for basic community partnership necessitate that the researcher should do all of the above, plus:
  - a. Respect the community partner's interest in the project and be open to ways that the community might benefit or want to use the information.
  - b. Disseminate research findings to both community stakeholders and individual research subjects.
3. Principles for close community partnership research (sometimes referred to as Community-based Participatory Research or CBPR) will want to do all of the above along with:
  - a. Having the research topic address a community-defined need, question or problem, and strive to combine knowledge with action to achieve necessary changes.
  - b. Recognizing the research as a partnership and be open to the guidance of community insight and experience.



- c. Having the partnership appropriately balance power and decision-making between the researchers and the community participants in a way that is mutually acceptable.
- d. Partners making clear and open communication an ongoing priority by striving to understand each other's needs and self-interests.
- e. Partners recognizing race, ethnicity, class, and other aspects of culture matter and talk openly about these issues.
- f. Feedback among all stakeholders in the partnership, with the goals of continuously improving the partnership and its outcomes.
- g. Realizing partnerships can dissolve and plan a process for closure.

### 13.3 IRB Review of Community-Based Research

The IRB review process will include an assessment of whether the IRB application submission includes sufficient information to assess a community-based research focus using the principles above.

To support the IRB review of community-based research projects, the Office of Research Support and Compliance staff will offer periodic training to IRB members that cover topics related to the design, implementation, and dissemination of results of such research. The training may include presentation of pertinent information (e.g., principles of community-based research as outlined above) during IRB meetings, providing written guidance, or other resources on this topic. IRB staff are also available to assist IRB reviewers and researchers with education, project-specific questions, and IRB submission requirements.

Additionally, the HRPP makes an effort to include IRB members and/or consultants with expertise in community-based participatory research by identifying and recruiting investigators and community members whose experience reflect such knowledge.

### 13.4 References

University of Minnesota, Clinical Trials Office. Performance of Community-Based Research: Guidance Statement.

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Israel BA, Schultz AJ, Parker EA and Becker AB. Review of community-based research: Assessing partnership approaches to improve public health. *Ann Rev Pub Health* 19: 173-202, 1998.

## Section 14: Transnational Research

### 14.1 General Researcher Considerations

It is a relatively common occurrence that RSSPMC of Hematology researchers will perform human subjects research outside the borders of the Republic of Uzbekistan. When performing human subjects research in foreign countries, expectations of the RSSPMC of Hematology are that the research activities are consistent with the ethical principles and guidelines contained in the Belmont Report and provide levels of subject protections equivalent to those provided when performing human subjects research at the RSSPMC of Hematology. It is also expected that researchers will comply with local laws and take into account the cultural context of the country in which the research is taking place.

When performing human subjects research in other countries, RSSPMC of Hematology researchers are expected to comply with Uzbek regulations and guidelines and any applicable regulations of the country in which the research is performed. In addition, for biomedical research there are international guidelines that may be applicable and with which the RSSPMC of Hematology researchers should be familiar; e.g., The Declaration of Helsinki, the International Conference of Harmonization – Good Clinical Practice (E6) Guidelines and the [International Compilation of Human Research Standards compiled by Office for Human Research Protections](#) .

### 14.2 Specific Principal Investigator Considerations

Government regulations for oversight of transnational research, as well as expectations of the HRPP accrediting body, the U.S. Association for Accreditation of Human Research Protection Programs (AAHRPP) require that when conducting transnational research the researcher:

1. Will provide the same or equivalent protections to human subjects in research conducted in other countries.
  - a. The protections need not be the same as provided in the U.S. but should be equal in function or effect.
  - b. Subject autonomy and dignity should be respected.
  - c. Protections should encompass the ethical principles of respect for person, beneficence, and justice.
2. Is aware of local laws, regulations, political and socio-economic factors, and cultural context in all locations where the research is conducted.
  - a. Researchers must have sufficient knowledge of the local context to enable carrying out of the research in ways that protect the rights and welfare of subjects.
  - b. Knowledge of the local context may influence all aspects of the research design.
3. Will comply with local laws and adhere to cultural norms.
4. Will demonstrate whether the university or researcher has permission to conduct research in the country by local ethics committee review and approval or by certification (approval) by the local government when there is no local ethics committee.

Researchers conducting transnational research are required to complete and submit Supplemental Form International Research, which addresses the above requirements, during the application process.

Post-approval monitoring of transnational research will follow the same procedures used for monitoring of locally conducted research as described in Section 3.18. Monitoring will usually consist of a face-to-face meeting with the investigator to discuss the conduct of the research prior to beginning or at some time during the conduct of the study when the investigator is located at RSSPMC of Hematology.

### 14.3 General Reviewer Considerations

There are also requirements and expectations for reviewing proposed transnational research. Generally:

1. The IRB must ensure that equivalent protections are provided to research subjects enrolled in research in another country, and;
2. The IRB will make determinations and decisions based on laws and knowledge of the country in which the research will be conducted, such as:
  - a. If there are laws or guidance related to human research subject protections.
  - b. If there are other laws that will need to be factored into the research.
  - c. If the local or government has their own required approvals.

### 14.4 Specific Principal Investigator and Reviewer Considerations

More specifically, IRB reviewers and the IRB will require certain information in order to fulfill the requirements and this information should be addressed in the submitted protocol. For example, the information provided should include but not be limited to:

1. Whether the researcher speaks the language of the country in which participants will be enrolled and the research will be conducted. If the researcher does not speak the local language, describe how communication with the research subjects will be accomplished.
2. Whether the researcher is familiar with the local customs and culture or whether a local collaborator will be used and the involvement of the local collaborator will have in the conduct of the research.
3. Whether the subjects will be paid and, if paid, the amount and how it relates to the local economy and subject income.
4. If consent will be obtained, how or from whom will consent be obtained along with the following information, if applicable:
  - a. Describe local customs/culture in which the subject might not have the autonomy to provide consent and a family member or other person will be providing consent to participate.
  - b. How the researcher will assure that there is no coercion for participation if a person other than the subject will be providing consent.
5. If written documentation of consent will be obtained, and:
  - a. If so, a description of how or from whom the consent will be translated.
  - b. If not, a description of how consent will be documented or if there are cultural/other prohibitions regarding use of consent forms. Describe how the privacy for the subjects and confidentiality of their research data will be assured

and if there is a local custom that research data be revealed to someone other than the subject. Describe how the communications with the University IRB/local Ethics Committee (EC) will be achieved for requesting amendments or reporting unanticipated problems.

6. For student researchers, a description how the academic advisor/faculty sponsor will oversee conduct of the research.

### 14.5 Exemptions

A great deal of research in the social and behavioral sciences poses no more than minimal risk to subjects and may qualify for exemption. Performance of research in another country does not exclude the research from consideration for exemption.

There may be other factors, specific to the locale that could disqualify the research from exemption.

Even in exempt research, informed consent, parental permission, and child assent may be ethically appropriate and/or required under local law.

### 14.6 Risk Assessment

The IRB must assure, perhaps through consultation with experts, as needed, that the risk assessment is accurate for the foreign site. Research methods that have minimal risk in the Uzbekistan might have greater than minimal risk when conducted at certain foreign sites. The following must be given consideration:

1. Questions that might be innocuous in Uzbekistan could be offensive at certain foreign sites.
2. Assuring and maintaining confidentiality may be difficult in other countries.
3. Breach of confidentiality in the research locale could have dangerous consequences.
4. Depending on political and other factors, there may be dangers to the researcher.

### 14.7 Informed Consent

1. The informed consent process must honor local custom.
  - a. Some cultures may have a different authority structure for consent.
  - b. The local consent structure may seem coercive and clash with the researcher's, reviewer's, or IRB/EC's views on autonomy.
2. Surrogate consent/permission should not substitute for a subject's informed consent unless the IRB/EC has approved an alteration or waiver to the consent process.
3. The consent process/form should, unless waived by the IRB/EC, contain all required elements of informed consent.
4. Consent is best obtained using the language that is most familiar to the subjects taking into account:
  - a. Some languages/dialects are not written.
  - b. Subjects may be unable to read.
  - c. There may be words in the foreign language that do not translate to/from English.
  - d. If researchers are not fluent in the local language, interpreters/translators who are fluent should be used.
5. Documentation of consent may be difficult because:
  - a. Subjects may be illiterate.
  - b. In some cultures, it may be inappropriate to ask for a signature.
  - c. There may be legal implications when signing documents.

- d. Subjects may be suspicious, distrustful, or fearful they are giving up their rights when asked to sign documents.
- 6. Alternate consent procedures may have to be considered such as:
  - a. Use of pictures, video, or computers.
  - b. Alternate forms of documentation such as thumbprints.

#### 14.8 International Research Involving Children

The following should be considered when the research involves children:

- 1. In the locale of the research, when a child is considered an adult.
- 2. The relationship between parents and their children in the specific country.
- 3. Acceptable and effective parental permission processes.
- 4. If child assent is acceptable/permissible by local custom.
- 5. If there are laws pertaining to orphans.

#### 14.9 Communication with IRB/Ethics Committee and Faculty Sponsor

With the research occurring outside of the country there should be consideration on how the communication between the researcher and the RSSPMC of Hematology will take place. The protocol should describe the following:

- 1. How communication will occur with the University IRB and the local EC.
- 2. How ongoing review, amendments, or reporting of unanticipated problems or complaints will be handled and by whom.
- 3. If it is a student researcher abroad, the student's knowledge of the country and how the student will communicate with their faculty advisor.
- 4. List local contact in case Principal Investigator or faculty sponsor cannot be reached.

## Section 15: Research Using Deceptive or Incomplete Disclosure

### 15.1 Background and Rationale

Research involving deception and incomplete disclosure involves intentionally communicating information to research subjects in a way that produces false beliefs. Obfuscation or withholding information at the outset of a study is also considered deception. Any research in which information is withheld until subjects have participated to some degree should be considered as a deception study. This type of research methodology is sometimes used to:

1. Improve study validity,
2. Assure study integrity, or
3. Allow data collection that would otherwise be unobtainable because of defensiveness, shame, etc.

### 15.2 General Guidelines

The following are general guidelines regarding the design, review and conduct of studies involving deception and incomplete disclosure:

1. Use of deception and incomplete disclosure is usually only acceptable for studies that are minimal risk.
2. The use of deception/incomplete disclosure should have no adverse effects on the well-being of subjects.
3. The IRB must be supplied with sufficient information to determine that the value of the research outweighs the risk of waiving some aspects of the requirement for full disclosure in the informed consent process. (See Section 6.7 Waiver of Informed Consent and Waiver of Documentation of Consent)
4. There is no reasonable alternative to scientifically and effectively address the research question without the use of deception/incomplete disclosure.
5. Subjects are not deceived about any aspect of the study that would alter their willingness to participate.
6. As soon as it is appropriate, debriefing should be accomplished and the deception/incomplete disclosure explained to subjects.
7. When appropriate, subjects should be informed prospectively of the use of deception/incomplete disclosure and consent to its use.
8. During debriefing inform subjects of their right to withdraw their data, if they wish, and how that will be accomplished.

### 15.3 Principal Investigator Requirements

To assist the IRB in its review and determination of the appropriateness of the research study, Principal Investigator(s) should address the following items in the relevant documents:

1. Explain the reason(s) for use of deception/incomplete disclosure in the study design. Specifically, address why complete disclosure would compromise the scientific validity of the study.
2. Describe the extent of the deception/incomplete disclosure in detail and how it relates to the study aims and design.
3. Justify and discuss how the proposed research, involving deception/incomplete disclosure involves no more than minimal risk to subjects. Consider all levels of

increased risk subjects could experience as a result of the deception/incomplete disclosure methodology.

4. Justify and discuss why there are no feasible or scientifically valid alternative methods, which do not involve deception/incomplete disclosure, to conduct the research.
5. Describe the methods for prompt disclosure to debrief subjects. This should be accomplished as soon as possible after subjects complete research related activities. Also describe how you will assure that subjects leave the study setting with a clear and accurate understanding of the deception/incomplete disclosure and the reasons for using this methodology. If debriefing is not planned, justify why.

#### 15.4 Potential Risks

There are several potential risks associated with use of deception/incomplete disclosure and these should be considered when designing the study:

1. Subjects may feel that they were coerced to act against their will. If so and if they had been completely informed, they may have chosen not to participate.
2. Subjects may feel ashamed, guilty, stressed, or embarrassed because they now have knowledge about themselves that they otherwise would not have known or would not want to know.
3. Subjects may feel a loss of control that will cause distrust and suspicion regarding human subjects research in general.
4. The research may undermine the trust in professional standards governing human subjects research.

## Section 16: Research Utilizing Surveys and Internet Research

### 16.1 Survey Research

Research utilizing surveys, varying from brief and informal to lengthy and large scale questionnaires designed for large samples, has been one of the most used data collection tools in the social sciences. What was once done using paper-based surveys is now being accomplished using the Internet and, due to the relative ease of Internet distribution, results in a large increase in the number of surveys people are asked to complete. Some researchers feel that over-surveying has led to survey fatigue and a widespread decrease in survey response rates. Therefore, to ease the potential for survey fatigue and to assure a good response rate for the survey, consideration should be given to:

1. Choose a target audience and attempt to limit the people who will receive the survey to those that will provide data most relevant.
2. Have clarity and brevity in the communications. Be clear regarding why the participants are getting the survey, how long it will take to complete and how the data will be used.
3. Have efficient survey design; the survey should be no longer than absolutely necessary.

Regardless of how surveys are distributed, the IRB must review the proposed research, including the surveys, to evaluate subject recruitment methods, the informed consent process and document, data collection and storage methods, risks of participation, and other features of the research to assure adequate subject protections. Therefore, the appropriate IRB forms must be completed and submitted. Research involving the use of surveys is usually minimal risk and can be reviewed by an expedited process or deemed exempt from IRB review, unless the survey questions are sensitive, potentially provoking psychological distress.

As stated previously, there is always a requirement to obtain informed consent from research subjects. Researchers must discuss the study purpose, procedures, potential risks and benefits, the voluntary nature of participation, researcher contact information if subjects have questions, and the other required elements of informed consent. However, the regulations allow the IRB to approve a waiver or alteration of the consent process in which some of the required elements may be omitted and/or the method of obtaining and documenting consent altered (See Section 6.7 Waiver of Informed Consent and Waiver of Documentation of Consent).

For research utilizing surveys, approval is usually granted for an informed consent process that includes a consent document in the form of a cover letter that is at the beginning of the survey. It is recommended that researchers use the Compact Informed Consent Template when creating a consent form for survey research. In this consent cover letter, subjects are informed about the study and told that they can opt out of the research simply by not continuing to the survey questions and they may withdraw at any time by exiting the survey. The requirement for obtaining written documentation of consent (a signature) is waived as subjects agree to participate is signified by completing the survey.

Researchers who conduct online research should add the following information to their message:

1. The words "Research" should be in the "Subject" line.
2. The message should state at the outset where the e-mail addresses were obtained.



3. Include either a statement that there will be no future mailings or an “opt-out” message that directs the researcher to remove the subject’s name from future mailings.
4. If there will be future e-mails, add the statement, “If you do not respond to this survey or return the “opt-out” message, you will receive repeat e-mail messages X times during the next Y weeks.
5. Include a contact e-mail address and telephone number in the last sentence of the e-mail message.
6. Use a “blind copy format” so that the list of recipients will not appear in the message header.

## 16.2 Internet Research

Internet communication is extensively used and provides access to an enormous amount of information to “Internet communities.” Access to these communities and the information associated with them raises a number of ethical questions and challenges for researchers and IRB. Perhaps the biggest challenges that are faced relate to privacy and informed consent.

In their research proposals, RSSPMC of Hematology researchers should, at a minimum describe:

1. The Internet methods and technology that will be used to interact with “Internet communities.”
2. Potential risks and benefits of the research and how risks will be minimized.
3. The informed consent process that will be used, i.e., how Internet community members will be informed that research data is being collected, how community members can “opt-out” of having their data collected, etc. or justify why a waiver from the requirement to obtain informed consent is appropriate.
4. The methods they will use to assure protection of privacy for subjects and how confidentiality of the data will be provided.

Proposals for Internet research may meet criteria for exemption from IRB review. However, other issues may dictate a higher, more stringent level of review such as:

1. The complexity of reducing potential risks.
2. Protecting privacy and confidentiality.
3. Obtaining true informed consent.
4. Justifying a waiver.

## Section 17: Genetic Materials

### 17.1 Collection and Storage of Genetic Materials

For the purpose of this manual, "Genetic Materials" are defined as human tissue samples (saliva, blood, serum, tumor, etc.) on which genetic-related research, such as identification and location of specific genes, study of gene products, inherited human traits, or identification and analysis of DNA mutations, may be performed.

It should be noted that research involving genetic materials may require the [Institution Biosafety Committee](#) approval prior to beginning the research.

#### 17.1.1 Previously Acquired Samples

1. Previously acquired samples and genetic material, collected without identifiers (including no codes linking to identifiers) may be used, without further IRB approval, if future use was generally discussed in the original consent form.
2. If identifiers are present, experiments not described in current protocols must be submitted for IRB review.

#### 17.1.2 Prospectively Acquired Anonymous Samples

For research in which samples (blood, tissue, saliva, etc.) will be prospectively acquired without identification, the following issues must be presented in the consent form and discussed with the research subjects.

1. How anonymity of the samples will be accomplished. Some basic information, such as age and gender, may be retained with the sample;
2. Ownership of genetic material (usually the RSSPMC of Hematology);
3. The general scope of the investigations, but new avenues of investigation in the future are permissible if this possibility is presented and explained during the consent process;
4. Whether the sample or its genetic material will be shared by other investigators
5. That information specific to individual subject cannot be shared due to sample de-identification. However, information that accrues from the study that is valuable to society will be shared through publications.

#### 17.1.3 Identified Samples

As for research acquiring anonymous samples, research utilizing samples collected with identifiers must clearly presented in the consent form and discussed with research subjects. The following issues should be considered and discussed as appropriate:

1. If genetic material is linked to the donor by specific identifiers, ownership of the material will generally remain with the institution. If a commercial use is anticipated for the genetic material, the individual must be notified. The general policy of ownership should be stated in the consent form.
2. If identifiers are present, new experiments (not described in the original consent form) must be reviewed by the IRB and new consent obtained from the research subject regardless of the details of ownership.

3. The Principal Investigator may include a provision in the consent form for new experiments not requiring new consent if identifiers are irrevocably removed from the samples. If the PI anticipates future experiments without identifiers, this possibility should be presented in the original consent form. The methods for removal of identifiers must be approved by the IRB. Removal of identifiers must not be employed as a method of avoiding ownership issues.
4. A satisfactory method for sharing or withholding information gained by the research must be in the research protocol and clearly indicated in the consent form.
5. Details for sharing or not sharing the genetic material with other investigators must be present in the protocol and clearly indicated in the consent form.
6. The length of time the genetic material will be maintained must be indicated in the consent form.

## Section 18: Stem Cell Research

### 18.1 Human Embryonic Stem Cells

**Human Embryonic Stem Cells** are pluripotent cells that are derived from early stage of embryos, up to and including the blastocyst stage, are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers.

#### 18.1.1 Applicable Guidance, Regulations, and Laws

All clinical research involving stem cell-derived test articles is subject to Uzbek UCPPS/U.S. US FDA regulations at 21 CFR Parts 312 and 812, regardless of the source of funding. This research is also subject to FDA's IRB and informed consent regulations at 21 CFR Parts 50 and 56. Clinical investigations involving the transplantation of cells or test articles derived from hESC or fetal tissue into human recipients is subject to Public Law 103-43, "[Research on Transplantation of Fetal Tissue](#)".

#### 18.1.2 Human Embryonic Germ Cells Derived from Fetal Tissue

Research involving the derivation or utilization of human embryonic germ cells from fetal tissue must also comply with the fetal tissue transplantation research statutes and may be conducted with federal funding support.

Research deriving or utilizing human embryonic germ cells from fetal tissue should comply with the informed consent law applicable to fetal tissue transplantation research. The informed consent process should inform potential donors, pursuant to making the decision whether to donate fetal tissue for research purposes, with the following information:

1. A statement that fetal tissue will be used to derive human pluripotent stem (hPS) cells for research that may include human transplantation research.
2. A statement that the donation is made without any restriction or direction regarding the individual(s) who may be the recipient(s) of transplantation of the cells derived from the fetal tissue.
3. A statement as to whether or not information that could identify the donors of the fetal tissue, directly or through identifiers linked to the donors, will be removed prior to the derivation or the use of hPS cells.
4. A statement that derived cells and/or cell lines may be kept for many years.
5. A disclosure of the possibility that the results of research on hPS cells may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development; and
6. A statement that the research is not intended to provide direct medical benefit to the donor.

### 18.2 Research with Adult Stem Cells

Generally, the collection or derivation of human multi-potent and pluripotent stem cells from sources other than embryos does not involve the same ethical issues as encountered with hESC and is subject to

the guidance and regulations for sampling any tissue from human research subjects.

### 18.3 IRB Review Requirements

The following criteria apply concerning the requirement for IRB review of proposed research:

1. *In vitro* research involving stem cells from which the identity of the donor cannot readily be ascertained by the investigator is not considered to be human subjects research and is not subject to IRB review. This assumes that the investigator and research institution do not have access to private information related to the cell line and that the holder of the identifiable private information related to the cell line has agreed that such information will not be released.
2. Research involving cells that have already been derived and established, where the donor may be identified, including cells that retain links (such as a code) to identifying information, is considered to be human subjects research and is required to undergo IRB review and approval.

## Section 19: Health Record Research

### 19.1 Purpose

The following is the IRB policy concerning research involving the study of medical records or other forms of protected health information (PHI) (See Section 2: Definitions). The policy is not intended to supersede any current medical records guidelines or other policies concerning PHI.

### 19.2 Protected Health Information (PHI) & U.S. HIPAA

The U.S. Health Insurance Portability and Accountability Act (HIPAA), also known as “The Privacy Rule,” set standards and regulations to protect patients from inappropriate disclosures of their protected health information (PHI) that could cause harm to their insurability, employability, and/or their privacy. HIPAA allows for researchers to access and use PHI when necessary to conduct research. Not all research is subject to HIPAA regulations; HIPAA only affects research that uses, creates, or discloses PHI.

Protection Health Information (PHI) is any information in the medical record or designated record set that can be used to identify an individual and that was created, used, or disclosures in the course of providing a healthcare service such as treatment or diagnosis. HIPAA defines 18 specific identifiers that create PHI when linked to health information: names, geographic subdivisions smaller than a state, all elements of dates (except year) for dates that are directly related to an individual (e.g., birth date, admission date, discharge date), telephone numbers, vehicle identification and serial numbers (including license plate numbers), fax numbers, device identifiers and serial numbers, email addresses, URLs, social security numbers, internet protocol (IP) addresses, medical record numbers, biometric identifiers (including finger and voice prints), health plan beneficiary numbers, full-face photographs and any comparable images, account numbers, account numbers, certificate/license numbers, and any other unique identifying number, characteristic, or code.

HIPAA regulations allow researchers to obtain approval to access and use PHI when necessary to conduct research.

### 19.3 De-identified PHI

PHI can be used or disclosed for research purposes if it has been de-identified and linkage back to a specific subject would not be possible. National Institutes of Health Department of Health Regulations at [45 CFR 164.514\(e\)](#) provides more details for de-identified information.

See also: [OHRP Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act \(HIPAA\) Privacy Rule.](#)

### 19.4 Identifiable PHI

Research use or disclosure of identifiable PHI with authorization of the research subject is permitted providing that use or disclosure is for only the PHI that was originally authorized. In order to use or disclose additional information, the PI would either have to obtain authorization or request a waiver of the requirements to obtain authorization.

To use or disclose identifiable PHI without authorization of the research subject, the PI must accomplish one of the following:

1. Complete the HIPAA waiver sections of either IRB Supplemental Form PHI or IRB Proposal Secondary Use Submission Form, depending on the nature of the research.
2. Provide written documentation that the use or disclosure of PHI is solely used to design a research protocol or to assess feasibility of conducting a study.
3. Document that the use or disclosure is solely for research on the PHI of decedents.

### 19.5 Waiver of the Requirement for Obtaining Authorization

The IRB must review requests for waiver of the requirement for obtaining authorization for use and disclosure of PHI. If a waiver is approved, the IRB must notify the investigator in writing of its determination. PIs must maintain in their files the letter from the IRB which, in addition to the other required information listed below, identifies the IRB and the date on which the waiver or alteration of the requirements to obtain authorization was approved by the IRB. The letter should also include a statement that the IRB has determined that the waiver or alteration satisfies the following criteria:

1. The use or disclosure of PHI involves no more than minimal risk to the research subjects;
2. The alteration or waiver will not adversely affect the privacy rights and welfare of the subjects;
3. The research cannot practicably be conducted without the alteration or waiver;
4. The research could not practicably be conducted without access to or the use of the PHI;
5. The privacy risks to individuals whose PHI is to be used or disclosed are reasonable in relation to the anticipated benefits, if any, to the individuals, and the importance of the knowledge that may reasonable be expected to result from the research;
6. There is an adequate plan to protect the identifiers from improper use and disclosure;
7. There is an adequate plan to destroy the identifiers at the earliest possible opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers, and;
8. There are adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by this policy.

## Section 20: Human Tissue and Data Repositories for Research Use

### 20.1 Applicability

This section does not apply to principal investigators (PI) who collect biological fluids or other types of human tissue for analysis as a part of a specific research project. A human tissue or data repository is a collection of tissue samples or data with the intent of establishing a relatively large collection of data or tissue that will be accessed by other investigators who may or may not be located at the RSSPMC of Hematology.

### 20.2 Review and Oversight

The U.S. Department of Health & Human Services (HHS), Office of Human Research Protections (OHRP) requires operation of data and tissue repositories be overseen by an IRB. The IRB must review, approve the procedures and conditions under which data and/or tissue specimens are collected, stored, and shared, and ensure that there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. As part of its oversight responsibility, the IRB must review and approve a tissue and/or data collection protocol, or section of a protocol, and an informed consent document relating to the collection of the tissue specimens and/or data. For specific OHRP guidance refer to <http://www.hhs.gov/ohrp/policy/reposit.html>.

### 20.3 Considerations and Requirements

#### 20.3.1 IRB Review

Collection of data or tissue for storage in a repository must be reviewed and approved by the IRB. The IRB is familiar with the particular circumstances of the local research setting and must weigh considerations like local professional and community standards, institutional policies and resources, and the needs of differing subject populations. An IRB application must be submitted and, along with the standard requirements, address 1) what data or tissue is being collected; 2) a description and location and operation of the repository; 3) the type(s) of research that will be conducted using the data or tissue; 4) the conditions under which data and/or specimens will be released to recipient-investigators; and 5) the procedures to be used by during collection, storage, and release of the data or tissue for protecting the privacy of subjects and maintaining the confidentiality of data.

#### 20.3.2 Informed Consent Documentation

1. Written documentation of informed consent (consent form) should be obtained from each donor subject. An informed consent document/addendum specific to the repository should be used in addition to any other consent forms or the information may be included in a consent form that describes the entire research project.
2. Included among the basic elements of informed consent should be a clear description of 1) the operation of the repository; 2) the specific types of research to be conducted; 3) conditions under which data and specimens will be released to recipient-investigators; and 4) procedures for protecting the privacy of subjects and maintaining the confidentiality of data. Informed consent information describing the nature and purposes of the research should be as specific as possible. Where human genetic research is anticipated, informed consent information should include information about the consequences of DNA typing, and the consent form should also include a section for the participant to choose whether or not to allow the specimen to be used in genetic research.



3. Informed consent documents may not include any exculpatory language through which subjects are made to waive or appear to waive any legal rights.
4. The informed consent document should also contain an acknowledgement that collector-investigators and the repository are prohibited from providing recipient investigators with access to the identities of donor-subjects or to information through which the identities of donor-subjects could be readily ascertained.

### 20.3.3 Submittal Agreements

A written submittal agreement for tissue collectors should require written informed consent of the donor-subjects utilizing an informed consent document approved by the local IRB. It should also contain an acknowledgment that collectors are prohibited from providing recipient-investigators with access to the identities of donor-subjects or to information through which the identities of donor-subjects may readily be ascertained.

### 20.3.4 Usage Agreements

Investigators are encouraged to obtain a written usage agreement from recipient investigators that states the following: “Recipient acknowledges that the conditions for use of this research material are governed by the IRB overseeing the repository in accordance with HHS regulations at 45 CFR 46. Recipient agrees to comply fully with all such conditions and to report promptly to the repository any proposed changes in the research project and any unanticipated problems involving risks to donor-subjects or others. Recipient remains subject to applicable State or local laws or regulations and institutional policies that provide additional protections for human subjects.”

### 20.3.5 Certificate of Confidentiality

It is highly recommended that, for federally funded projects, a [Certificate of Confidentiality](#) is obtained to protect the confidentiality of repository specimens and data. See section 4.11.5 for additional information.

## 20.4 Repository Requirements

1. The research material may be only utilized in accordance with the conditions stipulated by the IRB overseeing the repository. Any additional use of this material requires prior review and approval by the IRB overseeing the repository, and where appropriate, by an IRB at the recipient site.
2. Recipient investigators may never be given information that would allow identification/re-identification of specimens of data to a specific donor.
3. A covered entity’s use or disclosure of PHI to create a research database or repository, and the use or disclosure of the PHI from the database or repository for a future research purpose are each considered as a separate research activity under the U.S. Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. In general, the Privacy Rule requires authorization for each activity unless an IRB waives or alters the authorization requirement. A single authorization can cover uses and disclosures for multiple activities of a specific research study, including the collection and storage of data and or tissue specimens. However, a compound authorization is not allowed where the provision of research-related treatment, payment, or eligibility for benefits is conditioned on only one of the authorizations and not the other. For example, if an investigator conducts a clinical trial that also involves collection of tissues and data (PHI) for storage in a central repository for future research use, the actual future research use

would require the investigator to obtain a separate authorization for use and disclosure of PHI or a waiver of the requirement for IRB authorization.

## Section 21: Data and Safety Monitoring in Research

### 21.1 General

For research involving human subjects, federal regulations require that, when appropriate, research plans make adequate provisions for monitoring data to ensure the safety of research participants. The regulations do not specify when or how this monitoring should be accomplished. For each study, researchers and the IRB must determine the type and level of monitoring required to assure subject safety and well-being.

### 21.2 Requirement for a Data and Safety Monitoring Plan

**Minimal Risk Studies** - Much of the research conducted at the RSSPMC of Hematology pertains to social and behavioral sciences and is generally considered to be not greater than minimal risk. Thus, many research studies may not be required to establish a Data and Safety Monitoring Plan (DSMP). However, sponsors or the IRB may require DSMPs regardless of risk. In all research, regardless of whether a formal data and safety monitoring plan is required, investigators are responsible for providing ongoing oversight to protect the safety and welfare of study participants.

**Greater Than Minimal Risk** - All human subjects research involving the use of investigational drugs, biologics, or devices require a DSMP. For other types of interventional human subjects research involving greater than minimal risk, a DSMP should be strongly considered and may be required by the IRB.

### 21.3 Types of Data and Safety Monitoring Plans

The methods and amount of monitoring required are somewhat dictated by the type and magnitude of risk involved, the population to be studied, and the complexity of the research, and can range from monitoring by the researcher or a group of researchers to the establishment of a Data and Safety Monitoring Board (DSMB).

**Monitoring by an individual investigator** – for studies that involve small numbers of research participants at a single site and interventions unlikely to lead to major changes in risks and benefits. Close, continuous monitoring by the researcher and prompt reporting of unanticipated problems to the IRB and sponsor are generally considered to be adequate.

**Monitoring by a group of investigators** – for studies where assessments may require additional expertise or objectivity from individual(s) who may or may not be directly involved with the design and/or conduct of the study. Studies overseen by a monitoring group of this type are generally short-term in nature, study endpoints do not include serious events, and risks to participants can be assessed through simple comparisons.

**Data and Safety Monitoring Board (or Committee)** – for studies involving large numbers of research participants, particularly vulnerable populations, multiple performance sites, blinded study groups, particularly high-risk interventions or when sophisticated data monitoring/statistical analysis is required. U.S. FDA regulated studies generally require establishment of a DSMB.

### 21.4 Components of DSMPs

Investigators should assure that the following issues are addressed in the plan:

1. The type of data or events that are to be captured under the monitoring provisions.

2. The frequency of assessments of data or events captured by the monitoring provisions (e.g., at certain points in time or after enrollment of a certain number of subjects).
3. The entity or person(s) responsible for monitoring the data collected, including data related to unanticipated problems and adverse events and their respective roles in the research activities (i.e., PIs, research coordinators, statisticians, independent medical monitor, etc.).
4. Procedures for monitoring study progress including specifics of how monitoring the data and safety of subjects will occur.
5. Procedures for minimizing research-related risk.
6. Procedures for analysis and interpretation of the data.
7. The procedures and time frames for reporting adverse events and unanticipated problems to the monitoring entity.
8. The definition of specific triggers or stopping rules that will dictate when some action is required and what the range of possible actions will be.
9. Reporting mechanisms/procedures for the data monitor and others who will communicate the outcome of the reviews of the monitoring entity with the IRBs, the study sponsor (if applicable), the PIs and other appropriate officials.
10. How data accuracy and protocol compliance will be assured.

## 21.5 IRB Review of DSMP

**Initial Review** – For research requiring a DSMP, the IRB will review the submitted DSMP to assure adequacy for protection of subjects from risks to the extent possible.

In order to approve research in which the IRB considers whether the provisions for monitoring data to ensure the safety of research participants are appropriate, the IRB must determine that the research plan makes adequate provisions for monitoring the data. In the review, the IRB might consider provisions such as:

- For studies that do not have or are not required to have a data monitoring committee (DMC) and are blinded, have multiple sites, enroll vulnerable populations or employ high-risk interventions, the IRB will carefully review the DSMP and determine whether a DMC is needed.
- If not using a DMC and, if applicable, whether there are statistical tests for analyzing data to determine whether harm to participants may be occurring.
- Provisions for the oversight of safety data, such as requiring a DMC.

**Continuing Review** – Researchers with DSMPs should submit information indicating that monitoring occurred as described in the research protocols. If a DSMP was not initially required, researchers should submit a summary of unanticipated problems along with any new information or literature that may be relevant to the research.

## Section 22: Protocol Deviations and Noncompliance

### 22.1 Reporting to the IRB

When a protocol deviation that meets the criteria for an unanticipated problem or incident of noncompliance (See Section 2 – Definitions) becomes known to a researcher, they must complete and submit a Protocol Deviation or Noncompliance Report via the Reportable New Information (RNI)

submission pathway with IRB. It is expected that researchers and research staff promptly self-report events that may meet the criteria for an unanticipated problem or noncompliance to the IRB.

Allegations or reports of protocol deviations and incidents of noncompliance may be identified via monitoring visits or via communication by someone other than the researcher through telephone calls, letters, e-mails, or any other method of communication and may be made to the ORSC office, the ORSC Director, the IRB Chair, or to the RSSPMC of Hematology Compliance Services Hotline (+998955157572). Change The identity of individuals making a report will remain confidential unless the individual provides permission to disclose his/her identity.

## 22.2 Response to Report

### 22.2.1 Initial Assessment

Upon receipt of a report or allegation of noncompliance, or upon identifying noncompliance as part of the review process, the IRB staff will make an initial assessment to determine whether the problem may rise to the level of serious and/or continuing noncompliance. Problems that are clearly not serious and/or continuing noncompliance may be managed by IRB members who are designated to conduct expedited reviews. Problems that may or may not constitute noncompliance should be referred to IRB leadership for further consideration. Problems that indicate a significant risk or severity will be evaluated to determine if immediate actions are necessary to ensure the ongoing protection of research subjects. The IRB Chair may elect to immediately suspend the research at any time to protect the safety, rights, or welfare of subjects.

When the facts of a situation are unclear, ORSC IRB staff may communicate with the study team to gather additional information. Upon receipt of the researcher's response, the allegation and response will be discussed with the ORSC Director, HRPP Director or IRB Chair or designated reviewer if necessary. The ORSC Director or HRPP Director will then determine whether the allegation is substantiated or requires further investigation.

If the noncompliance is clearly neither serious nor continuing, and there is a corrective action plan that can be readily implemented to prevent recurrence, if applicable, then the matter may be handled as a noncompliance that is neither serious nor continuing with the report being acknowledged by the designated reviewer.

### 22.2.2 IRB Investigation

Incidents appearing to involve serious and/or continuing noncompliance with a basis in fact, or if it cannot be determined if there is a basis in fact, may be the subject of further inquiry. The inquiry will be conducted by the ORSC Director, HRPP Director, the IRB Chair, or others as appropriate. If deemed necessary by the IRB Chair, an *ad hoc* subcommittee of the IRB may be appointed and may include any or all of the following: IRB Chair, IRB Vice Chair, ORSC Director, HRPP Director, other IRB members, and IRB staff. It will be determined whether anyone assigned to the *ad hoc* subcommittee has a conflict of interest with the investigator or the research that is the subject of the inquiry and, if a conflict exists, assign other members to replace those with the conflict.

In the event the investigation finds evidence that serious and/or continuing noncompliance may have occurred, the problem will be referred to the convened IRB. Applicable documents (may include

the study protocol, consent form(s), initial application, description of alleged noncompliance, and results of the investigation) pertaining to the incident and the investigation will be sent to IRB members prior to the meeting. Members are expected to review all documents prior to the meeting.

At a convened meeting, the IRB will determine if the incident of noncompliance was serious or continuing and what restrictions, conditions, or other remedial actions are necessary to resolve the noncompliance and the procedures required to prevent future occurrences. The researcher is notified in writing of the IRB's determination and of any required corrective actions. Notification of regulatory agencies, as applicable, will be accomplished according to Section 24.2. All documents relating to the investigation will be retained by the IRB Office.

### 22.2.3 Possible IRB Actions

1. **Research Suspension:** Suspension is when research activities are suspended due to serious concerns regarding investigator noncompliance. For example, subjects may be at increased risk due to inappropriate investigator actions. The investigator will be notified in writing of such a determination and any other actions required. The suspension will be reported to appropriate individuals and agencies as described in Section 24.
2. **Research Termination:** Termination of research activities occurs when the issues of noncompliance cannot be resolved. The investigator will be notified in writing of such a determination and the termination will be reported to appropriate individuals and agencies as described in Section 24.
3. **Other possible IRB actions include:**
  - a. Notification of current subjects when the information may relate to subjects' willingness to continue to participate in the research.
  - b. Modification of the protocol.
  - c. Modification of the information disclosed during the consent process.
  - d. Providing additional information to past subjects.
  - e. Requiring current subjects to re-consent to participate.
  - f. Modification of the continuing review schedule.
  - g. Monitoring of the research or the consent process.
  - h. Referral to other institutional units, including the Institutional Official who may impose additional corrective actions and/or disciplinary measures.
  - i. Referral to other organizational entities.

Note: If an IRB suspends or terminates a protocol, the IRB must:

- a. Consider whether procedures for withdrawal of enrolled subjects take into account their rights and welfare.
- b. Consider whether current subjects should be informed of the suspension or termination.
- c. Require any adverse events or outcomes of withdrawal to be reported to the IRB.

### 22.2.5 Noncompliance that is Not Serious or Ongoing

When noncompliance is reported or identified, the PI will be notified of the noncompliance determination in writing. Correspondence between the IRB member reviewing the noncompliance and the PI may occur as needed to determine appropriate corrective action. The noncompliance notification

from the IRB will denote any required corrective action. Incidents of noncompliance that were not found to be serious or ongoing will be in the IRB minutes.

#### 22.2.6 Reporting to IO and Others

If the incidents of noncompliance are serious or continuing, and/or the IRB determines that a protocol must be suspended or terminated, the incidents and IRB actions are reported to the IO, the applicable regulating agencies, and sponsor (if applicable) according to the requirements of the institutions U.S. Federalwide Assurance (FWA). (See Section 24).

## Section 23: Suspensions and Terminations

### 23.1 Reasons for Suspension or Termination

Common reasons for suspending or terminating a research protocol or research activities include, but are not limited to, instances when the research:

1. Has led to or is associated with an unexpected, serious increase in risks of harm to subjects.
2. Is associated with subject injuries.
3. Is not being conducted in accordance with IRB requirements (researcher noncompliance).

The IRB may suspend or terminate research based on information received during its continuing review, from the findings of the Quality Improvement visit, or from complaints made to the IRB.

Whenever a suspension or termination is enacted, the following must be taken into consideration:

- Actions that may be necessary to protect the rights and welfare of currently enrolled participants.
- Whether procedures for withdrawal of enrolled participants 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).
- Whether there is a need to inform current participants of the termination or suspension.
- The need to report any adverse events or outcomes to the IRB.

### 23.2 Authority to Suspend or Terminate Research Activities

#### 23.2.1 Principal Investigator

As the “front line” in subject protections, a principal investigator (PI) should always be aware of subject safety issues and should suspend research activities on a study in order to remove immediate hazards to subjects. If it is apparent that hazards cannot be eliminated by modification of various aspects of the study (e.g., the study design or inclusion/exclusion criteria) the study should be terminated. PIs must notify the IRB in writing immediately after suspending research activities or terminating a study. The notification should contain information on the facts leading to the decision for the action, a plan for notifying and safely withdrawing current subjects, if applicable, that considers whether the plan takes the subjects rights and welfare into account and, if applicable, a plan for notifying former subjects of the suspension/termination and any follow-up that may be required to assure their ongoing safety. The IRB will review reports of suspensions or terminations, determine what, if any further actions are required on the part of the PI, and report the suspension/termination to the IO and others as described in Section 24 of this manual.

#### 23.2.2 IRB Chair

The IRB Chair (and the Vice Chair if so delegated) can suspend or terminate IRB approval of a study, prior to discussion by the IRB, in order to remove immediate hazards to subjects or in the event there is sufficient evidence of noncompliance by the research team and that the noncompliance results in increased risk for subjects. The IRB Chair must consider protection of the rights and welfare of currently enrolled subjects (e.g., making arrangements for medical or other care of subjects). The PI will be



notified of the decision immediately and be required to submit a response to the IRB Chair's concerns. At a convened meeting of the IRB, the IRB Chair will report the suspension/termination, discuss the reasons for the decision, review the PI's response to the suspension/termination and lead an IRB discussion of the action, response, and possible further required actions. Possible further actions imposed by the IRB may include requiring the PI to submit a plan for notifying and safely withdrawing current subjects, a plan for notifying former subjects of the suspension/termination and any follow-up that may be required to assure their ongoing safety, if applicable, and a requirement that all adverse events or outcomes resulting from the research or the suspension/termination are reported to the IRB. A report of the suspension/termination will be submitted to the Institutional Official (IO) and others as described in Section 24 of this manual.

### 23.2.3 IRB

The IRB, at a convened meeting, may suspend research activities or terminate as a result of the following:

1. Reports of unanticipated problems involving risks to subjects and others (including adverse events).
2. Other reports that relate to subject safety in a particular protocol.
3. Reports of serious or ongoing non-compliance by the PI and/or research team.

The PI will be notified of the decision immediately and be required to submit a response to the IRB's concerns. At a subsequent convened meeting of the IRB, the IRB will review the PI's response to the suspension/termination, discuss the response and possible further actions required to lift the suspension or rescind the decision to terminate the research. Possible further actions imposed by the IRB might include requiring the PI to submit a plan for notifying and safely withdrawing current subjects and a plan for notifying former subjects of the suspension/termination and any follow-up that may be required to assure their ongoing safety, if applicable, and a requirement that all adverse events or outcomes resulting from the research or the suspension/termination are reported to the IRB. A report of the suspension/termination will be submitted to the IO and others as described in Section 24 of this manual.

### 23.2.4 Others

The IO or Director of ORSC may suspend a research activity or study should the need arise. Any such suspension must be promptly reported to the IRB Chair and to the convened membership at the next panel meeting.

## 23.3 Notification of Suspension or Termination

In the event of a suspension or termination of approval, the IRB or person directing the suspension or termination will inform the investigator in writing. If immediate action is required, the person imposing the suspension or termination may give the directive verbally to the PI and the letter will follow. If the IRB did not suspend or terminate the research, members will be notified at the next convened meeting. Letters to the PI will be sent within five working days of the effective date of suspension or termination. Such letters will include:

1. The effective date of suspension or termination.
2. If notification was initially done verbally the letter will reference the date of verbal notification.

3. The reason for the suspension or termination.
4. Identification of the research activity, in whole or in part, that must stop or suspension.
5. Any corrective action or clarification that must occur.
6. If the reason for suspension may bear on the participant's decision to continue participation, a directive that currently enrolled participants will be informed of the suspension.
7. For terminations, a directive that all currently enrolled participants will be informed of the termination.
8. If applicable, a directive of how to deal with any currently enrolled participants.
9. A direction to the PI regarding to whom to submit responses.

### 23.4 Lifting a Suspension or Termination

Only the IRB can lift a suspension using either the expedited review process or full board review. If the IO or Director of ORSC imposed the suspension, that person is responsible for notifying the IRB Chair in writing when they are satisfied that all concerns, that led the suspension, have been satisfied and recommend lifting the suspension. That person must attach a copy of the responses from the PI to the letter to the IRB. The IRB Chair may use the expedited review process to lift a suspension that was directed under the following conditions:

1. That was directed by the Chair.
2. That was directed by the IO or Director of ORSC providing the documentation noted above is received.
3. That was directed by the convened board when the board specifically delegates to the IRB Chair the authority to lift the suspension.
4. Otherwise, the convened IRB will determine whether to lift a suspension.

The IRB will send written notification to the PI when the suspension is lifted. The letter will be prepared by the IRB staff, reviewed by the Chair, and sent out by the staff. The IRB staff will also send a copy of the letter lifting the suspension to all entities who received a copy of the notification of suspension (see section 24.2.3).

## Section 24: Institutional Reporting Requirements

### 24.1 Reporting Requirements for the Institution

When the IRB makes any of the following determinations, the decision will be reported within 30 days to applicable regulatory and sponsoring agencies, as required by the institution's FWA.

- Serious and/or continuing noncompliance,
- Unanticipated problem involving risk to subjects or others, or
- Suspension or termination of a study

### 24.2 Notification of Regulatory and Sponsoring Agencies

IRB determinations of reportable events will be reported to the appropriate regulatory agency or agencies, if applicable under the RSSPMC of Hematology's U.S. Federal-Wide Assurance and/or FDA regulations. Reports of unanticipated problems involving risks to subjects and others, incidents of serious and/or continuing noncompliance, and suspensions and terminations of research activities should be sent to the following entities within 30 days of the IRB's determination.

### 24.3 Report Distribution and Content

U.S. Federal reports should be copied to the following, as applicable:

1. The Institutional Official
2. OHRP (if the research is federally funded)
3. FDA (if the study is subject to FDA regulations)
4. Any other federal agency that may have oversight of the study
5. The PI
6. PI's Chairperson and/or Dean
7. The Office of Sponsored Programs (if funded)

Reports should contain the following information:

1. The nature of the event (unanticipated problem involving risks to subjects and others, incident of serious and/or continuing noncompliance, or suspension or termination of research activities).
2. Name of the institution conducting the research.
3. Title of the research protocol and/or grant proposal in which the problem occurred.
4. Name of the PI.
5. The number assigned to the protocol by the IRB and the number of any applicable federal award, grant, contract, or cooperative agreement.
6. The IND or IDE number associated with the study, if applicable.
7. A description of the problem including findings of the organization and the reasons for the IRB's determination.
8. A description of any corrective action plan approved by the IRB.

## Section 25: Additional Requirements for U.S. Federal Agency Funded Research

### 25.1 Department of Defense (DoD)

All research involving human subjects supported by the Department of Defense (DoD) must comply with additional requirements established by the DoD in order to be approved by the IRB. The DoD follows the DHHS and FDA regulations on human subjects research, but also applies [DoD Directive \(DoDD\) 3216.02 “Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and DoD-Support Research.”](#) DoD supported research includes:

- The research is funded by a DoD component, including when RSSPMC of Hematology is the recipient of a subaward from the direct recipient of DoD funds;
- The research involves cooperation, collaboration or other type of agreement with a DoD component;
- The research uses property, facilities, or assets of a DoD component; of
- The subject population will intentionally include personnel (military and/or civilian) from a DoD component. DoD requirements to not apply when DoD personnel incidentally participate as research subjects where they are not the intended research population or where the project is not otherwise DoD supported.

The IRB or IRB staff will notify investigators of relevant DoD regulations, as appropriate.

Research involving an interaction or intervention with a living individual is defined as research involving “experimental subjects.” Research involving “experimental subjects” is a subset of human subject and is defined as an activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention.

When following DoD regulations, the definition of minimal risk based on the phrase, “ordinarily encountered in daily life of during the performance of routine physical or physiological examination or tests” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone), resulting from or associated with high-risk behaviors or pursuits, or having a medical condition (e.g., frequent medical tests or constant pain).

Also, as a practice, the University of Texas at Austin does not currently conduct classified human subject research. However, if practice changes, the University will follow the requirements of DoD Directive 3216.02 when conducting such research. The University also does not conduct human subject research involving chemical agents as defined by 50 USC 1520a, including research for prophylactic, protective, or other peaceful purposes, or involving biological agents as defined by DoD Directive 5120.65.

#### 25.1.1 Additional Protections for Pregnant Women, Fetuses, and Neonates

The DoD requires additional protections when research involves pregnant women, fetuses and neonates, including application of 45 CFR 46 Subpart B. These requirements include:

- For purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge”.
- The applicability of Subpart B is limited to research involving pregnant women as participants in research that is greater than minimal risk and includes interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
  1. No research on nonviable living human fetuses ex utero or a living human fetus ex utero for whom viability has not been ascertained may be conducted unless the research:
    - May enhance the well-being or meet the health needs of the fetus or enhance the probability of its survival to viability; or
    - Will pose no added risk of suffering, injury, or death to the fetus and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
  2. The risk standard must be the same for fetuses which are intended to be aborted and fetuses which are intended to be carried to term.
  3. For human subject 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 DOHRP must be obtained through the COHPR prior to research starting.

#### 25.1.2 Additional Protections for Prisoners as Subjects

The DoD requires additional protections when research involves prisoners as subjects, including application of 45 CFR 46 Subpart C. These requirements include:

- Research involving prisoners must be reviewed by the convened IRB; the expedited procedure may not be used.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
- In addition to allowable categories of research on prisoners in Subpart C, to additional categories are permissible:
  1. Epidemiological research is also allowed when:
    - The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
    - The research presents no more than minimal risk.
    - The research presents no more than an inconvenience to the participant.
  2. Human subjects research that would otherwise meet exemption criteria may be conducted, but must first be approved by an IRB and must meet the requirements in Subpart C of 45 CFR 46.
- If a participant becomes a prisoner and if the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-participant may

continue to participate until the convened IRB can review the request to approve a change in the research protocol and until the organizational official and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB chair shall require that all research interactions and interventions with the prisoner-participant (including obtaining identifiable private information) cease until the convened IRB can review the request to approve a change in the research protocol.

The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and well-being of the human participant, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert, having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. The convened IRB may approve the prisoner-participant to continue when it is determined that:

- The prisoner- participant can continue to consent to participate and is capable of meeting the research protocol requirements,
- The terms of the prisoner-participant's confinement do not inhibit the ethical conduct of the research and
- There are no other significant issues preventing the research involving human participants from continuing as approved

This approval is limited to the individual prisoner-participant and does not allow recruitment of prisoners as participants.

- Research involving any person captured, detained, held or otherwise under the control of DoD personnel (military and civilian, or contractor employee) is prohibited.
  - This prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.
- Research involving prisoners of war is prohibited. In order to make this determination, the IRB must be made aware of the definition of "prisoner of war" applicable to the specific DoD component granting the addendum.

### 25.1.3 Research Involving Children

Human subjects research involving children as participants must comply with Subpart D. Research involving children cannot be determined to qualify as exempt category 2 research except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

For purposes of legal capacity to participate in DoD-supported research involving human subjects, all Service members and all Reserve Component and National Guard members in a Federal duty status are considered for the purpose of DoD Instruction 3216.02 to be adults. If a Service member, Reserve Component of National Guard member in a federal duty status, student at a Service Academy, or trainee

is under 18 years of age, the IRB shall carefully consider the recruitment process and the necessity to include such members as human subjects.

#### 25.1.4 Consent by a Legally Authorized Representative

If consent is to be obtained from the experimental subject's legal representative, the research must intend to benefit the individual participant. The determination that research is intended to be beneficial to the individual experimental subject must be made by the IRB.

#### 25.1.5 Scientific Review

DoD requires scientific review for all new, non-exempt DoD supported human research. The IRB will evaluate the scientific merit of a study during its review of a study. In the event that the IRB lacks adequate expertise to conduct scientific or scholarly review, the IRB may rely on outside experts to conduct this review.

#### 25.1.6 Education Requirements

DoD requires that all individuals involved in the "design, conduct, or approval of human subjects research" complete human subjects research training. The RSSPMC of Hematology's requirements for mandatory and continuing education meet the requirements. The DoD component may evaluate the RSSPMC of Hematology's education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

Individual DoD components may have stricter or specific educational requirements and may require recertifications more frequently than currently mandated by the RSSPMC of Hematology IRB. Researchers should contact their Program Officer at the DoD, or DoD component, to ensure adherence to any unique requirements. It is the Principal Investigator's responsibility to ensure that research staff has completed all appropriate educational requirements as mandated by DoD policy.

#### 25.1.7 Research Involving International Citizen Populations

For research conducted internationally, refer to Section 14: Transnational Research. This section must meet the DoD requirements. This includes taking into consideration subject populations, the cultural context, the languages understood by the human subjects, identifying and considering local laws, regulations, customs, and practices. In addition, determinations are made as to whether the sponsoring DoD Component requires an additional ethics review by the host country or a local DoD IRB with host country representation.

#### 25.1.8 Waiver or Alteration of Consent and Exception from Informed Consent in Emergency Medicine

The IRB may waive or alter some elements of informed consent for research involving human beings as experimental subjects, so long as it preserves the informed consent of the subject (i.e., the consent indicates that participation in the research is voluntary, and the subject or the subject's legally authorized representative is informed of the research risks).

The DoD defines "experimental subject," as an activity, for research purposes where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. This definition relates only to the application of Section 980 of Title 10, U.S.C.; it does not affect the application of 32 CFR 219.), DoD regulations prohibit a waiver of consent unless the PI obtains a waiver from the DoD Officer for Human Research Protections (DOHRP).

The requirement for consent may be waived by the DOHRP or its delegate, if the following three conditions are met:

1. The research is necessary to advance the development of a medical product for the military services;
2. The research might directly benefit the individual experimental subjects;
3. The research is conducted in compliance with all other applicable laws and regulations;

The IRB may waive the consent process if the research does not meet the definition of “experimental subject.”

#### 25.1.9 Multi-site or Collaborative Research Requirements

Any investigator developing a proposal for DoD funding or other support that involves collaborating institutions needs to consult the sponsoring DoD component to identify additional requirements for multi-site research. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party. When RSSPMC of Hematology is collaborating with a DoD component, RSSPMC of Hematology will not serve as the reviewing IRB.

The use of a single IRB will be required in accordance with 32 CFR 219.114. If a DoD Institution believes that the research is not subject to those provisions, the applicable DoD Component Office of Human Research Protections may determine and document, that use of a single IRB is not appropriate for the particular context of the proposed human subject research. Studies already in progress before January 20, 2020 are not required to transition to a single IRB, nor request exception. Additional policy information relating to reliance and the use of a single IRB is in Section 26.3.

#### 25.1.10 Provisions for Research Related Injury

The PI is responsible for informing the IRB if there are any additional requirements from the DoD Component regarding the provision of care in the case of a research-related injury. If the DoD Component has stricter requirements than the Common Rule or the RSSPMC of Hematology’s policies, the verbiage will need to be discussed with the RSSPMC of Hematology’s Legal Affairs Office and the ORSC Director. These requirements will also need to be disclosed in the informed consent document.

When research is determined to be greater than minimal risk, consent documents must include the disclosure that subjects may, for the duration of the study, be eligible for health care services for research-related injuries at a military treatment facility, and this eligibility for health care services extends beyond subjects’ participation in the study to such time after the study has ended. The informed consent document must disclose how subjects with research-related injuries will be cared for, including injuries that are the direct result of activities performed by DoD-affiliated personnel through the conduct of a collaborative study with a DoD organization.

#### 25.1.11 Research Involving Department of Defense Personnel as Research Subjects

If any research includes Department of Defense personnel as subjects, the following is required:

- Additional elements of informed consent, as applicable:
  - A statement that the DoD or a DoD organization is funding the study.
  - A statement that representatives of the DoD are authorized to review research records.



- If the research includes any risks to fitness for duty (e.g., health, availability to perform job, data breach), the informed consent document must inform DoD-affiliated personnel about the risks for the revocation of clearance, credentials, or other privileged access or duty, and that command or Component guidance should be sought before agreeing to participate.
- The key investigator must receive command or Component approval to execute the research.
- Military and civilian supervisors, officers, and others in the chain of command are prohibited from influencing their subordinates to participate in human subjects research.
- Military and civilian supervisors, officers, and others in the chain of command must not be present at any HSR participant recruitment sessions or during the HSR consent process. Excluded supervisors or those in the chain of command may participate in separate HSR recruitment sessions, if applicable.
- Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
- In a study determined to be greater than minimal risk where recruitment is in a group setting, the IRB must appoint an ombudsperson. For minimal risk studies, the IRB will consider whether an ombudsperson is necessary. The ombudsperson:
  - Must not have a conflict of interest with the research or be part of the research team.
  - Must be present during recruitment, monitoring that the recruitment and informed consent explain that participation is voluntary and that the information provided about the research is consistent with the IRB-approved script and materials, including digitally provided materials.
  - Should be available to address the DoD-affiliated personnel's concerns about participation.

## **Compensation**

Compensation to DoD-affiliated personnel for participation in research while on duty is prohibited in accordance with Title 5, U.S.C., with particular reference to Subparts G and H, with some exceptions for purposes consistent with Section 30 of Title 24, U.S.C.

The following limitations on dual compensation for U.S. military personnel apply for DoD funded research:

An individual may not receive pay from more than one position for more than 40 hours of work in one calendar week. This limitation on dual compensation includes temporary, part-time and intermittent appointments.

- Individuals may receive compensation for research activities if the research activities take place outside of scheduled work hours.
- Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
- Non-federal persons may be compensated for research participation other than blood draws in a reasonable amount approved by the IRB according to local prevailing rates and the nature of the research.

#### 25.1.12 Additional DOD Review Requirements

After the IRB completes its review and issues approval, the PI will need to submit documentation of IRB approval, the risk level, and the expiration date of the research to the DoD component funding or otherwise supporting the study. The DoD may also request additional documentation to verify compliance with federal and DoD policies, including minutes related to the research.

The PI is responsible for ensuring that DoD component-level administrative review is completed for all non-exempt research when any of the following occur:

- Research is conducted in a foreign country, unless conducted by a DoD overseas institution, or only involves DoD-affiliated personnel who are U.S. citizens.
- The research requires a waiver of informed consent.
- The research is fetal research.
- Large Scale Genomic Data (LSGD) is collected from DoD-affiliated personnel.
- Research is required to be approved the DOHRP.

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. The investigator is responsible for obtaining appropriate approvals.

Investigators may not initiate the study until the human research protection officer within the sponsoring DoD Component reviews and approves the study.

#### **Large Scale Genomic Data**

Large Scale Genomic Data (LSGD) is data derive from genome-wide association studies; single nucleotide polymorphisms arrays; genome sequencing; transcriptomic, metagenomic, epigenomic analyses; and gene expression data; etc. Research involving LSGD may or may not also constitute human subjects research. Examples of research involving LSGD incudes, but is not limited to, projects that involve generating the whole genome sequence data for more than one gene from more than 1,000 individuals, or analyzing 100 or more genetic variants in more than 1,000 individuals.

When research involves large scale genomic data (LSGD) collected on DoD-affiliated personnel, additional protections are required:

- 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)
- The study team will apply for an HHS Certificate of Confidentiality
- The research is subject to DoD Component security review and DOHRP approval.

#### 25.1.13 Reporting Requirements

The PI is responsible for promptly reporting to the DoD-specific component's Human Research Protection Official (HRPO) (30 days or less):

- When significant changes to the research are approved by the IRB
- Results of IRB continuing review, if required

- Change of reviewing IRB
- Closure of a study
- Changes to key investigators or institutions
- Decreased benefit or increased risk to subjects in greater than minimal risk research
- Transfer of human subject research oversight to a different IRB
- Addition of vulnerable populations or DoD-affiliated personnel as subjects
- Change in status when previously enrolled subject meets criteria for Subpart B or C and the protocol was not reviewed and approved by the IRB under those Subparts.

The ORSC is responsible for promptly reporting to the DoD-specific component's human research protection official or office (30 days or less):

- Notification by any federal department, agency, or national organization that any part of the HRPP is under a "for-cause" investigation involving DoD-supported research.
- Serious and/or continuing noncompliance.
- Any unanticipated problem involving risks to subjects or others for DoD-supported research.
- Any suspension or termination of DoD-supported research.

#### 25.1.14 Records Accessibility

Records documenting compliance (or noncompliance) with DoD regulations will be made accessible for inspection and copying by DoD representatives at reasonable times and in a reasonable manner.

#### 25.1.15 References

32 CFR 219, 10 USC 980, DoD Directive 3216.02, SECNAVINST 3900.29D, OPNAVINST 5300.8B, DoD Dual Compensation Act 24 U.S.C 301.

## 25.2 U.S. Department of Education (ED)

### 25.2.1 Family Educational Rights and Privacy Act (FERPA) 34 CFR Part 99

The Family Educational Rights and Privacy Act is a Federal law that protects the privacy of student education records. In general, schools must have written permission from the parent or eligible student in order to release any information from a student's education record. However, FERPA allows schools to disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:

- Develop, validate, or administer predictive tests.
- Administer student aid programs.
- Improve instruction.

A school district or postsecondary institution that uses this exception is required to enter into a written agreement with the organization or researcher conducting the research that specifies:

- The determination of the exception.
- The purpose, scope, and duration of the study.
- The information to be disclosed.
- That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements in 34 CFR 99.31(a)(6) on re-disclosure and destruction of information.
- That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the organization with legitimate interests.
- That the organization is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study.
- The time period during which the organization must either destroy or return the information.

It is the responsibility of the PI and school district/postsecondary institution providing the FERPA protected data to determine when an agreement is required and to ensure appropriate documentation of such agreement.

FERPA compliant schools are required to develop and adopt policies in conjunction with parents regarding the following:

- Any applicable procedures for granting a request by a parent for reasonable access to a survey within a reasonable period of time after the request is received.
- Any applicable procedures for granting a request by a parent for reasonable access to instructional material received.
- The collection, disclosure or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student privacy that are provided by the agency in the event of such collection, disclosure or use.
- The right of a parent of a student to inspect, upon request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student.
- Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received.

#### 25.2.2 Exception to Written Permission for Records Release under FERPA

If written student/parent permission will not be obtained based on an accepted condition in 34 CFR 99.31, check with the registrar to see if a formal written exception is required. IRB approval of a waiver does not guarantee that the school providing the records will allow such a process. Investigators are encouraged to communicate with the schools.

Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

- Student's name and other direct personal identifiers, such as the student's social security number or student number.
- Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address, and personal characteristics or other information that would make the student's identity easily traceable; date and place of birth and mother's maiden name.
- Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.
- Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

### 25.2.3 Protection of Pupil Rights Amendment PPRA (34 CFR Part 98)

#### 25.2.3.1 *Informed Consent/Parental Permission Requirements*

Research funded by the Department of Education must comply with additional protections under PPRA, 34 CFR Part 98. No student shall be required, as part of any research project, to submit without prior consent to surveys, psychiatric examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:

1. Political affiliations.
2. Mental and psychological problems potentially embarrassing to the student or his or her family.
3. Sex behavior and attitudes.
4. Illegal, anti-social, self-incriminating, and demeaning behavior.
5. Critical appraisals of other individuals with whom the student has close family relationships.
6. Legally recognized privileged and analogous relationships, such as those of lawyers, physicians, and ministers.
7. Religious practices, affiliations, or beliefs of the student or student's parent.
8. Income, other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under a program.

As used above, prior consent means prior consent of the student, if the student is an adult or emancipated minor; or prior written consent of the parent or guardian, if the student is an un-emancipated minor. Schools and contractors must obtain prior written parental consent before minor students are required to participate in any ED-funded survey, analysis, or evaluation.

#### 25.2.3.2 *Parental Access to Instructional Material Used in a Research or Experimentation Program*

All instructional material—including teachers' manuals, films, tapes, or other supplementary instructional material—which will be used in connection with any research or experimentation program or project shall be available for inspection by the parents or guardians of the children engaged in such program or project. As used above:

**Research or experimentation program or project** means any program or project in any program under in any research that is designed to explore or develop new or unproven teaching methods or techniques.

**Children** means persons who have not reached the age of majority (18 in Uzbekistan) who are enrolled in research not above the elementary or secondary education level, as determined under state law where the research is taking place.

#### 25.2.4 Additional Requirements for School Research Not Funded by the ED

Even if the research is not funded by the ED, the IRB may verify compliance with ED regulations regarding the following, as appropriate:

1. The right of parents to inspect, upon request, a survey created by a third party before the survey is administered or distributed by a school to students.
2. Arrangements to protect student privacy in the event of the administration of a survey to students, including the right of parents to inspect, upon request, the survey, if the survey contains one or more of the same eight items of information noted above.
3. The right of parents to inspect, upon request, any instructional material used as part of the educational curriculum for students.
4. The administration of physical examinations or screenings that the school may administer to students.

#### 25.2.5 Other Conditions Pertaining to Waivers of Parent Permission or Informed Consent

The IRB may waive the requirement for obtaining consent from a parent or legal guardian if:

1. The research meets the provisions for waiver in Section 6.7 of the IRB Policies and Procedures Manual [45 CFR 46.116(d)(1-4)] and if the IRB determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children).
2. An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and 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.

### 25.3 U.S. Department of Energy (DoE)

DoE requirements apply to all research conducted with DoE funding, at DoE institutions (regardless of funding source), or by DoE or DoE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research. When research involves contractors, DoE “Contractor Requirements Document” describing contractor responsibilities for protecting human research participants must be included in contracts.

As a practice, the RSSPMC of Hematology does not currently conduct classified human subject research.

Research that involves one or more of the following must be submitted to the appropriate IRB for human subjects research review and determination:

- Study of humans in a systematically modified environment. These studies include but are not limited to intentional modification of the human environment:
  - Study of human environments that use tracer chemicals, particles or other materials to characterize airflow.
  - Study in occupied homes or offices that:
    - Manipulate the environment to achieve research aims.
    - Test new materials.
    - Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups.
  - Use of social media data.
  - Human terrain mapping (HTM) (not currently supported at the RSSPMC of Hematology).
  - All exempt human subjects research determination must be made by the appropriate IRB and/or IRB office.

Classified and unclassified human subjects research that is funded through the Strategic Intelligence Partnership Program (SIPP) must be reviewed and approved by the Central DoE IRB-Classified.

The DoE has published additional requirements for research it supports or conducts as described in [DOE Order 443.1C](#), Protection of Human Research Subjects. The IRB reviews and approves the "Checklist for IRBs to Use in Verifying That HHS Protocols are in Compliance with DOE Requirements" submitted by the researchers to verify compliance with the DOE requirements for the protection of Personally Identifiable Information. When the IRB reviews research supported by the DoE, the following conditions are required:

- The non-affiliated IRB member must be a non-governmental member with the appropriate security clearances. This individual cannot be a current federal employee or contractor.
- Any IRB member can appeal a vote to approve research to the Institutional Official, Secretary of Energy, and Director of the Office of Science and Technology, in that order.

Research involving human subjects involving multiple DoE sites (e.g., members of the research team from more than one DoE site and/or data or human subjects from more than one DoE site) must be reviewed and approved by one of the Central DoE IRBs prior to initiation, unless review by another appropriate IRB of record is authorized by the DoE HSP Program Manager. If authorized by the DoE HSP Program Manager, research may be reviewed by other appropriate IRB of record. In all cases, an IRB Authorization Agreement (IAA) or Memorandum of Understanding (MOU) must be in place between the organization(s) conducting the human subjects research and the organization responsible for the IRB review.

#### 25.3.1 Personally Identifiable Information

In accordance with the U.S. Privacy Act, the DoE has established requirements for the protection of Personally Identifiable Information (PII) with the DoE Privacy Program (DoE Order 206.1), DoE Manual

(M) for Identifying and Protecting Official Use Only Information (DoE M 471.3-1), and DoE Cyber Security Incident Management Manual (DoE M 205.1-8).

### 25.3.2 Description of Processes

Research protocols must include description of processes for:

1. Keeping PII confidential.
2. Releasing of PII, where required, only under a procedure approved by the IRB and DoE.
3. Using PII only for purposes of the DoE approved research.
4. Handling and marking documents containing PII as “containing PII” or “containing PHI.”
5. Establishing reasonable administrative, technical, and physical safeguards to prevent unauthorized use or disclosure of PII.
6. Making no further use or disclosure of the PII except when approved by the responsible IRB and DoE, where applicable, and then only:
  - a. In an emergency affecting the health and safety of any individual.
  - b. For use in another research project under these same conditions and with DoE written authorization.
  - c. For disclosure to a person authorized by the DoE program office for the purpose of an audit related to the project.
  - d. When required by law.
7. Protecting PII data stored on removable media (CD, DVD, USB Flash Drives, etc.) using encryption products that are Federal Information Processing Standards (FIPS) 140-2 certified.
8. Using passwords to protect PII in conjunction with FIPS 140-2 certified encryption that meet the current DoE password requirements cited in DoE Guide 205.3.1.
9. Sending removable media containing PII, as required, by express overnight service with signature and tracking capability, and shipping hard copy documents double wrapped via express overnight service.
10. Encrypting data files containing PII that are being sent by e-mail with FIPS 140-2 certified encryption products.
11. Sending passwords that are used to encrypt data files containing PII separately from the encrypted data file, i.e. separate e-mail, telephone call, separate letter.
12. Using FIPS 140-2 certified encryption methods for websites established for the submission of information that includes PII.
13. Using two-factor authentication for logon access control for remote access to systems and databases that contain PII. Two-factor authentication is contained in the National Institute of Standards and Technology (NIST) Special Publication 800-63.
14. In addition to other reporting requirements, reporting the loss or suspected loss of PII immediately upon discovery to:
  - a. DoE Project Officer
  - b. IRB
15. Classified projects that use PII must also comply with all the requirements for conducting classified research.

### 25.3.3 Research Involving DOE Personnel

DOE and DOE site contractors are considered vulnerable subjects when participating in research and additional care must be taken to ensure their participation is truly voluntary (e.g., by ensuring they do not report to members of the research team), and that data collected about them is kept confidential.



The IRB must consider if additional protections are required for research involving employees and contractors.

#### 25.3.4 Research Reporting Requirements

Researchers must report the following within 48 hours to the human subject research program manager:

- Any significant adverse events, unanticipated risks and complaints about research, with a description of any corrective actions taken or to be taken.
- Any suspension or termination of IRB approval of research.

Researchers must immediately report a suspected or confirmed data breach involving Personally Identifiable Information in printed or electronic form to the DOE-Cyber Incident Response Capability in accordance with the requirements of DOE O 206.1. Within 48 hours the DOE or NNSA HSP Program Manager must also be notified of any corrective actions taken and consulted regarding the plan for any remaining corrective actions.

Researchers must report within 48 hours, the following to the human subject program manager:

- Any known or potential incidents of noncompliance with a description of corrective actions taken.

Any compromise of personally identifiable information must be reported within 2 days of determining that there was a compromise.

### 25.4 U.S.Department of Justice (DOJ)

#### 25.4.1 Principal Investigator Responsibilities

Principal Investigators (PIs) who are recipients of funds from the National Institute of Justice (NIJ) are required to comply with the DoJ regulations at 28 CFR 46 (Protection of Human Subjects) which include the following additional requirements:

1. Obtain a privacy certificate approved by the NIJ Human Subjects Protection Officer. Information about Privacy Certificates may be found at the NIJ website at <https://nij.ojp.gov/funding/privacy-certificate-guidance>
2. Include the following in the informed consent document under the section dealing with confidentiality:
  - a. Confidentiality can only be broken if the subject reports the probability of immediate harm to self or others.
  - b. Private, identifiable information will be kept confidential and will only be used for research and statistical purposes. If, due to sample size or some unique feature, the confidentiality of the identity of the individual cannot be maintained, the subjects need to be explicitly notified. If the researcher intends to disclose any information, the subject needs to be explicitly informed what information would be disclosed, under what circumstances, and to whom. The

subject must be informed of any risks that might result from this disclosure and must explicitly provide written consent prior to participating in the research.

3. Identify in the informed consent document the name(s) of the funding agency(ies).
4. Submit a copy of the IRB approval as well as supporting documentation of the IRB's institutional affiliation, assurance, etc. to the NIJ prior to initiation of any research activities that are not exempt from the requirements of 28 CFR 46.
5. Submit supporting documentation of the IRB's approval of the research meeting the criteria for exemption under 28 CFR 46.101(b).
6. Sign and maintain an Employee Confidentiality Statement for themselves and their research staff. A model employee confidentiality statement can be found at <https://nij.ojp.gov/funding/model-employee-confidentiality-statement>
7. Send a copy of all de-identified data, including copies of the informed consent document, data collection instruments, surveys and other relevant research materials to the National Archive of Criminal Justice Data.

#### 25.4.2 Bureau of Prisons

Additional requirements for prospective researchers to obtain approval to conduct research within the Bureau are described at 28 CFR Part 512. Although some research may be exempt from 28 CFR part 46 under 46.101(b)(5), as determined by the Office of Research and Evaluation (ORE) of the Bureau, no research is exempt from 28 CFR Part 512. However, implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research. The following additional requirements are included in 28 CFR Part 512:

1. Obtain review of the research proposal by the Bureau of Research Review Board (BRRB).
2. Sign an agreement to adhere to the provisions of the Bureau under 28 CFR 512.
3. Respect the rights, health, and human dignity of individuals involved in the research.
4. Adhere to applicable provisions of the Privacy Act of 1974 and regulations pursuant to this act.
5. Provide a research project design that contributes to the advancement of knowledge about corrections.
6. Provide a research project design that is compatible with both the operation of the prison facilities and protection of human subjects.
7. Observe the rules of the institution or office in which the research is conducted;
8. Provide a research project design that does not involve medical experimentation, cosmetic research, or pharmaceutical testing.
9. Provide documentation that:
  - a. Risks to participants are minimized and risks are reasonable in relation to the anticipated benefits;
  - b. Selection of participants within any one organization is equitable; and
  - c. Incentives may not be offered to help persuade inmates to participant, unless snacks or soft drinks are consumed at the test setting.
  - d. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research subjects who are both:
    - i. No longer in the Bureau custody, and
    - ii. Participating in authorized research being conducted by Bureau employees or contractors.
10. Provide documentation of experience in the area of study of the proposed research.

11. Provide documentation of review of related literature.
12. Provide documentation that research records will be destroyed or individual identifiers will be removed from the records after the research is completed;
13. Assume responsibility as the investigator for actions of any research staff engaged to participate in the project.
14. Provide documentation for maintaining confidentiality of data preliminary to the research, during and after the conclusion of the research by assuring:
  - a. Records are not in an individually identifiable form.
  - b. Advance written assurance has been provided to the Bureau that the records will be used solely for statistical research or reporting.
15. Agree not to provide research information that identifies a subject to any person (i.e. cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding) without the subject's prior written consent to release the information.
16. Agree not to maintain records electronically that contain non-disclosable information directly traceable to a specific person at the institution (NOTE: Computerized data records may only be maintained at an official DoJ site).
17. Negotiate arrangements, prior to the beginning of the data collection of the project, to provide non-identifiable computerized data on individual subjects along with documentation to the ORE if requested.
18. Obtain informed consent of subjects prior to initiating the research activity.
19. Submit planned methodological changes in the research to the IRB for review and approval prior to initiation and revise study procedures in accordance with the new methodology, if required.
20. Provide, at least yearly, a report on the progress of the research and at least one report of findings to the ORE Chief.
21. Acknowledge the Bureau participation in any publication of the results.
22. Include a disclaimer in the results for publication that the approval or endorsement of the published material is an expression of the policies or view of the Bureau.
23. Provide, at least 12 working days before any report of findings to be released, one (1) copy of the report, which shall include an abstract of the findings, to each of the following:
  - a. Chairperson of the BRRB.
  - b. The regional Bureau Director.
  - c. The warden of each institution which provided data or assistance.
24. Submit two (2) copies of the results of the research project for informational purposes only to the ORE Chief prior to submission for publication.

#### 25.4.3 Research Proposals

When submitting a research proposal to the Bureau, the PI shall provide the following information in the proposal:

1. A summary statement which includes:
  - a. Name(s) and current affiliation(s) of the researcher(s).
  - b. Title of the study.
  - c. Purpose of the project.
  - d. Location of the project
  - e. Methods to be employed.

- f. Anticipated results.
  - g. Duration of the study.
  - h. Number of subjects (staff/inmates) required and amount of time required from each
  - i. Indication of risk or discomfort involved as a result of participation.
2. A comprehensive statement which includes:
- a. Review of related literature.
  - b. Detailed description of the research method.
  - c. Significance of anticipated results and their contribution to the advancement of knowledge;
  - d. Specific resources required from the Bureau;
  - e. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur;
  - f. Description of steps taken to minimize any risks.
  - g. Description of physical and/or administrative procedures to be followed to:
    - i. Ensure the security of any individually identifiable data that are being collected for the project, and
    - ii. Destroy research records or remove individual identifiers from those records when the research has been completed.
  - h. Description of any anticipated effects of the research project on institutional programs and operations; and
  - i. Relevant research materials such as vitae, endorsements, sample informed consent statements, questionnaires, and interview schedules.
  - j. A statement regarding assurances and certification required by 28 CFR part 46, if applicable.

#### 25.4.4 Informed Consent

Before commencing a research project requiring participation by staff or inmates, the researcher shall give each participant a written informed consent statement containing the following information (The researcher may not be required to obtain the signature if the researcher can demonstrate that the only link to the subject's identity is the signed statement of informed consent or that there is significantly more risk to the subject if the statement is signed.):

- 1. Identification of the PI(s);
- 2. Objectives of the research project;
- 3. Procedures to be followed in the conduct of research;
- 4. Purpose of each procedure;
- 5. Anticipated uses of the results of the research;
- 6. A statement of benefits reasonably to be expected;
- 7. A declaration concerning discomfort and risk, including a description of anticipated discomfort and risk;
- 8. A statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable);
- 9. A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a

researcher may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself/herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization. Under the privacy certificate investigators and research staff do not have to report child abuse unless the participant signs another consent form to allow child abuse reporting.

10. A statement that participation in the research project will have no effect on the inmate participant's release date or parole eligibility;
11. An offer to answer questions about the research project; and
12. Appropriate additional information as needed to describe adequately the nature and risks of the research.

## 25.5 U.S. Environmental Protection Agency (EPA)

### 25.5.1 Research Involving Intentional Exposure of Any Human Subjects

The EPA prohibits research involving intentional exposure of any human subjects who is a pregnant woman (and therefore her fetus), a nursing woman, or a child to any substance. Other adults who voluntarily choose to participate are protected under the EPA's rule, "Protections for Subjects in Human Research", which requires proposed protocols describing intentional exposures be reviewed by EPA and its Human Studies Review Board.

### 25.5.2 Observational Research Involving Pregnant Women and Fetuses

The EPA requires application of 40 CFR 26 and 45 CFR 46 Subpart B to provide additional protections to pregnant women as subjects in observational research, i.e., research that does not involve intentional exposure to any substance.

### 25.5.3 Observational Research of Children Not Involving Greater Than Minimal Risk

The EPA requires application of 40 CFR 26 and 45 CFR 46 Subpart D to provide additional protections to children as subjects in observational research, i.e., research that does not involve intentional exposure to any substance.

### 25.5.4 Observational Research of Children Involving Greater Than Minimal Risk

Observational research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects is allowable only if the IRB finds that (See Section 12.4):

1. The intervention or procedure holds out the prospect of direct benefit to the individual subject or is likely to contribute to the subject's well-being;
2. The risk is justified by the anticipated benefit to the subjects;
3. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
4. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

### 25.5.5 Final Review by EPA

EPA policy requires submission of IRB determinations and approval to the EPA Human Subjects Research Review official for final review and approval before the research can begin.

## 25.6 Research Not Conducted or Supported By Any U.S. Federal Agency

For research not conducted or supported by any federal agency that has regulations for protecting human research participants and for which the intention of the research is submission to the EPA, the EPA regulations protecting human research participants apply, including:

1. EPA extends the provisions of the 40 CFR 26 to human research involving the intentional exposure of non-pregnant, non-nursing adults to any substance.
2. EPA prohibits the intentional exposure of pregnant women, nursing women, or children to any substance.

## Section 26: Cooperative and Collaborative Research

### 26.1 Cooperative Activities

Cooperative activities are those in which the RSSPMC of Hematology faculty, students or staff, obtain access to human subjects involved through one or more cooperating institutions, or when PIs from cooperating institutions obtain access to human subjects at the University. Activities involving investigators from one or more institutions who may exchange or pool similar data obtained from human subjects who participate in independently sponsored projects are not cooperative activities. When a PI plans to conduct research at a site external to the RSSPMC of Hematology (not owned or operated by the RSSPMC of Hematology), the PI is responsible for ensuring that the non-RSSPMC of Hematology site is willing to engage in the collaboration.

If the non-RSSPMC of Hematology site is engaged in the conduct of the research, the PI will provide the following information as part of the IRB submission:

1. The contact information of the site(s);
2. Whether the site(s) has an IRB;
3. If the site has an IRB, has the IRB approved the research or does the site plan to defer to the RSSPMC of Hematology IRB.

### 26.2 Lead Investigator of a Multicenter/Multisite Study

For PIs performing research in which the RSSPMC of Hematology is the lead or coordinating institution, the PI should note in the initial IRB application that the RSSPMC of Hematology is the lead or coordinating institution of a multi-site study. The PI should also provide the following information:

1. The name(s) of each participating institution that will be engaged in human subjects research.
2. Confirmation that each engaged institution has an U.S. FWA if required.
3. The contact name and information for the PI at each institution.
4. The method of multilateral communication between institutions/IRBs of any unanticipated problems involving risks to subjects or others and other study related information.

When the PI is the lead investigator of a multi-site study, the PI must submit information to the IRB regarding the communication process between sites and the management of information obtained during the course of the study such as:

- Unanticipated problems involving risks to subjects or others
- Interim results
- Protocol modifications

The IRB will evaluate the management plan as it relates to the adequacy of the protection of subjects.

### 26.3 IRB Reliance

The University may, at the discretion of the Office of Research Support and Compliance, permit reliance on a non-RSSPMC of Hematology IRB. The RSSPMC of Hematology IRB may also agree to serve as the reviewing IRB for multi-site projects in which RSSPMC of Hematology faculty, staff or students are engaged. All instances of such reliance for non-exempt research will be documented in a reliance agreement that describes the responsibilities of the reviewing and the relying IRB. Such agreements will be signed by the Vice President for Research, Scholarship and Creative Endeavors or designee.

Examples of situations in which RSSPMC of Hematology may agree to rely on an external IRB include, but are not limited to:

- Use of the Central Institutional Review Board for the U.S. National Cancer Institute (NCI CIRB).
- When Uzbek/U.S. regulations require use of a single IRB for cooperative research.
- Government regulations or local policies require use of a specific IRB.

Reliance agreements and/or local context documents, at a minimum, must document the following responsibilities:

- Application of Uzbek/U.S. federal regulations to the research as required by reviewing and relying sites
- Initial and continuing review of research, including determining risks to subjects are minimized by using procedures that are consistent with sound research design
- Responsibility for obtaining additional approvals from Uzbek MoH/U.S. DHHS for inclusion of vulnerable populations, as applicable
- Responsibility for certifying with federal agencies requirements for certificates of confidentiality or genomic data sharing
- Review of unanticipated problems involving risk to subjects or others
- Review and reporting of serious and/or continuing noncompliance
- Preparation, review, and submission of reports to federal agencies
- Conflict of interest and organizational conflict of interest review
- Post approval monitoring and access to research records
- Maintenance of IRB records
- Terms for continued oversight and transfer of records should early termination occur

Reliance agreements are signed by the Institutional Official or designee.

### 26.3.1 Reliance on a Non-RSSPMC of Hematology IRB

When a request to rely on a non-RSSPMC of Hematology IRB is received, the ORSC will evaluate the requested IRB to assess whether comparable standards are upheld by the reviewing IRB. The evaluation may include the following depending on the risk of the proposed research:

- Verifying AAHRPP accreditation of the reviewing IRB
- Determining that the reviewing IRB has engaged in a quality self-evaluation
- Reviewing relevant policies and procedures of the reviewing IRB
- Reviewing IRB meeting minutes pertaining to the proposed study

The RSSPMC of Hematology IRB may rely upon IRBs of another institution or organization provided that the IRB is part of an AAHRPP accredited institution or organization or if the IRBs are not part of an AAHRPP accredited institution or organization, but where reasonable steps have been taken to ensure that subjects are adequately protected (e.g., IRBs will adhere to applicable standards and regulations).

All research in which RSSPMC of Hematology faculty, staff, or students are engaged must be submitted to the Office of Research Support and Compliance (ORSC), even if another IRB will be named as the reviewing IRB. The ORSC will conduct a local compliance review of the submission to ensure the study procedures and documents adhere to university policies. The compliance review will include:

- Verification of the Principal Investigator's qualifications and privileges to conduct the research
- Verification of completion of all required training by research personnel
- Completion of conflict of interest reviews (as applicable)
- Verification of Institutional Biosafety Committee or Institutional Radiation Safety Committee approval, if needed
- Inclusion of required informed consent language, as appropriate

Reliance agreements will only be signed when the local compliance review is complete, and any other conditions are satisfied.

The ORSC will work with investigators to prepare materials requested by reviewing IRBs, such as local context information forms. Once IRB review has been ceded to another IRB, Principal Investigators are responsible for being aware of and adhering to the policies and procedures of the reviewing IRB.

### 26.3.2 Reliance on the RSSPMC of Hematology IRB

When this institution provides IRB review for other institutions, the IRB will review the research in accordance with established policies and procedures to determine that research is ethically justifiable, according to all applicable laws, including initial review, continuing review, review of modifications to previously approved research and reportable events (e.g., unanticipated problems involving risks to subjects or others, allegations of noncompliance).

The IRB will notify the researcher (and organization) of its decisions regarding initial site approval as well as any unanticipated problem, noncompliance, suspension, or termination determinations, make relevant IRB policies and records available upon request to the relying institution or organization and specify an IRB contact for communication. The RSSPMC of Hematology PI is responsible for communicating to relying PIs relevant policies (e.g., timelines for reporting unanticipated problems), approved study documents and any interim IRB decisions, such as continuing review approvals and



protocol changes approved via a modification.

Relying sites are responsible for providing local context information to the RSSPMC of Hematology IRB to enable a thorough review. This information is necessary for the RSSPMC of Hematology IRB to determine that study conduct at the site is approvable and adheres to any local regulations or policies. The information required will not duplicate information that has already been provided to the RSSPMC of Hematology IRB as part of the initial review of the research.

The addition of participating sites is considered a minor modification. These modifications are reviewed by designated reviewers.

## Section 27: Topics Specific to Clinical Research

### 27.1 Clinical Trials Registration and Results Reporting

#### 27.1.1 Registration

All applicable Clinical Trials and all U.S. NIH funded clinical trials must be registered by the responsible party, typically the sponsor, on [ClinicalTrials.gov](https://clinicaltrials.gov) within 21 days of enrolling the first study participant.

Registration must include: a) descriptive information, b) recruitment information, c) location, and d) contact information.

Applicable clinical trials include:

- Device studies of health outcomes comparing an intervention with a device product against a control in human subjects
- Pediatric postmarketing surveillance of a device product
- Drug or biologic studies (other than phase 1) in human subjects designed to evaluate biomedical or health-related outcomes, including interventional and observational studies.

Small feasibility trials and larger clinical trials of prototype devices with a primary measure of feasibility rather than health outcomes and trials using only de-identified human specimens are not Applicable Clinical Trials.

Members of the International Committee of Medical Journal Editors (ICMJE) will consider the results of clinical research for publication only if the trial has been registered prior to enrollment of the first subject. ICMJE defines a clinical trial as: “Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and health outcome.” ...This definition includes drugs, surgical procedures, devices, behavioral treatments, process-of-care changes and the like.” ICMJE further defines “medical intervention” as “any intervention used to modify a health outcome.”

#### 27.1.2 Results Reporting

Summary results information must be published within 1 year of the completion date of the clinical trial (date of final data collection for the primary outcome measure). Results data must include participant flow, demographic and baseline characteristics, primary and secondary outcomes, results of any scientifically appropriate statistical test, and adverse event information, as well as the full protocol and statistical analysis plan.

#### 27.1.3 Posting Clinical Trial Informed Consent Form

For each clinical trial supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects has to be posted by the PI on a publicly available Federal website that will be established as a repository for such forms. The form must be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject.

#### 27.1.3 Penalties for Noncompliance

Noncompliance can result in an inability to publish in certain journals. ICMJE journals require verification of registration and results reporting before accepting manuscripts for publication.

Federal penalties for noncompliance with this federal policy include civil or criminal judicial actions, as well as civil monetary fines of up to \$10,000 per day. In addition, noncompliance may be considered in future grant funding selection decisions.

## 27.2 Participant Withdrawals from U.S. FDA Regulated Research

When a participant withdraws from an U.S. FDA regulated study, the data collected on the participant to the point of withdrawal must remain part of the study database and may not be removed. The informed consent document cannot give the participant the option of having data removed. When a participant is withdrawing, the investigator may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. The Investigator may continue data collection when a participant withdraws from the intervention portion of a study only under the following circumstances:

- the discussion with the participant distinguishes 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 participant's information.
- The investigator must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.

If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

## 27.3 Emergency Use of an Investigational Drug, Device or Biologic – U.S. FDA-Regulated Studies

Situations may arise when a physician finds it is in the best interest of a patient who is in a life-threatening situation to administer an investigational product prior to receiving IRB approval. Such a use is deemed an emergency use.

In accordance with U.S. FDA regulations, the IRB may allow for the emergency use of an investigational drug or device if the situation meets the definition of Emergency Use (21 CFR 56.102(d) and if the emergency use is reported to the IRB within 5 working days of the actual use of the drug or device. The Emergency Use criteria are:

- The patient is in a life-threatening or severely debilitating situation,
- No standard acceptable treatment is available, and
- There is not sufficient time to obtain IRB approval.

The PI should make every effort to notify the IRB prior to an emergency use of an investigational drug or device. Notification may occur by phone or email. Acknowledgement of receipt of the notification is

not necessary prior to proceeding with the emergency use procedure. Regardless of whether a pre-notification has occurred, the PI must submit a report of the use to the IRB within 5 working days of the use. The use report will be reviewed to ensure the emergency use complied with U.S. FDA requirements and acknowledged by the IRB Chair. Instruction on how to submit an emergency use request or an emergency use request follow-up report can be found on Template Emergency Use Request Form.

Emergency use of unapproved drugs or biologics is research according to U.S. FDA regulations. As such, the emergency use of a test article, other than a medical device, is considered a clinical investigation by the FDA, and the patient is considered a research subject. If the research involves an investigational drug, the FDA must issue an IND prior to the use. The FDA may require data from an emergency use to be reported in a marketing application.

Conversely, U.S. DHHS regulations do not permit data obtained from patients to be classified as human subject research, nor permit the outcome of such care to be included in any report or a research activity subject to DHHS regulations.

Obtaining informed consent consistent with 21 CFR 50 and 21 CFR 50.27 from the subject or the subject's legally authorized representative is expected, unless before the use of the test article, both the PI and a physician who is not otherwise participating in the clinical investigation certify in writing that:

- The patient is confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally effective consent from, the patient.
- Time is not sufficient to obtain consent from the patient's legal representative.
- There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

The above written certification must be submitted to the IRB within 5 working days after the use of the test article. If time is not sufficient to obtain the independent determination in advance of using the test article, the use must be reviewed and the above criteria evaluated in writing by a physician who is not participating in the clinical investigation.

Any subsequent use of the test article at the University requires prior IRB approval. However, the FDA and the IRB acknowledge that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene to review the proposed use. In instances when the IRB has received more than one request for emergency treatment (multiple requests from the same researcher or isolated requests from more than one researcher), the IRB will review the request but will ask the researcher to submit a study for review by the convened IRB for subsequent use. In instances where a second researcher requests approval for an identical use, the IRB will suggest that s/he collaborate with the PI who made the initial request.

## Section 28: Transition to the New Common Rule

The revised U.S. Common Rule requires existing research (approved or determined to be exempt prior to January 21, 2019) to remain compliant with the pre-2018 regulations. Therefore, for existing studies, researchers do not need to take any action at this time beyond maintaining active IRB approval.

Existing non-exempt (approved via Expedited or Full Board review) studies will be considered for re-classification to an Exempt category at the time of continuing review, if applicable. If, at continuing review, the non-exempt studies cannot be re-classified to exempt, the studies will remain under the pre-2018 regulations until conversion to the RSSPMC of Hematology-IRB system. ORSC will work with researchers to transition studies as appropriate. Existing exempt studies will remain unchanged unless an amendment submission requires a re-classification.

## Section 29: Humanitarian Use Device (HUD)

### 29.1 General

The use of Humanitarian Use Devices in clinical investigations and for treatment or diagnosis requires prospective IRB review according to U.S. FDA regulations at [21 CFR 56.103](#) and [21 CFR 814.124](#). Data from HUD treatment activities MUST NOT BE USED for research purposes; however, safety information may be provided to the manufacturer.

### 29.2 Description

A Humanitarian Use Device (HUD) is a “medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year” ([21 CFR 814.3\(n\)](#)).

A Humanitarian Device Exemptions (HDE) is an application to the FDA requesting approval to market a HUD. The FDA approval process for an HDE does not have the same requirements as a drug or device. FDA approval of an HDE allows the applicant to market a HUD, subject to some profit and use restrictions. The HDE is usually held by the manufacturer of the HUD.

There are generally three types of uses for HUDs:

1. **Treatment or diagnosis under an HDE for the HUD’s approved labeling and indications** – This type of use is not considered a research activity; however, federal regulations require IRB approval, including continuing review of use of the device. ([21 CFR 814.124](#))
2. **Treatment or diagnosis under an HDE for an off-label use of the HUD** – This type of use is not considered a research activity. IRB approval is not required; however, the HUD/HDE must already have IRB approval for its approved indication. The UT IRB requires pre-notification, as described in Section 29.3.6 below.
3. **Clinical investigation (i.e., collection of safety and effectiveness data) involving an HUD, whether for its HDE-approved indication(s) or for a different indication** – This type of activity is considered research. As such, prospective IRB approval is required.

### 29.3 Procedures and Guidance

#### 29.3.1 IRB Review of a HUD for Treatment or Diagnosis (Non-Research)

##### 29.3.1.1 Initial Review

Regulations (see [21 CFR 814.124\(a\)](#)) require IRB review and approval before a HUD is used. There is an exception to this rule for emergency situations in which the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient (see Section 27.3 Emergency Use of an Investigational Drug, Device, or Biologic for additional information). In non-emergency use situations, full board review by the convened IRB is required for initial review of HUDs.

The IRB requires the following information, if available, to be submitted for approval.

- Completed [Template IRB Proposal Humanitarian Use Device Submission](#) form.
- Proof of the HDE (FDA letter).
- Product labeling information.

- Patient information packet.
- A clinical protocol describing the use (matching the approved use as outlined in the FDA letter, if available)
- Informed consent (additional information regarding informed consent for treatment use can be found in Section 29.3.3.1.3).

Most HDE holders develop patient information packets that generally contain a discussion of the potential risks and benefits of the HUD and any procedures associated with its use. If patient information packets are available, the IRB should ensure that physicians distribute them to patients prior to their receiving the HUD. Even when the IRB requires patients to sign a written consent document that describes the use of the HUD (and which may provide similar information found in the HDE holder's packet), the patient should always receive the HDE holder's patient information packet. For HUD information packets, go to <https://www.fda.gov/medical-devices/hde-approvals/listing-cdrh-humanitarian-device-exemptions#2> and select the HDE#.

#### *29.3.1.2 Continuing Review*

Continuing review of HUDs may be done using expedited review procedures ([21 CFR 56.110](#)) unless the IRB determines that full board review should be performed. The FDA notes that the expedited review procedures are appropriate for continuing review since the initial review would have been performed by the convened board and use of a HUD within its approved labeling does not constitute research.

The IRB requires the following information to be submitted for continuing review:

- A continuing review action with RSSPMC of Hematology.
- A summary of the use that has occurred during the review period including:
  - Any uses outside of the approved device indication,
  - De-identified information pertaining to the patients who received the device, and
  - Discussion of any adverse events.
- Copies of medical device reports (see section 23.1.9 below) submitted to the FDA or HDE holder if not already provided in another report.
- Copies of annual reports or related summaries from the HUD manufacturer, and the PI's evaluation of whether the reports indicate any changes needed to the HUD protocol, patient information, or consent process.

#### *29.3.1.3 Informed Consent Requirement*

The RSSPMC of Hematology IRB requires that an informed consent process and document be approved, even though federal regulations do not require informed consent. If prospective informed consent will not be practicable (e.g., give the study population or procedures for use of the HUD), a different consent process or waiver of this informed consent process must be approved by the IRB.

The informed consent document may be provided by the manufacturer. The informed consent process should ensure that patient clearly understands that the effectiveness of the device has not been fully tested, the risks and benefits of the device, as well as any possible alternative treatment options.

Most HDE device patient labeling contains a discussion of the potential risks and benefits of the device as well as any procedures associated with the use of the HUD. Patient labeling also states that the device

is a humanitarian use device for which effectiveness for the labeled indications has not been demonstrated. This information may be used in the informed consent process.

The following information should be conveyed to the patient through the patient labeling and/or the informed consent form:

- A statement that the effectiveness of the device for the use has not been demonstrated;
- An explanation that the HUD is designed to diagnose or treat the disease or condition described in the HDE labeling (except in an off-label use) and that no comparable device is available to treat the disease or condition;
- A description of any ancillary procedures associated with the use of the HUD that are not described elsewhere, such as in a hospital consent;
- A description of the use of the HUD;
- All known risks or discomforts associated with the use; and
- An explanation of how the HUD will work in relation to the disease or condition.

The requirements and procedures outlined for translation and interpretation of consent and study documents apply whenever a HUD study will be consenting patients or LARs with limited English proficiency unless a different consent process was specifically approved by the IRB.

#### *29.3.1.4 HIPAA Requirements*

When using a HUD for treatment or diagnosis, the activity is not considered research. As such, an Authorization for research is not necessary. Use of protected health information (PHI) about a patient defers to the HIPAA policy in the clinical practice setting.

#### *29.3.1.5 Multiple Uses of the HUD within the Approved Indication(s)*

Once the IRB has granted approval for the use of the HUD, subsequent use according to the HDE-approved indication(s) should be reported to the IRB at the time of continuing review. The IRB is not required to review and approved each individual use of a HUD. However, according to [FDA Guidance](#):

*The IRB may use its discretion to determine how to approve use of a HUD. For example, if it so wishes, with the input of members with the appropriate expertise in the clinical area (21 CFR Part 56), an IRB may specify limitation on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB or IRB Chairperson, appropriate follow-up precautions and evaluations, or any other criteria it determines to be appropriate.*

#### *29.3.1.6 Use of a HUD Outside of the Approved Indication(s)*

Once a HUD is approved by the IRB for its indicated use, the HUD may be used outside of its approved indication(s) for treatment or diagnosis. When this situation exists, the IRB advises the following:

1. Notify the IRB in advance of the use whenever possible and provide the IRB # of the associated approved HUD protocol (unless the use is an emergency situation), a description of the need for the use, as well as when and how the use will occur. Written notification may include submission of an email or submission or an amendment or report directly within the associated approved HUD protocol, as appropriate to the situation. IRB approval is not required, but the use should be reported to the IRB at the time of continuing review.



2. The physician obtained patient consent as described in section 29.3.1.3 above. The informed consent discussion must clearly explain that the HUD is being used outside of its approved indication.

#### *29.3.1.7 Modifications*

The Principal Investigator is responsible for obtaining approval from the RSSPMC of Hematology IRB before implementing any changes in the approved documents or procedures for the use, control, and/or storage of the HUD, unless such changes are necessary to protect the safety of patients. Departures from the approved documents or protocol that are made to protect the safety of patients should be reported to the RSSPMC of Hematology IRB within 5 days through a report submission.

#### *29.3.1.8 Unanticipated Problem Reporting*

The Principal Investigator is responsible for reporting all unanticipated problems involving risk to patients to the IRB according to procedures in Section 9.2.

#### *29.3.1.9 Medical Device Reporting (MDR)*

The Principal Investigator is required to submit medical device reports to the FDA, the manufacturer, and the IRB whenever the HUD may have caused or contributed to a serious injury ([21 CFR 803.30](#) and [814.126\(a\)](#)).

Serious injury means an injury or illness that (1) is life threatening, (2) results in permanent impairment of a body function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure ([21 CFR 803.3](#)).

[MDR reports](#) must be submitted when the HUD is being used for its approved indications and unapproved indications, as described in Section 29.3.1.6 above. MDR reports submitted to the FDA should be submitted to the IRB in a Report via the Reportable New Information (RNI) process within five days of submission to the FDA.

#### *29.3.1.10 Closure from IRB Oversight*

The Principal Investigator may close a non-research HUD protocol from IRB oversight only once the conditions for closure outlined in their FDA letter have been met. Closure submissions should include a description of how the criteria have been met.

### **29.3.2 IRB Review of HUD for Clinical Investigation (Research)**

#### *29.3.2.1 Initial Review*

When a HUD is being used in a clinical investigation (e.g., collection of safety and effectiveness data), whether for its HDE-approved indication(s) or for a different indication, the investigation is considered research involving human participants. As such, IRB review and approval by the convened IRB is required prior to initiating the research. Investigators should submit the study to the IRB via UTRMS-IRB. Full board review will occur by the convened IRB.

#### *29.3.2.2 Need for an Investigational Device Exemption*

**Approved Indication:** When an HUD is used in accordance with its approved indication(s), the FDA considers the study exempt from the requirement for an IDE, even when safety and effectiveness data are collected. As such an IDE is not required. The IRB does not make a significant risk/non-significant risk determination when the HUD is being used for approved indication(s) and no IDE is needed.

**Unapproved Indication:** Clinical investigations using the HUD for an unapproved use or indication must comply with the IDE regulations at 21 CFR Part 812. An IDE is required in this case. The IRB review should include a significant risk/non-significant risk determination unless the determination has already been made by the FDA.

#### *29.3.2.3 Continuing Review*

The IRB will determine the frequency of continuing review, with a maximum review period of one year. Continuing review will be conducted by the convened IRB unless it is determined to qualify for expedited review. Investigators should submit continuing review form.

#### *29.3.2.4 Informed Consent Requirement*

An informed consent process and a standard research consent form compliance with 21 CFR 50 should be provided to the IRB for review and approval.

#### *29.3.2.5 HIPAA Requirements*

When using a HUD in a clinical investigation, the use is considered research and is subject to HIPAA for research regulations. Patient authorization must be obtained for the use of PHI unless the IRB approves a waiver of authorization.

## Section 30: Expanded Access to Unapproved Drugs or Biologics

### 30.1 General

Under U.S. FDA regulations (21 CFR 312.300), expanded access allows for the use of unapproved drugs and biologics outside of a clinical trial for patients with serious diseases or conditions when there is no satisfactory alternative therapy to treat the patient's disease or condition. This is sometimes referred to as compassionate use or treatment use. For all expanded access use, prior IRB review and approval is needed, with the exception of Emergency Use situations.

### 30.2 Key Terms

**Immediately life-threatening disease or condition** means a state of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

**Serious disease or condition** means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

**Expanded Access Programs (EAPs)** refer to the various types of allowable expanded access use.

### 30.3 Criteria for all expanded access uses for drugs and biologics

All expanded access programs (EAPs) use must meet the basic criteria in 21 CFR 312.305(a). The FDA must determine that:

1. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
2. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
3. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

### 30.4 Reporting and Monitoring Requirements

Investigator Responsibilities:

- Reporting adverse drug events to the sponsor
- Ensuring that the informed consent requirements are met
- Ensuring that prospective IRB approval of the expanded access is obtained
- Maintaining accurate case histories and drug disposition records/retaining records in a manner consistent with the requirements of 21 CFR 312.62.

#### Sponsor Responsibilities:

- Submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to the FDA
- Ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use
- Providing licensed physicians with the information needed to minimize risk and maximize the potential benefits of the investigational drug (investigator's brochure must be provided if one exists for the drug)
- Maintaining an effective IND or IDE for the expanded access use
- Maintaining adequate drug disposition records and retaining records (21 CFR 312.57)

Additional responsibilities may apply (see each EAP category below).

### 30.5 Types of expanded access for drugs and biologics

#### 30.5.1 Single Patient Expanded Access, Non-Emergency Use

In addition to the criteria for all expanded access uses listed above, the following must also be met:

1. The physician must determine that the probable risk to the person from the investigational drug is not greater than the probably risk from the disease or condition; and
2. The FDA must determine that the patient cannot obtain the drug under another IND or protocol.

If the drug is the subject of an existing IND, the expanded access IND submission may be made by the sponsor or by a licensed physician.

##### *30.5.1.1 Procedures for IRB submission of single patient, non-emergency expanded access protocols*

Single patient, non-emergency expanded access protocols must be submitted and require IRB review and approval under FDA regulations. ORSC is cognizant of the need for timely review for these cases and will make every effort to assign these submissions to the first available meeting with expertise.

The Investigator should submit the following along with the new study submission:

1. Template Expanded Access, Single Patient Treatment Form
2. IND number (entered on Drug Smartform page in IRB application)
3. [Form FDA 3926](#)
4. Approval letter from the FDA
5. Consent form for the patient
6. Approval from the sponsor for the treatment use, as applicable
7. Other supporting documents as needed.

During review of an expanded access use of an investigational drug request for single use treatment only situation, the FDA may approve a waiver of full IRB review in response to a request for alternative IRB review when submitting Form FDA 3926 to the FDA. If this process is approved, IRB Chair concurrence can be obtained prior to beginning treatment in lieu of full committee review. If the FDA does not

approve the process or if the full IRB waiver is not requested on the submission to the FDA, the full IRB committee must review the expanded access request. The RSSPMC of Hematology IRB recommends checking box 10b on the Form FDA 3926 to allow for an alternative review should the FDA approve the request.

#### 30.5.1.2 Reporting and Monitoring Requirements

At the conclusion of treatment, the licensed physician or sponsor must provide a written summary of the results of the expanded access use, including adverse effects, to the FDA.

#### 30.5.2 Single Patient Expanded Access, Emergency Use

For information regarding Emergency Use, please see Section 27.3.

#### 30.5.3 Expanded Access for Intermediate-Sized Populations

FDA may permit an investigational drug to be used for treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. In cases where the FDA has received a significant number of requests for individual patient expanded access for the same use, a sponsor may be asked to consolidate expanded access under this category. The use of this EAP is fully addressed in [21 CFR 312.315](#).

#### Criteria

In addition to the basic EAP criteria (listed above), the FDA must also determine:

1. There is enough evidence that the drug is safe at the proposed dose and duration proposed for the expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under the expanded access; and
2. There is at least preliminary evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

##### *30.5.3.1 Procedures for IRB submission of expanded access protocols for intermediate-sized populations*

Intermediate sized expanded access protocols must be submitted through usual new study procedures and require convened IRB review and approval under FDA regulations.

The Investigator should submit the following along with the UTRMS-IRB new study application:

1. Template IRB Proposal Standard Submission
2. IND number
3. Approval letter from the FDA
4. Consent form
5. Other supporting documents, as needed.

#### 30.5.4 Expanded Access for Large Patient Populations

Expanded access protocols for large patient populations are also referred to as treatment IND or treatment protocols. This category is used for widespread treatment use of an investigational drug. In addition to the criteria listed as the beginning of this section for all expanded access, the FDA must also determine that the drug is being investigated in a controlled trial under an IND to support a marketing

application for the expanded access or all clinical trials of the drug have been completed, the sponsor is actively pursuing marketing for approval of the expanded access and there is sufficient data supporting safety and effectiveness of the drug for the expanded access.

#### *30.5.4.1 Procedures for IRB submission for expanded access protocols for large patient populations*

Expanded access protocols for large patient populations must be submitted per usual procedures and require convened IRB review and approval under FDA regulations.

The Investigator should submit the following along with the new study application to the IRB:

1. Template IRB Proposal Standard Submission
2. IND number
3. Approval letter from the FDA or sponsor protocol with IND number present
4. Consent form
5. Other supporting documents, as needed.

## Section 31: Expanded access to Unapproved Devices

### 31.1 General

According to the FDA regulations, an unapproved medical device may normally only be used on human subjects through an approved clinical study in which the subjects meet certain criteria and the device is only used in accordance with the approved protocol by a clinical investigator participating in the clinical trial. However, the FDA recognizes that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which no other alternative therapy exists. Patients/physicians faced with these circumstances may request access to investigational devices under one of the following mechanisms by which FDA may make an unapproved device available.

### 31.2 Key Terms

An **unapproved medical device** is a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval under section 515 of the U.S. Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e)(the Act) or an approved IDE under section 520(g) of the Act (21 U.S.C. 360j(g)).

An **investigational device exemption (IDE)** permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.

### 31.3 Reporting and Monitoring Requirements

An investigator shall prepare and submit the following reports:

- Unanticipated adverse device effects: An Investigator shall submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effects within 10 working days after the investigator first learns of the effect.
- Progress: An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals. See [FDA IDE Reporting](#) guidance for additional information.
- Deviations from the investigational plan: An investigator shall notify the sponsor and reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency no later than 5 working days after the emergency has occurred.
- Final Report: An investigator shall, 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.

### 31.4 Emergency Use of an Unapproved Device

For information regarding Emergency Use, please see Section 27.3.

### 31.5 Compassionate Use (or Single Patient/Small Group Access)

The FDA's compassionate use provision is designed to provide access to an investigational device for patients who are not eligible for the clinical trial but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. Compassionate use may

be used only during the clinical trial for which the device is being tested. Compassionate use may be approved for a single patient or a small group of patients.

Prior FDA approval is required before compassionate use occurs. The sponsor of the IDE is required to submit an IDE supplement requesting approval under [812.35\(a\)](#) in order to treat the patient. The supplement should include:

- Description of the patient's condition and circumstances necessitating treatment
- Discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probably risk from the disease or condition
- Identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient
- Patient protection measures that will be followed, e.g., informed consent, concurrence of IRB chairperson, clearance from the institution, independent assessment from uninvolved physician, authorization from IDE sponsor
- The number of patients to be treated (when use is for small groups)

For further instructions about FDA requirements for the IDE supplement, refer to the FDA website, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm>.

The physician should not treat the patient identified in the supplement until the FDA approves use of the device under the proposed circumstances.

### **Criteria**

This provision allows access when:

- There is an existing concurrent clinical trial but the patient(s) do not meet the inclusion criteria, and
- The treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition.

#### **31.5.1 Procedures for IRB submission of protocols for compassionate use of unapproved devices**

Single patient (or small group), non-emergency compassionate use of unapproved device protocols must be submitted and will be reviewed by an IRB chairperson or another designated IRB member with appropriate expertise.

The Investigator should submit the following along with the new study application for single patient expanded access device/compassionate use:

1. Template Expanded Access, Single Patient Treatment Form
2. IDE number
3. Approval letter from the FDA
4. Consent form for the patient
5. Approval from the sponsor for the treatment use, as applicable
6. Other supporting documents, as needed.



### 31.5.2 Reporting and Monitoring Requirements

The attending physician should devise an appropriate schedule for monitoring the patient(s), considering the investigational nature of the device and specific patient needs. The patient(s) should be monitored to detect any possible problems arising from the use of the device.

Following the compassionate use of the device:

- A follow-up report should be submitted to the FDA within 45 days of using the device as an IDE supplement in which summary information regarding patient outcome is presented
- Any problems which occurred as a result of device use should be discussed in the supplement and reported to the IRB as soon as possible
- Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

### 31.6 Treatment Use of Investigational Devices – Larger Group/More Widespread Use

The FDA will consider expanded access under a Treatment IDE ([21 CFR 812.36](#)).

An approved treatment IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases.

The device may be made available for treatment use:

- After completion of all clinical trials – for serious disease
- Before completion of all clinical trials – for immediately life-threatening disease.

#### Criteria:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
4. The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

A treatment IDE application must be submitted to FDA and approval must be obtained prospectively.

**31.6.1 Procedures for IRB submission of protocols for treatment use of unapproved devices**  
for treatment IDEs, treatment use protocols must be submitted through the usual new study procedures and require convened IRB review and approval under FDA regulations.

The Investigator should submit the following along with the new study application:

1. Template IRB Proposal Standard Submission

2. IDE number
3. Approval letter from the FDA or sponsor protocol with IDE number
4. Consent form
5. Other supporting documents as needed.

### 31.6.2 Reporting and Monitoring Requirements

The sponsor (or sponsor-investigator) of a treatment IDE must submit semi-annual progress reports to the IRB and FDA until the filing of a marketing application. After filing of a marketing application, progress reports must be submitted annually in accordance with [21 CFR 812.150\(b\)\(5\)](#).

See:

- [IDE Reports](#) [FDA]
- [IDE Early/Expanded Access – Treatment Use](#) [FDA]

### References

[21CFR 312.300 \(Subpart I\)](#)

[21 CFR 56.102](#)

[21 CFR 812](#)

[FDA Guidance on IDE Policies and Procedures](#)

## Section 32: Exception from Informed Consent for Planned Emergency Research

### 32.1 General

Planned emergency research involves the systematic investigation of a condition experienced by individuals “in a setting where the emergency circumstances require prompt action and generally provide insufficient time and opportunity to locate and obtain from each subject’s legally authorized representative” informed consent ([FDA Guidance: Exception from Informed Consent Requirements for Emergency Research](#)). When research begins before there is an opportunity to obtain informed consent, additional participant protections must be in place before the IRB can approve planned emergency research.

Please note, planned emergency research is different from emergency use of a test article in a single patient. Planned emergency research involves prospective identification and enrollment of participants into a study. Emergency use of a test article involves the treatment of a patient using a test article outside of the research setting. Please see Section 27.3 for information about emergency use in a single patient treatment scenario.

### 32.2 Review of Planned Emergency Research under RSSPMC of Hematology IRB Oversight

RSSPMC of Hematology IRB reviews proposed emergency research and applies required regulations as appropriate. Planned emergency research under a waiver of consent may be conducted under either FDA regulations ([21 CFR 50.24](#)) and/or the DHHS Common Rule ([Secretarial waiver](#) pursuant to authority granted under 45 CFR 46.101(i)). The IRB does not approve this waiver for research involving prisoners (Subpart C of 45 CFR 46), research involving fetuses, pregnant women, or human in vitro fertilization (subpart B of 45 CFR 46).

The convened IRB reviews research subject to 21 CFR 50. If the research is FDA regulated, the IRB will determine and document that the FDA regulatory criteria to allow an exception to the requirement to obtain consent (Sec. 50.24) and DHHS criteria outlined below are met. The criteria will be documented in the minutes and uploaded checklists indicating that each of the criteria are met before the study is determined to be approvable.

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly (no longer than within 30 days) in writing to the clinical investigator and to the sponsor of the clinical investigation.

The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

- 1) The human subjects are in a life-threatening situation, available treatments are either unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

- 2) Obtaining informed consent is not feasible because:
  - i. The subjects will not be able to give their informed consent as a result of their medical condition;
  - ii. The intervention under investigation must be administered before consent from the subjects' legally authorized representative (LAR) is feasible; and
  - iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- 3) Participation in the research holds out the prospect of direct benefit to the subjects because:
  - i. Subjects are facing a life-threatening situation that necessitates intervention;
  - ii. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supports the potential for the intervention to provide a direct benefit to the individual subjects; and
  - iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- 4) The clinical investigation could not practicably be carried out without the waiver.
- 5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent. The investigator must summarize efforts made to contact LARs and make this information available to the IRB at the time of continuing review.
- 6) Informed consent consistent with the RSSPMC of Hematology IRB Policy on Obtaining Informed Consent and 21 CFR 312.50.25 will be obtained and documented from subjects or their LARs when feasible.
- 7) Procedures and information exist which provide an opportunity for a family member to object to a subject's participation in the research in accordance with this policy.
- 8) Additional protections of the rights and welfare of subjects are provided, including, at least:
  - i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
  - ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation, of the clinical investigation, of plans for the investigation and its risks and expected benefits;
  - iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
  - iv. Establishment of an independent data monitoring committee to oversee the clinical investigation; and
  - v. If obtaining informed consent is not feasible and a LAR is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not an LAR, and asking whether the family member objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

### 32.2.1 Additional Informed Consent Requirements

The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each participant or, if the participant remains incapacitated, their LAR, of the following:

- That the subject was enrolled in the clinical investigation
- The details of the investigation
- Other information contained in the informed consent document
- That they may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

If an LAR or family member is told about the research and the participant's condition improves, the participant is also to be informed as soon as feasible.

If a participant is enrolled into a clinical investigation with waived consent and the participant dies before an LAR or family member can be contacted, information about the research is to be provided to the participant's LAR or family member, if feasible.

### 32.2.2 Planned Emergency Use with Investigational Products

When the research involves testing an investigational product, the protocol must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies the associated protocol as one that might include participants who are unable to consent. A separate IND or IDE is required even if an IND for the same drug product or an IDE for the same device already exists.

### 32.2.3 U.S. Department of Defense Covered Planned Emergency Research

For planned emergency research that is subject to DoD Requirements (32 CFR 219), the additional criterion must be met: the Secretary of Defense must approve a waiver of the advance informed consent provision of 10 USC 980.

### 32.2.4 Procedures for IRB submission of EFIC for planned emergency research

Research protocols must be submitted through the usual new study procedures and require convened IRB review.

The Investigator should submit the following along with the new study application:

1. Template IRB Proposal Standard Submission
2. Sponsor protocol, as applicable
3. Approval letter from the FDA or sponsor protocol with eIND/IDE number
4. Consent form
5. Community consultation plan, including materials used during community consultation
6. Other supporting documents as needed.

## 32.3 Local Review of Planned Emergency Research Relying on non-RSSPMC of Hematology IRB

The RSSPMC of Hematology IRB may rely on an external IRB for the regulatory oversight of planned emergency research with exception from informed consent. Researchers should consult with the RSSPMC of Hematology IRB reliance support staff **prior** to submission to ensure that RSSPMC of Hematology will defer oversight. IRB review may be ceded to an external IRB as described in IRB Policies and Procedures Section

## 26.3-IRB Reliance.

In the instance where an external IRB will provide regulatory oversight, the RSSPMC of Hematology IRB's role may be limited to a local context review of the study's plans for community consultation and public disclosure and any other routine local context considerations. In its review, the RSSPMC of Hematology IRB represented by a subcommittee of IRB committee members and IRB support staff shall confirm the proposed community consultation and disclosure plan:

- Informs the communities that informed consent will not be obtained for most (or all) research subjects, including an explanation as to why consent is not feasible.
- Informs the communities about all relevant aspects of the proposed study, including potential risks and expected benefits.
- Includes procedures to hear from and respond to questions, comments, concerns from the communities on the proposed research.
- Provides information about ways, if any, in which individuals wishing to be excluded from the research indicate this preference.
- Includes the people most likely to be affected by the research and incorporates plans to engage these groups within their communities.

### 32.3.1 Procedures for IRB submission

Requests to rely on an external IRB for oversight of planned emergency research involving EFIC must be submitted through the usual reliance procedures and local context review and review by a subcommittee of IRB members. It is strongly recommended investigators consult with the IRB office prior to submission to confirm RSSPMC of Hematology's willingness to rely on an external IRB.

The Investigator should submit the following along with the IRB reliance submission:

1. Template Request to Rely on an External IRB Form
2. Research protocol (e.g., sponsor protocol, lead site protocol)
3. Approval letter from the UCPPS/FDA or protocol with eIND/IDE number
4. Consent form to be used for local subjects
5. Community consultation plan, including materials used during community consultation
6. Other supporting documents as needed.

### 32.3.2 Local IRB Review

The local RSSPMC of Hematology IRB review shall confirm that any requirements related to local context are met, e.g., investigator qualifications, appropriate language in consent forms, recruitment materials, and ancillary reviews.

Once a subcommittee of the RSSPMC of Hematology IRB has determined local context considerations are met, reliance on the external IRB will be confirmed.

The RSSPMC of Hematology Principal Investigator is expected to provide the RSSPMC of Hematology IRB with follow-up submissions including:

- Submit a study modification to the RSSPMC of Hematology IRB detailing results of the community consultation efforts and include the reviewing IRB's assessment of community consultation results.

- The RSSPMC of Hematology PI will be notified of approval to begin study enrollment when they receive approval for the modification. Study enrollment can only begin once approval from the reviewing IRB and approval from IRB is obtained.
  - Other site approvals may be required prior to enrollment (e.g., Seton Site Approval). The RSSPMC of Hematology PI is responsible for ensuring all local site approvals are obtained.
- The RSSPMC of Hematology PI must submit to the IRB an annual continuing review to apprise the RSSPMC of Hematology IRB of study progress.
- Throughout the approval period of the study, the RSSPMC of Hematology HRPP retains the authority to conduct post approval monitoring of study conduct.
- After the study is completed and public disclosure of study results have been approved by the reviewing IRB, the RSSPMC of Hematology PI must submit results of the public disclosure to the RSSPMC of Hematology IRB.

## Section 33: RSSPMC of Hematology HRPP Emergency Preparedness Plan

The RSSPMC of Hematology and the HRPP routinely assess potential emergency scenarios and threats to the institution to improve its emergency preparedness and response plan. The RSSPMC of Hematology annually prepares and certifies an emergency operations plan that addresses concerns related to campus and personnel safety and information technology infrastructure. This plan is reassessed annually by RSSPMC of Hematology leadership. The highest risk threats and hazards are identified in the RSSPMC of Hematology emergency operations plan and include severe thunderstorm and lightening, cyber threat, information technology system failure, infectious disease, civil unrest, and power outage.

The HRPP emergency preparedness plan focuses on continuity of IRB operations in the event of an emergency that could impede normal IRB business operations and the conduct of human subject research. The HRPP relies on the RSSPMC of Hematology's emergency operations plan to address concerns related to campus and personnel safety and information technology infrastructure. The ORSC Director or designee reviews updates to the university emergency operations plan as they are released to assure HRPP emergency preparedness continues to align with the RSSPMC of Hematology emergency operations plan.

In the event of an emergency, the ORSC Director or designee will work with the IO and other RSSPMC of Hematology leadership to implement appropriate emergency response procedures for oversight and conduct of human subject research that align with the RSSPMC of Hematology's overall emergency response.

The RSSPMC of Hematology HRPP staff work primarily in a remote environment. As a result, the impact of specific threats and hazards are somewhat mitigated by the dispersed nature of support personnel. It is anticipated that enough staff will be available at any given time to process emergency submissions as needed. HRPP leadership will assess staffing availability throughout the duration of an emergency situation to ensure urgent IRB needs are met.

The electronic systems supporting IRB operations, COI, and grants are hosted external to the RSSPMC of Hematology, minimizing disruptions due to localized emergencies. Daily backups are stored, enabling a full system restoration. Should vendor services be interrupted, system access should be restored within two business days and at most ten business days from a disaster event. In the event the electronic system is unavailable, the IRB will implement alternative measures to receive time critical IRB submissions for review.

IRB meetings are generally held in person or virtually using a Zoom platform. As a result, it is anticipated that IRB meetings will be able to continue even if members must shelter in place. In the event the Zoom platform is unavailable, a teleconference will be scheduled. In instances where the convened IRB is unable to meet or quorum cannot be obtained and IRB approval for a study may lapse, the IRB Chair can determine whether subjects can continue to participate in research activities if it is in the best interest of already enrolled subjects.

The nature of each emergency will dictate the specific response taken by the HRPP leadership. These plans will be determined by the ORSC Director or designee and other HRPP leaders. Response actions may include implementing flexibilities for non-federally funded research such as extension of continuing



review dates or eliminating the need for prospective IRB review for minor procedural changes necessitated by the emergency. These plans will be disseminated to the research community in a just-in-time manner via email and website communication. In addition, researchers will be referred to worksheets and tools to help in their response planning, including:

- Worksheet – Protocol Specific Emergency-Disaster Risk Mitigation Planning
- Flowchart – Study Specific Emergency-Disaster Risk Mitigation Planning

In the event an emergency necessitates limitations on the conduct of human subject research, the RSSPMC of Hematology will implement a risk-based approach to determining how and when research with human subjects may continue. Research will be categorized by risk level, and risk levels will correspond to overall RSSPMC of Hematology-wide research operations. In emergencies caused by potential viral transmission, the table below provides an example risk rubric that may be implemented by the RSSPMC of Hematology.

#### Categories of Viral Transmission Risk to Inform Decision-Making about Human Subjects Research

		Incremental Risk of Viral Transmission			
		No-Risk Scenarios	Low-Risk Scenarios	Moderate-Risk Scenarios	High-Risk Scenarios
Risks to Human Subjects & Research Personnel	Contact	<ul style="list-style-type: none"> <li>Completely virtual*</li> </ul>	<ul style="list-style-type: none"> <li>Outdoor with social distancing and PPE</li> <li>Participant alone</li> <li>No close contact</li> <li>Brief close contact <u>but no</u> direct physical contact</li> <li>Individual researcher interacts with low participant numbers</li> </ul>	<ul style="list-style-type: none"> <li>Indoor with social distancing, PPE, and/or physical barriers between participant and researcher</li> <li>Brief direct physical contact</li> <li>Extended close contact that may be accompanied by brief direct physical contact</li> <li>Individual researcher interacts with moderate participant numbers</li> </ul>	<ul style="list-style-type: none"> <li>Indoor without social distancing, PPE, or barriers</li> <li>Extended direct physical contact</li> <li>Individual researcher interacts with high participant numbers</li> </ul>
	Vulnerability of Participants	Any population	<ul style="list-style-type: none"> <li>Persons who do not self-identify as being at higher risk of adverse outcomes from infection</li> <li>Pregnant women</li> <li>Children 18 and under</li> </ul>	<ul style="list-style-type: none"> <li>Persons who do not self-identify as being at higher risk of adverse outcomes from infection</li> <li>Pregnant women</li> <li>Children 18 and under</li> </ul>	<ul style="list-style-type: none"> <li>Age &gt; 65 years</li> <li>Immunocompromised persons</li> <li>Persons who self-identify as being at higher risk of adverse outcomes from infection</li> </ul>
	Infectious Status of Participants	<ul style="list-style-type: none"> <li>No prior positive test result and passes symptom check</li> </ul>	<ul style="list-style-type: none"> <li>Recovering and more than 10 days after symptom onset and/or a positive test and at least 3 days without fever or other symptoms</li> </ul>		<ul style="list-style-type: none"> <li>Known positive test result within past 10 days</li> </ul>

**Minimum PPE requirements for ALL face-to-face human subjects research:** Level 2 medical grade mask, regardless of level of contact  
**Additional PPE requirement for direct contact scenarios:** Goggles or face shield

The table below provides an example of how the RSSPMC of Hematology may apply the risk rubric to specify the nature of human subjects research that may be carried out depending on the overall status of the Center and research operations.

**Matrix of Benefits and Risks**

		Incremental Risk of Viral Transmission			
		No-Risk Scenarios	Low-Risk Scenarios	Moderate-Risk Scenarios	High-Risk Scenarios
Benefits to Research/ Scholarship & Individual Participants	Benefits to research/scholarship + life-saving and life-extending benefits	Tier A	Tier A	Tier A	Tier A
	Benefits to research/scholarship + direct benefits that are difficult to replace through other means	Tier A	Tier B	Tier B	Tier B
	Benefits to research/scholarship + direct benefits to individual participants that overlap with other means	Tier A	Tier B	Tier C	Tier C
	Benefits to research/scholarship + primarily or solely indirect benefits to individual research participants	Tier A	Tier B	Tier C	Tier D

The HRPP Director or designee will periodically provide IRB members and HRPP staff with information and training about the HRPP emergency plan. The information provided will be reassessed periodically to ensure it aligns with the RSSPMC of Hematology emergency operations plan and the HRPP emergency plan.

In the event the emergency plan needs to be implemented, information will be distributed to the RSSPMC of Hematology research community via email from the Vice President for Research, Scholarship and Creative Endeavors.