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1. Introduction

1.1. Purpose of Handbook
The purpose of the Chesapeake Institutional Review Board (Chesapeake IRB) Handbook is to orient Principal Investigators/research staff, sponsors, contract research organizations (CROs), and site management organizations (SMOs), to Chesapeake IRB’s policies, procedures, and guidelines. The Handbook includes information related to the initial review process through management of ongoing research activities and study closure. To comply with conditions of IRB approval, the policies, procedures, and guidelines outlined in this document must be followed during the conduct of a research study to ensure adequate protection for the rights and welfare of research subjects.

Please note “sponsor” is referenced throughout the Handbook. The term “sponsor” also applies to CROs and SMOs that act on behalf of sponsors.

Revisions to Chesapeake IRB’s Investigator, Sponsor, and Sponsors’ Representatives Handbook will be made on an as-needed basis to reflect changes in Chesapeake IRB’s policies and procedures and/or federal regulations and guidance documents. Any changes to the handbook are communicated via Chesapeake IRB’s web-based IRB platform, CIRBI (www.cirbi.net), and will always be posted under the Reference Materials section of CIRBI for immediate access.

1.2. Scope of Services
Chesapeake IRB reviews all phases of research involving the use of drugs, biologics, devices, as well as behavioral and social science and consumer product research. Chesapeake IRB also reviews research involving the use of “Treatment INDs”, “Treatment Protocols”, “Treatment IDEs”, and Humanitarian Use Devices.

Chesapeake IRB reviews protocols for sites in all 50 U.S. states and territories. In addition, Chesapeake IRB reviews international research to ensure compliance under ICH GCP and US federal regulations (if applicable)

Chesapeake IRB reviews research studies conducted by a single Principal Investigator or multiple Principal Investigators. Regardless of the number of investigators conducting the research, Chesapeake IRB keeps each Sponsor (for multi-site research), Principal Investigator/site informed of actions that occur during the conduct of the study and will provide written notification of Chesapeake IRB’s actions/determinations and requirements.

In addition to IRB services, Chesapeake IRB offers consulting, training and education services on all aspects of human research protection programs.

1.3. OHRP/FDA IRB Registration
Chesapeake IRB is registered with OHRP and FDA under registration number: IRB00000790. Chesapeake IRB’s registration number can also be confirmed at http://ohrp.cit.nih.gov/search/.
1.4. IRB Membership

Chesapeake IRB is one board consisting of multiple panels. Each panel includes at least 5 members; each member serves as an alternate to the other panels when their participation/expertise is needed.

As required by the federal regulations, the IRB is constituted in compliance with the federal regulations as described in 21 CFR Part 56, DHHS regulations as described in 45 CFR 46, and guidelines resulting from the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP). Although fully supported operationally and administratively, the IRB’s deliberative processes and actions are independent from Chesapeake IRB’s operations.

Chesapeake IRB’s membership includes individuals who have professional experience, knowledge, and expertise to review human subjects research. On occasion, the board requests the assistance of a consultant with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB.

Chesapeake IRB’s current Membership Roster is available on the CIRBI (www.cirbi.net) website under Reference Materials. Any changes to the roster are updated on the site and communicated via CIRBI.

1.5. Statement of Compliance

Chesapeake IRB operates in compliance with FDA regulations as described in 21 CFR Parts 50 and 56, DHHS regulations as described in 45 CFR 46, guidelines resulting from the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and potentially the Common Rule, as appropriate. In addition, the IRB operates in compliance with the portions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA Privacy Rule) that apply to research, as described in 45 CFR Parts 160 and 164. Chesapeake IRB has been awarded Full Accreditation from the Association for the Accreditation of Human Research Protection Programs, Inc. ® (AAHRPP) since 2004.

1.6. Timelines and Chesapeake IRB Meeting Schedules

Chesapeake IRB meets 5 days/week at a regularly scheduled time (see www.cirbi.net or Chesapeakeirb.com for the IRB meeting calendar). Ad hoc meetings are scheduled on an as needed basis; if faced with critical timelines, please contact Chesapeake IRB to discuss potential options to meet required timelines.
2. Sponsor and Principal Investigator Responsibilities

2.1. Sponsor Responsibilities

2.1.1. Site Selection/Monitoring:
Sponsors are responsible for selecting only Principal Investigators qualified by training and experience to conduct a research study. Sponsors must evaluate and ensure that the appropriate resources and infrastructure to support the conduct of clinical research is maintained at the site(s). The site(s) must be in compliance with the Sponsor’s requirements for handling medical emergencies.

Sponsors are also required to ensure proper monitoring of the research study and for communicating any finding(s) that may impact subject safety to Chesapeake IRB. The Sponsor must promptly notify the IRB of any decision to terminate a Principal Investigator’s participation in a research study that was due to non-compliance with the protocol, regulations, Chesapeake IRB, or impacted subject safety.

Please refer to section 2.2 regarding Chesapeake IRB’s expectation of what should be included in a contract (or other funding agreement) with a Principal Investigator/Site as it relates to subject safety. When the Sponsor is working directly with Chesapeake IRB, the contract should include the responsible party for submitting this information to Chesapeake IRB.

2.1.2. Investigational Test Article(s)
The Sponsor must ensure that the manufacture and formulation of the investigational product, as well as any comparator (if appropriate) conforms to federal regulations. The Sponsor must also ensure the appropriate control (storage, dispensation and accountability) of the investigational product at the site(s) as required by federal, state and local law.

2.2. Principal Investigator Responsibilities
The principal investigator is responsible for personally conducting or supervising the conduct of the research and for protecting the rights, safety, and welfare of subjects enrolled in the research. Therefore, prior to agreeing to participate in a study Principal Investigators should carefully consider protocol and sponsor/CRO requirements. In addition, Principal Investigators should thoroughly review and judge the research design to be sound enough to meet the study’s objectives before agreeing to participate in the study.

Chesapeake IRB expects all investigators participating in research and the sponsors of the research to be familiar with both the spirit and intent of the various ethical guidelines, including The Belmont Report, The Nuremberg Code, and the Declaration of Helsinki, as well as applicable local and federal regulations governing human subjects’ research.

Investigators and sponsors are encouraged to review the ethical guidelines, federal regulations, and various guidance documents available in order to become familiar with the ethical principles as well as compliance responsibilities underlying the involvement of human subjects in research. Please contact Chesapeake IRB with any questions.
The Principal Investigator must ensure that all human subjects research is ethically conducted and in accordance with all applicable federal, state, and local laws and regulations, Chesapeake IRB’s requirements/determinations, and Good Clinical Practice (GCP), as appropriate.

Principal Investigator’s are responsible for negotiating contracts (or other funding agreements), as applicable, with the Sponsor that are designed to contribute to protecting human research subjects participating in sponsored research. The contract should include the following:

a. Who is responsible for providing care and who is responsible to pay for it when a subject has a research-related injury. The terms specified in the contract must be consistent with the information provided in the informed consent form.

b. A well-defined time frame for the Sponsor to provide routine and urgent data and safety monitoring reports. Principal Investigators are subsequently responsible for reporting these to Chesapeake IRB.

c. That the Sponsor will promptly report any findings discovered during a monitoring visit(s), either remotely or in person, that may impact subject safety or influence the conduct of the study. Principal investigators must report these finding to Chesapeake IRB for review.

d. That any findings/new results from a research study discovered by the Sponsor, including after the study has ended, that could affect the safety of participants, affect their willingness to continue participation, or influence the conduct of the study will be promptly communicated to the Principal Investigator. Principal Investigators must subsequently report this information to Chesapeake IRB.

2.3. Institutional Relationships with Chesapeake IRB

Many organizations and institutions, including Hospitals, Academic Medical Centers, HealthCare/Hospital Systems, and Universities have contractual relationships with Chesapeake IRB and have designated Chesapeake IRB as an IRB of Record for some or all of their research studies.

Principal Investigators affiliated with such institutions are responsible for complying with the local policies and by-laws of the institution, including obtaining appropriate departmental approvals, fulfilling training and education requirements, and maintaining open communication regarding protocol requirements within applicable departments. Chesapeake IRB typically has a workflow/agreement with the institution that outlines any institutional-specific requirements; Principal Investigators/study staff should consult with their local Human Research Protections Programs (HRPP) office, applicable research office, or Institutional Official to determine if there are any additional communication procedures or institutional-specific requirements that must be followed and to determine which studies are eligible for review by Chesapeake IRB.

Principal Investigators/research staff must ensure that all institutional requirements and approvals have been obtained prior to commencing any human subjects research that has been approved by Chesapeake IRB.

2.4. Principal Investigator Medical Licensure

Chesapeake IRB ensures that Principal Investigators possess an active medical license, when appropriate, prior to protocol initiation. A copy of the Principal Investigator’s current professional license (i.e. MD, DO) with expiration date or the Principal Investigator’s license number is required at the time of initial submission. Chesapeake IRB will access the applicable state’s Licensing Board to
verify/confirm the Principal Investigator’s medical license is current and no professional, disciplinary, and/or legal actions exist.

Chesapeake IRB requires immediate reporting of any change to the investigator's licensure, including any professional, disciplinary, or legal actions.

2.5. Principal Investigator Training

Principal Investigators are expected to have completed training in the conduct of human subjects research. Such training can include topics such as good clinical practice, federal regulations, and investigator responsibilities. Investigators will be asked to declare their research training during the initial submission process. IRB members will consider the Principal Investigator’s credentials and training to determine if the Principal Investigator is appropriately qualified to conduct the research.

All Principal Investigators and their research staff are expected to maintain the qualifications necessary to conduct and oversee the research through on-going training and experience, including familiarity with the appropriate use of the investigational product(s) as described in the protocol, in the investigator's brochure, in the product information, and in other information sources provided by the Sponsor, as applicable.

2.6. Principal Investigator Delegation of Authority

Chesapeake IRB understands that the Principal Investigator may delegate authority for specific activities during the conduct of research studies, i.e. to sub-investigators and/or research coordinators/nurses. If there are study-related activities that are conducted by an individual other than the Principal Investigator, the Principal Investigator is responsible for the following:

- Delegating research-related tasks to knowledgeable and qualified study staff;
- Ensuring that the research does not commence until Chesapeake IRB has granted final approval;
- Ensuring that the research is conducted in compliance with applicable federal and local regulations, Good Clinical Practices (GCP), and requirements set forth in the protocol and throughout this document;
- Ensuring that subject complaints, questions, and concerns are adequately addressed in a timely manner; and,
- Ensuring that the research does not commence until the IND or IDE is in effect.

For more information on supervising the conduct of a clinical investigation, see:

FDA's Guidance for Industry

Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects (October 2009)

OHRP’s Investigator Responsibilities – FAQs
It is the IRB’s expectation that the Principal Investigator will maintain a list of qualified individuals to whom significant study-related duties have been delegated. Even though specific responsibilities may be delegated, the IRB expects the Principal Investigator to personally supervise the conduct of the research, including submissions to the IRB. The Principal Investigator maintains responsibility for the protection of the rights, safety, and welfare of subjects under his/her care during the research study.

2.7. Conflict of Interest

An investigator conflict of interest (COI) refers to any interest that competes with the investigator’s obligation to protect the rights and welfare of research subjects. One potential source of bias in clinical research is an investigator’s financial interest in the outcome of the study due to payment method (e.g. royalty), or because the investigator has a proprietary interest in the product (e.g. patent), and/or an equity interest in the Sponsor of the covered research study [please refer to 21 CFR 54.1(b)].

Chesapeake IRB requires that a series of questions be answered at the time of initial submission related to financial and non-financial COI relevant to the research protocol. These questions apply to the Principal Investigator, the study staff, and their immediate families inclusive of spouse and each dependent child. The IRB must be notified of any changes to financial and non-financial COI throughout the course of the study.

Conflicting interests that might adversely affect the protection of subjects must be managed. Principal Investigators must also have procedures in place to manage any actual and/or perceived financial or non-financial COI. Examples of an appropriate management plan may include:

- Require a sub-investigator/research staff conduct certain parts of the research, such as the informed consent process.
- Require sub-investigator/research staff to collect and report study data.
- Require sub-investigator/research staff to be involved in recruitment of potential subjects.

If Chesapeake IRB does not find the management plan acceptable, other protections may be imposed/required.

If the Principal Investigator is affiliated with an institution that has an in-house COI Committee, the investigator is required to inform Chesapeake IRB about any determinations, including appropriate management plan, made by the COI Committee as it relates to the research being reviewed by Chesapeake IRB.

2.8. Competing Studies at Research Sites

If a potential subject is eligible for multiple studies conducted at a research site, the Principal Investigator should have a procedure in place to address how the investigator and the subject determine which study is most appropriate for the subject.

A financial interest related to a research study may be a conflicting financial interest and may affect the rights and welfare of human subjects.


Other potential sources of bias in clinical research studies include an array of non-financial interests.
2.9. Investigational Site(s)

Principal Investigators are expected to maintain the appropriate resources and infrastructure to support the conduct of human subjects research, including protecting the rights and welfare of research subjects and integrity of the data at their site(s). Researchers should not commence a research study without adequate resources (e.g., personnel, time, and access to a study population) and should discontinue a research study if resources become available.

Principal Investigators are also responsible for being familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current investigator’s brochure, in the product information, and in other information sources provided by the sponsor. Principal Investigators must ensure the appropriate control (storage, dispensation and accountability) of the investigational product as required by federal, state, and local law. Each site must be in compliance with the Sponsor’s requirement for handling medical emergencies.

If research will be conducted at more than one location, the Principal Investigator must have a process by which s/he provides oversight for the research at each location, including how often s/he visits each location, how communication occurs between the Principal Investigator and research staff, and how often the Principal Investigator communicates with the sub-investigators.

For research studies conducted at an international location, the Principal Investigator should obtain permission to conduct research in the country by certification or local ethics review, when one exists. It is the IRB’s expectation that the Principal Investigator will follow local laws, regulations, customs, and practices. Please contact Chesapeake IRB for additional information on conducting international research.

When following ICH-GCP (E6), investigators/research staff must understand the responsibilities as noted in the sidebar.

2.10. Principal Investigator Study Records

Principal Investigators are expected to:

- ensure that research records are stored at each investigative site in such a way as to protect the confidentiality of subject information;
- maintain accurate and complete study records;
- make those records available for inspection by Chesapeake IRB; and

Good Clinical Practice (GCP) ICH-E6, section 4: Investigator

Investigators should understand their obligations under GCP as they relate to the following:

4.1 Investigator’s Qualifications and Agreements.
4.2 Adequate Resources
4.3 Medical Care of Trial Subjects
4.4 Communication with the IRB/IEC
4.5 Compliance with Protocol
4.6 Investigational Products
4.7 Randomization Procedures and Unblinding
4.8 Informed Consent of Trial Subjects
4.9 Records and Reports
4.10 Progress Reports
4.11 Safety Reporting
4.12 Premature Terminations/Suspension of Trial
4.13 Final Report(s)
• provide Chesapeake IRB with any required information before, during, or after the study.

2.11. Physician Referrals
During and following a subject’s participation in a study, the Principal Investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant medical laboratory values, related to the trial.

2.12. Relevant Findings
When the Principal Investigator is the lead investigator of a multi-site study or the organization is the lead site of a multi-site study, a description of the management of information obtained in the multi-site research that might be relevant to the protection of research participants, such as unanticipated problems, interim results, and protocol modifications, must be submitted to the IRB.

2.13. Sponsor Audits
Sponsors and Principal Investigators must promptly notify Chesapeake IRB about any Sponsor or CRO audit resulting in the Sponsor suspending or terminating the study at the site(s). A summary of the reasons for the suspension (and required corrective action(s)) or termination is also required.

Chesapeake IRB will review the information and take appropriate action (e.g. suspend enrollment, terminate IRB approval, etc), including determining if the corrective action plan is appropriate. Chesapeake IRB will also report any suspension or termination of IRB approval to the appropriate regulatory authority.

2.14. Federal, State, Local, and International Requirements
It is the responsibility of the Principal Investigator/Research Staff and Sponsor to be familiar with and comply with federal, state, local laws, codes and guidance governing their research, in addition to the requirements listed in the Investigator’s Agreement.

Principal Investigators are responsible for communicating any applicable state/local research requirements to Chesapeake IRB at the time of initial submission.

Principal Investigators/Research Staff are responsible for understanding and complying with their local institution’s by-laws, and policies and procedures as they relate to the conduct of research. Principal Investigators/Research Staff are also required to understand and comply with Chesapeake IRB’s and the Institution’s agreement related to which studies can be reviewed by Chesapeake IRB, as well as institutional requirements for submitting to Chesapeake IRB.
3. Using Chesapeake IRB

3.1. Submission Process

3.1.1. Electronic Submission via CIRBI, “Center for IRB Intelligence”
Chesapeake IRB utilizes a custom-designed, web-based electronic platform to facilitate research study submissions, regulatory compliance, and e-processing and tracking of research studies. The e-system is called “Center for IRB Intelligence” (CIRBI) and allows real-time communication among Sponsors, research sites, institutional representatives, and internal staff and IRB members. All parts of the IRB process from initial submission to study close-out/termination are supported by CIRBI.

3.2. Protocol Submission Requirements
Sponsors may submit a research study to Chesapeake IRB for review prior to or in conjunction with identification of the Principal Investigators/sites. This allows the IRB to review and approve the research study and finalize the master informed consent form for use by the Principal Investigators/sites.

A Principal Investigator may also submit a research study directly to Chesapeake IRB for review and approval; the Principal Investigator (or designee) is responsible for submitting all required protocol documentation as well as the information listed below under Principal Investigator and Site Submission Requirements.

Information required for IRB review of a research study is as follows:

- Finalized protocol;
- Product information (i.e. Investigator Brochure, Package Insert, device instructions for use), if applicable;
- Sponsor-approved informed consent form (Chesapeake IRB staff format the sponsor-approved informed consent form into the institutional template, if applicable);
- Federal grant, if applicable; and
- For multicenter research funded by DHHS, the DHHS-approved sample consent document and full DHHS-approved protocol (when they exist).

Please contact the CIRBI Help Desk at 1-866-99CIRBI (1-866-992-4724) with any questions.
3.3. Data Monitoring

The research plan makes adequate provisions for monitoring the data collected to ensure research subject safety (see sidebar); for example, studies that are more than minimal risk must implement a monitoring plan or Data Monitoring Committee (DMC)/Data and Safety Monitoring Board (DSMB) to ensure the safety of research subjects. Any research study greater than minimal risk requires an appropriate plan for monitoring the data collected to protect the safety and welfare of the research subjects. Sponsors and investigators should consider the size, complexity, phase, and level of risk involved in the research when determining whether a monitoring plan or formal DMC/DSMB is appropriate. In addition, sponsors and investigators should understand that monitoring might occur at specific points in time, after a specific number of participants have been recruited, or upon recognition of unexpected harms.

A formal DMC/DSMB should be considered for research involving intervention that entails potential serious risk to subjects, compares blinded treatments over a long time period, or which may call for "stopping rules" for certain endpoints to further protect the safety or welfare of subjects. If a DMC/DSMB has been established and the plan is not clearly delineated in the protocol or submission form, a detailed description of the DMC/DSMB’s operation (e.g. membership, function, frequency of review, stopping rules) may be requested.

Any recommendations made by a DMC/DSMB that address the safety of subjects and potentially their willingness to continue in the study must be submitted to the IRB. In addition, results from any study that could directly affect subject safety or the subject’s medical care must be submitted.

While all more than minimal risk studies must include some form of safety monitoring, not all require monitoring by a formal committee that is external to the Principal Investigator and Sponsor. The size, complexity, phase, and level of risk involved in the research should be considered when assessing the need for or appropriateness of a monitoring plan or DMC/DSMB. If a DMC/DSMB has been established and the plan is not clearly delineated in the protocol or submission form, a detailed description of the DMC/DSMB’s operation (e.g. membership, function, frequency of review, stopping rules) may be requested.

As part of their obligation to protect subjects, Chesapeake IRB expects Sponsors and Investigators understand the concept of minimizing risks. Sponsors and Investigators should design research that incorporates a plan to monitor data for the safety of subjects. Chesapeake IRB considers the following provisions for monitoring data to ensure subject safety during the review of research (as applicable):

- The type of safety information that will be collected, including SAEs.
- The method for collecting safety information (e.g. study visits, case report forms, etc.)
- The frequency of data collection.
- The frequency of review of cumulative safety data.
- The composition of a data monitoring committee and a plan for reporting the data monitoring committee’s findings to the IRB, including the frequency of reporting.
- Additional protections for monitoring the data for studies that are blinded, have multiple sites, enroll vulnerable populations, or employ high-risk interventions.
- When a data monitoring committee is not used, and if applicable, statistical tests employed for analyzing the safety data to determine whether harm is occurring.
- Provisions for the oversight of safety data.
3.4. Principal Investigator and Site Submission Requirements

Each Principal Investigator is required to submit investigator and site information to Chesapeake IRB for review. This information must include the details of the informed consent process, plans for subject recruitment, and information about the location(s) where the research is conducted. The following documents are also required during the submission process, as applicable:

- Current (within 2 years) signed and dated Curriculum Vitae of the Principal Investigator, demonstrating appropriate experience and knowledge to conduct the research.
- Regulatory Agency(ies) Audits of the site and/or Principal Investigator from the last five years. The submission should include the response to the regulatory agency audit that addresses the findings (if applicable).
- Additional text for the informed consent form may be submitted for multi-site studies for which Chesapeake IRB is the Central IRB. The Principal Investigator and site have the option to request modifications to the IRB-approved informed consent form to address site specific needs, including compensation for study participation details.
- Standard operating procedures may be included when the questions from the Principal Investigator and site submission do not accurately address the processes at the site, including the informed consent process.
- Waiver of IRB Oversight must be submitted when the Principal Investigator is at an institution that has an IRB, but the IRB waives study oversight authority to Chesapeake IRB. If a waiver, Master Service Agreement, or Institutional Authorization Agreement is already in place with Chesapeake IRB that covers all studies, a waiver for each protocol is not required.
- Recruitment material, including any advertising for study subjects, is considered to be the start of the informed consent process. Recruitment material and any changes to the content or presentation of approved recruitment material must be reviewed and approved by the IRB prior to use.

3.5. Informed Consent Form and Assent

The draft informed consent form must be submitted in a Microsoft Word compatible format.

Research studies which include subjects who are minors require the submission of an assent statement and/or an assent form for review. Chesapeake IRB requires the use of an assent statement (which is a separate signature block) for subjects who are minors, but who are old enough to understand the informed consent form as written (approximately age 14 through 17). An assent form is required when subjects (typically between the ages of 7 and 13) need information presented to them in age appropriate language. For most studies, subjects 6 years old or younger are not required to sign an assent statement or assent form.

Chesapeake IRB may determine assent is not necessary if the capability of some or all of the children is so limited that they cannot reasonably be consulted, or the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research study.

3.6. Transfer Studies or Studies Disapproved by another IRB

For studies that were previously reviewed and/or overseen by another IRB, Chesapeake IRB requires documentation regarding the status of the study and rationale for submission to Chesapeake IRB.
If the study was disapproved by another IRB, the submission must include the reasons for the disapproval.

3.7. Submission of 1572s
Chesapeake IRB does not require 1572s be submitted at initial review or when revisions to the 1572 are made.

4. IRB Review

4.1. IRB Review Process
Upon receipt, Chesapeake IRB staff members assess whether the protocol will be reviewed at a convened meeting or whether it can be reviewed via another regulatory pathway (i.e. expedited, exempt). Once Chesapeake IRB staff members make this assessment, they perform an administrative review, obtain any clarifications necessary for IRB review, and the protocol is then scheduled for IRB review, as appropriate.

The possible outcomes of the IRB review include:

- Approval;
- Approval with Modifications;
- Deferral; and
- Disapproval.

Chesapeake IRB may take an action to approve or approve with modification(s) a research study submitted for review. Once a research study is approved with modification(s), it is considered approved and can be conducted in accordance with the changes referenced in the approval with modifications letter and any revised documentation. The IRB-instituted modifications are either delineated in the letter, included in tracked changes documentation, or both. Once an approval with modifications letter has been issued, no further response is required unless the instituted modifications are being appealed.

Chesapeake IRB may defer taking an action when there is additional information or clarification(s) needed. Once the required information or clarifications are received by the IRB, the proposed research study is scheduled for re-review by the IRB.

If the protocol has been disapproved, a disapproval letter is sent to the submitting party in CIRBI outlining the reason(s) for disapproval and an appeal process. The appeal process includes the following:

1. Resubmit the project with the modification(s) that address the IRB’s findings and criticism(s);
2. Provide a written justification for relief of any IRB imposed condition or disapproval; or
3. Request a hearing.

The IRB then decides whether or not to reconsider the research study during a convened meeting and notifies the appropriate parties of its final determination.

IRB Review Outcomes:

- Approve— the proposed research or research activity is approved as submitted.
- Approved with Modifications — the proposed research is approved with the restrictions and/or changes required by the IRB.
- Deferral — the proposed research does not include enough information to determine if the
4.2. Expedited Review

Federal regulations allow for some research activities to be reviewed via expedited review procedures. Chesapeake IRB staff and Chesapeake IRB members follow the federal regulations for expedited review (21 CFR 56.110 and 45 CFR 46.110) and the Categories of Research That May Be Reviewed by the IRB via Expedited Review (Federal Register), as applicable. If submitted research is not approvable under expedited review, it is brought before the IRB during a convened meeting.

4.3. Exempt Research

Some federally funded and FDA-regulated research may be exempt from IRB review and oversight (45 CFR 46.101[b]; 21 CFR 56.104). In determining whether the proposed research meets the criteria for exemption, Chesapeake IRB also determines whether or not the proposed research is ethically sound and that adequate provisions are made for the protection of the research subjects, including:

- The research involves no more than minimal risk to subjects.
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of data.
- If there are interactions with participants, there is a consent process that discloses appropriate information.
- There are adequate provisions to maintain the privacy interest of participants.
- Subjects are equitably selected to participate in the research.

If Chesapeake IRB determines that a research protocol is exempt from the applicable regulations, this determination is communicated to the Principal Investigator via a determination letter in CIRBI. The letter includes instructions to submit any future modifications to the research to the IRB for review to ensure that the activities continue to qualify as exempt.

Chesapeake IRB expects that Principal Investigators will conduct exempt research following the ethical principals outlined in the Belmont Report, the Nuremberg Code, and the Declaration of Helsinki, and that they will ensure that subjects are appropriately protected during the research.

Research determined to be exempt from IRB oversight does not require continuing review.

4.4. FDA Regulated Research

A Sponsor is responsible for determining whether or not an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application is required for the proposed research. Chesapeake IRB requires that IND/IDE information be submitted at the time of initial review. If the Sponsor indicates that an IND is not required, the IRB may request additional supporting documentation (e.g., letter from the sponsor or FDA, other basis for that determination) be provided for review. If the IRB is questioning whether an IND or IDE is required, and is unable to resolve this issue, the IRB may delay approving the study pending additional information/documentation.

For studies that require an investigational new drug (IND) or investigational device exemption (IDE) application, it is Chesapeake IRB’s expectation that study activities will not begin, including advertising, recruitment, and screening, until after the end of the 30-day FDA review period or after receiving notification from FDA.

Any FDA required changes, based on the IND or IDE submission, should be submitted to Chesapeake IRB for review and approval prior to implementation.
4.5. Federally Funded Research

4.5.1. Federal Wide Assurance

Every institution engaged in non-exempt human subjects research, supported or conducted by the Department of Health and Human Services (DHHS), must obtain an assurance of compliance approved by the Office for Human Research Protections (OHRP). The assurance formalizes the institution’s commitment to comply with the requirements set forth in the regulations for the protection of human subjects at 45 CFR Part 46.

The arrangement between the FWA-holding institution and Chesapeake IRB must be documented in writing. Chesapeake IRB has an IRB Authorization Agreement that must be signed by both parties.

If the organization/submitting party is the direct recipient of federal funds, the grant must be uploaded into CIRBI. The grant is reviewed by the IRB to ensure that the research being conducted matches the research detailed in the grant submission. Please note that only the section of the grant outlining the research must be submitted; other sections, such as the bio-sketches and cost allocation summary, do not require submission.

Protocol submissions funded by DOD are subject to additional regulatory requirements under 32 CFR 219 (and Instruction 3216.02) and thus require additional consideration by the IRB as noted below. In certain circumstances, it is appropriate for a statement of work or standard operating procedure to be submitted in lieu of the grant submission for DOD funded research.

Institutions conducting the DoD-supported research (including DON-supported research) for which CIRB serves as the IRB of record are responsible for:

- Implementing an initial and continuing education/training policy for human subjects research and should determine that the PI and research team have met internal requirements.

- Promptly reporting to the DoD human research protection officer significant changes to the research protocol approved by Chesapeake IRB, results of continuing review, determinations of serious or continuing non-compliance, incidences/events determined to be unanticipated problems, and any other DoD reporting requirements. This reporting should occur within 30 days, or sooner as negotiated between DoD and the institution.

- Ensuring the investigator has permission to conduct research in that country by certification, or local ethics review.

- Ensuring the investigator follows all local laws, regulations, customs, and practices.

To determine if you are engaged in human subjects research (and need an FWA), refer to OHRP’s Guidance at:

incidences/events determined to be unanticipated problems, and any other DoD reporting requirements. This reporting should occur within 30 days, or sooner as negotiated between DoD and the institution.

- Ensuring the investigator has permission to conduct research in that country by certification, or local ethics review.
- Ensuring the investigator follows all local laws, regulations, customs, and practices.

### 4.6. Unplanned Emergency Use of a Test Article

The FDA regulations define emergency use as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval. In the event of the emergency use of a test article when there is no time to obtain IRB approval, please follow the FDA regulations found in 21 CFR 56.104(c). The use should be reported to the IRB within 5 working days. Please consult staff for additional instructions and guidance regarding any subsequent use of the test article.

In the event that an unexpected life-threatening emergency requires the use of a test article when informed consent cannot be obtained, please follow the FDA regulations found in 21 CFR 50.23. Both the investigator and an independent physician should certify in writing all of the following:

- The human subject is confronted by a life-threatening situation necessitating the use of the test article;
- Informed consent cannot be obtained from the subject;
- There is insufficient time to obtain consent from a legally authorized representative; and
- No alternative method is available that provides an equal or greater likelihood of saving the life of the subject.

If time is not sufficient beforehand, please obtain the determination of an independent physician after the fact.

Under FDA regulations, the emergency use of a test article other than a medical device, is a clinical investigation, the patient is a subject, and the FDA may require data from an emergency use be reported in a marketing application.

If your organization follows DHHS requirements (under the institution’s FWA) or the research study is also subject to DHHS regulations due to federal funding, patients receiving emergency use of a test article as defined by FDA regulations may not be considered to be a research subject. DHHS regulations do not permit the use of data obtained from patients to be classified as human subjects research, nor permit the outcome of such care to be included in any report of a research activity subject to DHHS regulations.

Please note that any anticipated subsequent use of the test article is subject to Chesapeake IRB review and approval.
5. Subject Recruitment

Subject Recruitment is considered the start of the informed consent process. As such, Chesapeake IRB requires prospective review of all recruitment materials that are intended to be seen or heard by prospective subjects to solicit their participation in a research study.

Investigators are responsible for understanding the importance of equitably recruiting and selecting research subjects (subject selection should be representative of the group that will benefit from the research), as well as implementing appropriate recruitment techniques.

5.1. Recruitment Materials

Recruitment material must be consistent with the IRB-Approved protocol and informed consent form. In addition to following the requirements outlined in this document, Chesapeake IRB requires that recruitment material follow the FDA Information Sheets section on recruiting study subjects (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm).

Recruitment material and any modifications made to the content or presentation of approved recruitment material must be approved by Chesapeake IRB prior to its use. While the IRB reviews scripts for audio and video recruitment materials, the final audio and/or video version must be submitted to Chesapeake IRB.

Examples of the types of recruitment material requiring IRB review include:

- Newspaper Advertisements
- Radio Advertisements
- Posters
- Television Advertisements
- Internet Advertisements
- Telephone Screen Scripts
- Recruitment Letters
- Flyers
- Bulletin Boards or Billboards

Please note that clinical trial listings, such as those seen on clinicaltrials.gov, are not considered to be recruitment materials by Chesapeake IRB.

Recruitment material should be limited to the information a prospective subject needs to determine their eligibility and interest in the research such as:

- The name and address of the Principal Investigator and/or research site.
- The condition under study and/or the purpose of the research.
- The criteria that is used to determine a subject’s eligibility for the study in summary.
- A brief list of study participation benefits, if any, and the risks for participating in a research study (a description of any benefits of the study must be balanced with the risks of the study).
- The amount of time or other commitment required of the subjects in the study.
- The location of the research site and the name of the person or office a potential subject can call to obtain additional information.

Chesapeake IRB requires that recruitment material must:
• Be clear that information concerns a research study.
• Be clear about what is investigational.
• Be clear in the procedures that are ‘study-related.”

Chesapeake IRB requires that recruitment material must NOT:

• Be unduly coercive or promise/imply a certainty of cure, favorable outcome or other benefit beyond what is contained in the IRB-approved protocol and informed consent form.
• Make any claim, explicitly or implicitly, that the test article is safe or effective for the purpose being studied, or that the test article is equivalent or superior to any other test article (drug, biologic or device).
• Use the word “new” without being clear as to what is the test article.
• Promise “free medical treatment” when the intent is only to say that subjects are not charged for participating in the study.
• Use exculpatory language.

Recruitment material may state that subjects are paid, if applicable, but should not emphasize the payment or the amount to be paid by such means as larger or bold type. Any mention of subject compensation must be balanced by a description of subject responsibilities during the study (for example, how many study visits is part of participation).

Print advertisements must be submitted in final format (free of typographical, grammatical and spelling errors) and include any graphics that are used.

Radio and television scripts should be reviewed and approved prior to taping in order to avoid re-taping, if modifications are required. Radio scripts being utilized for live broadcast use must be read exactly as approved by the IRB. Audio/visual recruitment materials should be submitted in final format after written script approval is received.

Press Releases require IRB review if they mention a specific study and will be seen by potential subjects. They are then considered recruitment material and their content would be guided by the same regulations as other recruitment.

5.2. Recruitment Material Translations

Chesapeake IRB uses a third party vendor to translate recruitment materials for the Sponsor and/or the site. Once the materials are translated, Chesapeake IRB provides the translated document(s) and the Affidavit of Accuracy to the client. If the Sponsor chooses to translate the materials, the translated document(s) and the Affidavit of Accuracy should be submitted to Chesapeake IRB for acknowledgement.

5.3. Finder’s Fees

Chesapeake IRB does not approve of “finder’s fees” or payments made to the Principal Investigator or research staff as incentives/bonuses that may be considered to be “unethical” and unduly influencing. Incentives/bonuses paid to research staff for recruitment and retention for such purposes may represent a potential conflict of interest for both parties; payment should only be made for specific study-related work performed by the site as outlined in the research protocol.

In addition, Chesapeake IRB does not approve of “finder’s fees” or payments to subjects in exchange for referrals of potential subjects unless they are judged not to increase the possibility of coercion or undue
influence on subjects by using unreasonable compensation or unreasonable conditions for distribution of compensation.

If such a program is being considered, notification and a description of the program must be submitted to Chesapeake IRB prior to implementation. Upon notification, Chesapeake IRB will assess whether the program directly impacts the subject’s rights or welfare.

6. Informed Consent

6.1. Informed Consent Process

Informed consent is an ongoing, continuous process that encompasses presenting the informed consent form clearly and carefully as well as assessing subject consent through the study. Presenting the informed consent form clearly and carefully includes giving the subject ample opportunity to ask questions and the ability to take the informed consent form home to review, as necessary and appropriate. A copy of the informed consent form should always be given to subjects after they have signed and dated the document.

Principal Investigators are responsible for delegating the process of obtaining informed consent to appropriately trained research staff, as appropriate. Research staff obtaining informed consent must understand the research, be able to answer questions the potential subject might have, and be experienced in conducting the informed consent process.

Principal Investigators and research staff should assess subject consent throughout the study and be responsive to participants’ complaints, concerns, and/or questions.

To comply with conditions of IRB approval, the following procedures must be followed:

- The Principal Investigator does not involve an individual in the research study unless the Principal Investigator or designated staff has obtained the legally effective informed consent of the subject (or the Legally Authorized Representative [LAR]).
- Subjects are provided sufficient opportunity to consider whether or not to participate in the research.
- The consent process minimizes the possibility of coercion or undue influence.
- The consent discussion is in a language understandable to the subject or LAR.
- The consent discussion is free of any exculpatory language.
- The most recent IRB-approved version of the informed consent form is used.
- The subject is given adequate time and place to read and review the informed consent form.
- The subject is given the opportunity to take the informed consent form home for review prior to signing the document, as appropriate.
- The consent discussion provides ample opportunity for the Principal Investigator or designated research staff to be available to answer any questions the subject or LAR may have.
- Each person on the IRB-approved informed consent form signs and dates the form on the same visit, as appropriate.
- Subject receives a signed and dated copy of the informed consent form.
- Research-only procedures are performed after obtaining consent.
6.2. Subject Withdraw from a Research Study

After providing consent, a subject may decide to prematurely terminate his/her participation in a research study. Although a subject is not obliged to give his or her reasons for withdrawing prematurely from a research study, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the subject’s rights.

According to FDA, when a subject withdraws from a research study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. If a subject withdraws from a study, removal of data that were already collected may undermine the scientific, and therefore, the ethical, integrity of the research. The informed consent document cannot give the subject the option of having data removed.

Chesapeake IRB recommends that Principal Investigators explain to the subject who wishes to withdraw participation in a research study the importance of obtaining follow-up safety data about the subject, especially in clinical trials evaluating safety and effectiveness of an intervention, and subsequently ask a subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial that the subject initially consented to, such as: (1) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging); or (2) obtaining identifiable private information from the subject’s medical, educational, or from the subject’s healthcare providers may continue.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information, the investigator must obtain the subject’s informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject’s medical record or other confidential records requiring the subject’s consent. However, an investigator may review study data related to the subject collected prior to the subject’s withdrawal from the study, and may consult public records, such as those establishing survival status.

7. Informed Consent Forms

Chesapeake IRB reviews the submitted informed consent form(s) to ensure that the information is accurate, complete, and that all elements of consent outlined in the applicable U.S. Federal Regulations are present.

The Principal Investigator, together with the Sponsor and the IRB, is responsible for review of the IRB-approved informed consent form to ensure that the information conveyed to the subject is accurate. The Principal Investigator may request site-specific changes to the IRB-approved informed consent form by submitting a modification request in CIRBI.

7.1. Health Insurance Portability and Accountability Act (HIPAA)

Chesapeake IRB is not a Privacy Board but will review HIPAA authorization language when it is included in or appended to the informed consent form. If HIPAA authorization is not included in or appended to
the informed consent form, it is the Principal Investigator’s/site’s responsibility to comply with all HIPAA requirements.

7.2. Use of the Short Form
A short form written consent document may be used under certain circumstances (i.e. for non-English speaking subjects). For use of the short form, the requirements are as follows:

- A written summary embodying the basic and appropriate additional elements of consent must be submitted to and approved by the IRB.
- The short form must state that the elements of informed consent required by the regulations (21 CFR 50.27(b)(2) and 45 CFR 46.117(b)(2)) have been presented orally to the subject or the subject’s legally authorized representative.
- There must be a witness to the oral presentation.
- For subjects who do not speak English, the witness will be fluent in English and the language of the subject.
- The subject or the subject’s LAR must sign and date the informed consent form.
- The witness must sign and date both the short form and a copy of the written summary.
- The person obtaining consent must sign and date a copy of the written summary.
- A copy of the short form and written summary must be given to the subject or the subject’s legally authorized representative.

Please contact Chesapeake IRB for additional information or assistance with short forms.

7.3. Observing Informed Consent
Chesapeake IRB has the authority to observe or have a third party observe the consent process and the research. Chesapeake IRB also has the right to conduct site visits and to designate an authorized third party or third parties to observe the informed consent process or the research, if concerns about subject safety arise or when other issues of non-compliance warrant such action. Chesapeake IRB reserves the right to review study records and the written operating procedures at the site to assure the integrity of the records and protection of the rights and welfare of the study subjects.

The IRB may determine that submission of a copy of a subject’s signed informed consent form is required in order to verify that the site is using the correct version of the document. If this determination is made, Chesapeake IRB notifies the investigator and the investigator is then responsible for submitting a complete copy of the subject’s signed informed consent form to the IRB.

7.4. Subject Payments
Payment to research subjects for participation in a research study is not considered a benefit; rather it is considered to be compensation for a subject’s time and expenses. Chesapeake IRB must review the amount, scheduling of, proposed method, and timing of payment disbursement to assure that it is not coercive or presents undue influence.

The Principal Investigator is required to inform the IRB of any plans to pay subjects for participation in a research study in the initial submission and when payment is modified. The IRB will not review the Principal Investigator/site for approval until the payment amount and timing of disbursement of subject payment is submitted.
If a Principal Investigator plans to provide subject payment, subjects should be paid in a timely manner at the end of their participation in the research study. Payment to subjects must not be contingent upon the site’s receipt of payment from the sponsor.

Compensation must be pro-rated if a subject’s participation ends early to assure that each participant receives fair compensation for participation and is not unduly influenced to complete participation.

While the entire subject payment should not be contingent upon completion of the study, payment of a small proportion at the end of the study as an incentive for completion may be considered acceptable if it is determined to be reasonable and not so large as to unduly influence a subject to stay in the study when they would otherwise have withdrawn. Compensation to subjects may not include a sponsor coupon good for a discount on the purchase price of the product once it has been approved for marketing.

If the research includes subjects that are minors, the appropriateness of any proposed payments to the parent(s) or guardian(s) and to the minor is also reviewed by the IRB.

7.5. Compensation for Research Related Injury
Sponsors and Principal Investigator(s) must ensure the following:

- The description of any compensation or medical treatment that will be provided to a subject or legally authorized representative for a research-related injury does not conflict with any information contained in the Clinical Trials Agreement between the Sponsor and the Principal Investigator(s) or the Principal Investigator’s Institution.
- Subjects or legally authorized representatives should be provided an explanation regarding the extent to which they will be responsible for any costs for medical treatment required as a result of research-related injury.
- The subjects or legally authorized representatives should understand who will bear financial responsibility for various aspects of the study.
- If research-related injury, i.e. physical, psychological, social, financial, or otherwise, is possible in research that is more than minimal risk, an explanation must be given as to whatever voluntary compensation and treatment will be provided.
- Detailed information about the provisions of any compensation for subject injury must be submitted in CIRBI and confirmed in the final IRB approved informed consent form(s) by the Sponsor and the Principal Investigator(s) before the research starts.

7.6. Informed Consent Translations
The informed consent form provided to the subject or legally authorized representative should be written in the language spoken by the potential study subject or legally authorized representative.

If non-English speaking subjects will be enrolled on the study, a certified translation of the IRB-approved informed consent form must be used. If a Principal Investigator(s) plans to enroll non-English speaking subjects, the Principal Investigator(s) must contact the IRB prior to non-English speaking subject enrollment to obtain a certified translation of the IRB-approved informed consent form.

Chesapeake IRB is able to provide translation services, along with an Affidavit of Accuracy/Translation Certificate, upon request. If a Sponsor chooses to use another vendor for the translation, a copy of the
7.7. Informed Consent for Potentially Vulnerable Subjects

For studies enrolling potentially vulnerable subjects, the following additional procedures must be followed, as appropriate:

Vulnerable subjects may not be targeted for enrollment into a study unless specifically allowed by the protocol. If the Principal Investigator plans to enroll potentially vulnerable subjects, there must be additional procedures/protections in place to protect the rights and welfare of these subjects. Some additional safeguards that may be taken into consideration include:

- An altered informed consent process (e.g. consideration for where the consent process takes place, the persons involved in the consent process, and/or additional information that should be provided to these subjects).
- The need for an LAR or surrogate to provide consent on behalf of a vulnerable subject.
- Study design changes or considerations that would minimize risk for the vulnerable subjects (e.g. removal of identifiers when such subject information is not essential to the research).
- The need for referral assistance for vulnerable subjects (e.g. psychiatric consult/care).

Subjects who may need extra time to decide whether to participate in the study (i.e. seriously/terminally ill or elderly subjects) must be given ample opportunity to involve family member(s) or significant other(s) during the informed consent process.

Information about the recruitment of potentially vulnerable subjects and the procedures used to protect their rights and welfare must be reviewed and approved by Chesapeake IRB before these potential subjects are recruited for the study.

7.8. Informed Consent for Minors

In research studies involving minors, the IRB determines whether assent of the child is required and if so, how assent should be documented. The assent requirements and the number of parents that must provide permission are communicated in the IRB approval letter.

The minor and the parent(s) or guardian(s) must be given adequate time and an adequate place to read and review the IRB-approved Informed Consent and Assent Form. The study must be explained to the minor in a language that the minor can understand. The minor must be given an opportunity to ask questions about the study (without the presence of the parent or guardian, if requested and appropriate). Depending on the age of the minor, the minor should be asked to sign the assent section of the ICF, as required by the IRB.

7.9. Informed Consent for Legally Authorized Representative (LAR) or Guardian

An LAR may be required to provide consent in a study where the subject does not have the legal capacity to consent to their participation in the study. Special care is needed when the LAR is reading the ICF because the LAR is giving permission for someone else to participate in a research study.

If an LAR is utilized to provide consent on behalf of a subject, sites must have a written procedure to identify and document who meets the criteria under state and local law to serve as an LAR.
When research is subject to DHHS regulations at 45 CFR 46 Subpart B, and involves non-viable neonates, the consent of an LAR of either or both of the parents is not permitted.

For DoD funded research, if consent is to be obtained from the “experimental” subjects’ LAR, the research must intend to benefit the individual participant.

7.10. Informed Consent for Non-Reading Subjects

If subjects who are unable to read are allowed by the protocol and approved by Chesapeake IRB, an impartial (not part of the research team) witness must be present during the entire informed consent discussion. Once the ICF is read and explained to the subject and the subject has orally consented to participate in the research study, as well signed and dated the ICF, if capable of doing so, the witness should also sign and date the form.

Chesapeake IRB incorporates an additional signature block for the witness into the Chesapeake IRB-approved ICF, if applicable.

7.11. Informed Consent for Non-English Speaking Subjects

The informed consent form provided to the subject must be written in the language spoken by the potential subject.

If non-English speaking subjects are recruited, a certified translation of the IRB-approved ICF is required. If Principal Investigators plan to enroll non-English speaking subjects, they must contact Chesapeake IRB prior to enrollment to obtain an IRB-approved certified translation.

An individual fluent in the language spoken by the potential study subject must be available during the informed consent process. If a Principal Investigator expects to enroll non-English speaking subjects, provisions should be made to accurately communicate study-related information during all subject interactions in a language the subject can understand.

7.12. Informed Consent for Potentially Decisionally-Impaired Subjects

Principal Investigators are required to provide a detailed plan when recruiting subjects with psychiatric, developmental, cognitive, environmental, or health conditions that may interfere with the subject’s ability to understand and make rational decisions about involvement in a research study.

The Principal Investigator or equally qualified designee must assess a potential subject’s competency to provide consent for the research. Subjects found to be incompetent to provide consent, or whose competency is in doubt, may not be enrolled into the research study unless the protocol allows for a legally authorized representative (LAR) and that representative is available during the informed consent process. The LAR must provide consent prior to subject participation in the research.

7.13. Waiver(s) of Informed Consent and/or HIPAA

Under certain circumstances, it may be appropriate to waive some or all of the elements of informed consent and/or HIPAA. Questions relevant to these determinations are completed at the time of initial submission to Chesapeake IRB.
8. Research with Vulnerable Populations

8.1. Research with Minors
Children are defined as persons who have not attained the legal age for consent to treatment or procedures involved in research, as determined under the applicable law of the jurisdiction in which the research is conducted. If children are recruited for a study, sites must be knowledgeable about the age of majority as defined by state and local law and have a process to determine who meets the definition of a child in the respective state. If a site permits a guardian (an individual who is not a parent but who is authorized under applicable state and local law) to consent on behalf of a child to a research study, the site must have a process to determine who meets the definition of a guardian in accordance with applicable state and local law and a process to document the legal relationship of the guardian to the child.

When research involving children is covered by FDA or DHHS regulations, Chesapeake IRB must make a pediatric risk assessment and only approve research that satisfies the regulatory criteria for research involving children. The IRB also determines whether assent of the child is required. If the IRB determines the assent of the child is necessary, the IRB also decides how assent should be documented.

The regulations provide criteria for research with children that the IRB considers during review of the research. The IRB documents the regulatory category for the research and communicates this determination in the IRB approval letter. The risk categories for pediatric research projects are defined as the following:

- 45 CFR 46.404/21 CFR 50.51: Not involving greater than minimal risk. Chesapeake IRB determines if permission of one or both parents is required.
- 45 CFR 46.405/21 CFR 50.52: Involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. Chesapeake IRB determines if permission of one or both parents is required.
- 45 CFR 46.406/21 CFR 50.53: Involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects’ disorder or condition. Permission of both parents is required. If wards are to be enrolled, an advocate must be appointed for each ward.
- 45 CFR 46.407/21 CFR 50.54: Not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Specific approval is required from the FDA Commissioner or DHHS Secretary. Research involving children that is not approvable under the published regulatory criteria is referred to the appropriate agency (FDA, DHHS) for additional consideration by an expert panel convened by the agency. Research assigned this category may not proceed until the appropriate regulatory agency has made a determination.

8.2. Permission by Parents or Guardians and Assent by Children
Assent is defined as a child’s affirmative agreement to participate in research/clinical investigation. Adequate provisions must be made for soliciting the assent of the children when, in the judgment of the IRB, the children are capable of providing assent. When the IRB determines that assent is required, it must also determine whether and how assent must be documented. Principal Investigators are provided an IRB-approved Assent form, as applicable.
When making a determination about requirements for consent from the parents or guardians of the children, the IRB considers the applicable regulations. A parent is defined as a child’s biological or adoptive parent. A guardian is defined as an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care, including participation in research.

Chesapeake IRB determines if permission of one or both parents is required for research projects. For research approved under categories 46.404/50.51 or 46.405/50.52, one parent may be sufficient to provide consent. When research studies are approved under categories 46.406/50.53 or 46.407/50.54, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child, if consistent with State law.

### 8.3. Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in clinical investigations approved under categories 46.404/21 CFR 50.51 and 46.405/21 CFR 50.52. For clinical investigations approved under categories 46.406/50.53 and 46.407/50.54, wards of the state may only be included if such clinical investigations are:

- Related to their status as wards; or
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.
- Chesapeake IRB requires appointment of an advocate for each child who is a ward of the state for any research approved under these two categories. The requirements for advocates include:
  - The advocate serves in addition to any other individual acting on behalf of the child as guardian or in loco parentis.
  - The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.
  - The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the Sponsor organization.

One individual may serve as an advocate for more than one child.

The protocol submission must indicate if wards of the state may be enrolled into the study.

### 8.4. Research with Prisoners

Chesapeake IRB is constituted to review research involving prisoners. All biomedical and behavioral research that is designed to enroll prisoners (or subjects who are likely to become prisoners) that is conducted or supported by DHHS is subject to and reviewed in accordance with the regulations found at 45 CFR 46, subpart C.

For studies that are not designed to enroll subjects who are prisoners or who are likely to become prisoners, Chesapeake IRB must be notified immediately if a subject participating in a research study at a site overseen by Chesapeake IRB becomes incarcerated. When notified of an incarceration, Chesapeake IRB assesses the type of research and advises the Principal Investigator as to whether IRB review under 45 CFR 46, subpart C is required.
8.5. Research with Pregnant Women, Human Fetuses and Neonates

Chesapeake IRB recognizes that special protections for research involving pregnant women, human fetuses and neonates apply to research conducted or supported by DHHS or conducted at an institution with an FWA under which it has voluntarily agree to apply Subpart B of 45 CFR 46 to all research, regardless of the source of support.

For DHHS funded studies, pregnant women and fetuses or neonates may be involved in research if the IRB finds and documents that all of the conditions found in 45 CFR 46.204 or 45 CFR 46.205, respectively, have been met.

Sponsors and investigators should understand the requirements and unique concerns when designing and conducting research studies using this vulnerable population, regardless of the source of funding. Sponsors and investigators are encouraged to contact Chesapeake IRB for assistance or questions regarding research studies using pregnant women, human fetuses and neonates.

9. Conducting IRB Approved Research: Changes in Research Activity

9.1. Modifications/Amendments

Changes in research activities must be submitted to the IRB for review and approval prior to implementation, except when necessary to eliminate immediate hazards to subjects. If changes are made to eliminate immediate hazards, the IRB must be promptly notified (refer to section: Unanticipated Problems). All changes in research activity must contain adequate information for IRB review.

Changes in research activity include but are not limited to amendments and modifications to the protocol, informed consent, Investigator’s Brochure, and other study documentation; changes at the investigational site; new information regarding the study therapy(ies); or changes in study status (including any change in the regulatory approval status of the test article, any FDA Clinical Hold, and any study hold/suspension or termination imposed by the Sponsor/CRO, Principal Investigator, other reviewing IRB, other government agency, or other party).

When submitting amendments/modifications to any study-related document that requires IRB review, a summary of changes and/or a rationale and a tracked change version of the document should also be included to facilitate a timely review. When ICF changes are requested, those changes must be made and tracked in the most current Chesapeake IRB-approved version of the ICF.

9.2. Clinical Holds and Suspensions or Terminations

Any IRB notification of FDA Clinical Hold or other study hold/suspension or termination imposed by the Sponsor/CRO, Principal Investigator, other reviewing IRB, other government agency, or other party, must include a summary of the reason(s) for the hold/suspension/termination and provide the IRB with adequate information to assess the impact to the study subjects.

The IRB must be notified when an FDA Clinical Hold, or any other study hold/suspension, is lifted. IRB notification should include a summary of how the issue(s) was resolved and any modifications made to study documents as a result of issue resolution, as applicable (e.g. protocol amendment).
9.3. Change of Principal Investigator/Site(s) Status

Chesapeake IRB must be notified prior to replacing the current IRB approved Principal Investigator at a site. The new Principal Investigator’s CV and the reason for changing Principal Investigators must be included with the submission.

The Principal Investigator must promptly report any pending or on-going legal, regulatory or professional actions or restrictions related to the practice of medicine or research at the site(s) (including Principal Investigator, Sub-investigators, and site personnel). This information is required at the time of initial submission and post-approval, as applicable.

In the event the sponsor becomes aware (e.g. during a monitoring visit) of any unanticipated problems, evidence of serious or continuing non-compliance, scientific misconduct, influence the conduct of the study, or any other event that may impact subject safety, or alter the IRB’s approval or sponsor’s/sponsor’s representative’s status of the Principal Investigator/site, Chesapeake IRB should be promptly notified.

9.4. Prompt Reporting Events (including Serious Adverse Events, Unanticipated Problems, Protocol Deviations, Violations, or Exceptions, and Non-Compliance)

9.4.1. Serious Adverse Events (SAEs)

Principal Investigators are required to submit any serious adverse events involving subjects enrolled at the site(s) that are determined to be UNEXPECTED and probably, possibly, or definitely RELATED to the test article or research procedures. This notification to Chesapeake IRB must occur promptly and no later than 2 weeks (10 business days) from the time the Principal Investigator learns of the event. [Note: SAEs that have been determined to be unrelated to the test article should not be submitted to Chesapeake IRB. In addition, for those SAEs where relatedness has not yet been determined (i.e. further analysis is required), submission to Chesapeake IRB should only occur once it has been determined that the SAE was related to the test article.]

A serious adverse event that is expected, as identified in the study documentation (e.g. product information, protocol, and/or informed consent form) but is occurring at greater frequency or severity should be reported to Chesapeake IRB as an Unanticipated Problem.

Principal Investigators are expected to provide the IRB and Sponsor with any additional requested information regarding SAEs, including follow-up reports, autopsy reports, and medical reports.

In addition, Principal Investigators are expected to report adverse events, and other findings identified in the protocol as critical to safety evaluations, to the Sponsor in accordance with the Sponsor’s reporting requirements and within the specified timeframe.

9.4.2. External Serious Adverse Events/Unexpected Adverse Device Events (including IND Safety Reports)

External SAEs (e.g. IND Safety Reports, SUSARs), which are SAEs that occur at sites not under the purview of Chesapeake IRB, should only be submitted if they meet the criteria of an unanticipated problem. Please refer to Unanticipated Problems below to determine which external SAEs may qualify for an unanticipated problem involving risks to subjects or others that must be reported to Chesapeake IRB.
Sponsors and Investigators are encouraged to review FDA’s Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection that was issued January 2009 found at:


The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

• For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

• Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

Prior to submitting copies of any Safety Report or Unanticipated Adverse Device Events (UADE) Report to Chesapeake IRB, Principal Investigators should confirm that the reports have not been submitted on their behalf by the Sponsor.

9.4.3. Protocol Deviations, Violations, or Exceptions

A Principal Investigator may not initiate a change in research activity without IRB approval unless the change is necessary to eliminate apparent immediate hazards to human subjects, in which case it should be reported to Chesapeake IRB as an unanticipated problem.

Principal Investigators and sites must notify Chesapeake IRB in writing of any unapproved Protocol Deviations/Violations (an accidental or unintentional change to the IRB-approved protocol) that, in the investigator’s judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity. Unplanned or unintentional deviations are to be reported to Chesapeake IRB as unanticipated problem or non-compliance as noted in sections, Unanticipated Problems and Non-Compliance.

This notification to the IRB must occur promptly and no later than 2 weeks (10 business days) from the time of identification of the unplanned or unintentional protocol deviation/violation. An automatic acknowledgement will be sent from CIRBI and no additional action is required, unless Principal Investigators are contacted by Chesapeake IRB to provide further information.
There are many unplanned or unintentional violations/deviations that do not cause harm or place participants at increased risk of harm, or adversely affect data integrity. Chesapeake IRB does not require that these minor violations/deviations be reported to Chesapeake IRB. Examples may include the following:

- Out of window visits
- Study procedures conducted out of timeframe
- Participant failure to initial each page of the informed consent form, as applicable
- Participant failure to return subject materials (e.g. diaries, journals, etc).

Examples of accidental or unintentional PVs/PDs that must be submitted to Chesapeake IRB include:

- Changes necessary to eliminate apparent immediate hazards to the subject
- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to report serious adverse event to the IRB and/or sponsor
- Failure to perform a required lab test that, in the opinion of the Principal Investigator, may affect subject safety or data integrity
- Drug/study medication dispensing or dosing error
- Study visit conducted outside of required timeframe that, in the opinion of the Principal Investigator, may affect subject safety
- Failure to follow safety monitoring plan

On occasion, a Principal Investigator may want to intentionally deviate from the IRB-approved protocol (i.e. protocol exception) for an individual research subject. The Principal Investigator must get sponsor approval and obtain prospective IRB approval. The planned protocol exception cannot be initiated until the sponsor AND the IRB have approved the deviation. Furthermore, to the extent Principal Investigators or sponsors request protocol exceptions for multiple research subjects, Chesapeake IRB may determine that a protocol amendment/modification to the IRB-approved protocol is the appropriate course of action.

9.4.4. Unanticipated Problems

Chesapeake IRB requires that Sponsors and/or Principal Investigators/sites (as appropriate) submit in writing any unanticipated problems (UAPs) involving risks to subjects or others, including adverse events that should be considered unanticipated problems as described below. Notification to the IRB of a UAP must occur promptly, but no later than 2 weeks (10 business days) from the time of identification.

UAPs are defined as any incidence, experience, or outcome that is unexpected (in terms of nature, severity, or frequency) given the information provided in research-related documents and the characteristics of the subject population being studied; related or possibly related to participation in the research; and suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. Chesapeake IRB uses the following criteria to determine whether an incidence, experience or event is a UAP involving risk to subjects or others:

1. Unanticipated or unexpected at the time of IRB approval,
2. Involved new or increased risk to subjects or others, and
3. Related to the research.

Examples of the types of events that must be promptly submitted to the IRB, regardless of whether they occur during the study, after study completion, or after subject withdrawal or completion may include, but are not limited to the following:

Adverse events (AEs) as follows:

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure; such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome.
2. A single occurrence, or more often a small number of occurrences, of a serious unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.
3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be a UAP. A determination should be made as to whether the series of AEs represent a signal that the AEs were not just isolated occurrences and involve risk to human subjects.
4. An AE that is described or addressed in the research-related documents (i.e. investigator’s brochure, protocol, informed consent form) but occurs at a specificity or severity that is inconsistent with prior observations.
5. A serious AE that is described or addressed in the research-related documents, but for which the rate of occurrence is a clinically significant increase in the expected rate of occurrence for the study.
6. Any other AE that would cause the sponsor to modify study-related documentation, or would prompt the IRB to take an action to ensure the protection of human subjects.
   - Any event that requires prompt reporting in accordance with the protocol or Sponsor;
   - Any accidental or unintentional change to the IRB-approved protocol that involved risks or has the potential to recur;
   - Any change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant;
   - Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research;
   - Any complaint of a participant that indicates an unanticipated risk or which cannot be resolved by the research staff/sponsor; and
   - Any “other” event that may impact subject safety.

Chesapeake IRB notifies the appropriate regulatory agency of any incidence, experience or outcome that the IRB has determined to be a UAP involving risks to subjects or others.

The Principal Investigator is responsible for the documentation, investigation, and follow-up of all unanticipated problems that occur at the site in which the investigator is responsible for the conduct of the research.

Sponsors must also report any unanticipated problems that occur at sites outside of Chesapeake IRB’s jurisdiction, which are relevant to the sites under Chesapeake IRB jurisdiction.

If there are questions about unanticipated problems involving risk to subjects or others, please contact Chesapeake IRB.
9.4.5. Non-Compliance

Principal Investigators/sites and sponsors are expected to comply with applicable regulations and IRB determinations/requirements when conducting research. Non-compliance with the regulations and/or IRB determinations and requirements can result in an action up to and including suspension or termination of IRB Approval.

Chesapeake IRB defines non-compliance as any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with applicable regulations, Chesapeake IRB’s Handbook, and/or the determinations and requirements of the IRB. Non-compliance may range from minor to serious; be unintentional or willful; and may occur once, sporadically, or continuously. The degree of non-compliance is evaluated on a case-by-case basis and takes into account whether subjects were harmed or placed at an increased risk of harm.

Serious non-compliance is defined as any action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risk to subjects, or compromises the scientific integrity or validity of the research.

Continuing non-compliance is defined as a pattern of repeatedly failing to comply with applicable regulations, Chesapeake IRB’s Handbook, and/or the determinations and requirements of the IRB that may affect subjects’ rights and welfare or increase risk to subjects, or may compromise the scientific integrity or validity of the research. Continuing non-compliance also includes frequent instances of minor non-compliance or failure to respond to a request to resolve an episode of non-compliance.

Sponsors/sponsor’s representatives, Principal Investigators and/or research staff must notify Chesapeake IRB in writing of any instance of non-compliance with the regulations, Chesapeake IRB’s Handbook, and/or determinations and requirements of the IRB. This notification must be as soon as possible but no later than 2 weeks (10 business days) from the time of the event.

Any allegation of non-compliance should also be promptly reported via telephone or in writing to Chesapeake IRB so that a thorough investigation can be conducted. Non-compliance reports or allegations should include the following information (as appropriate):

- Name of the submitting party;
- Chesapeake IRB assigned protocol number;
- Protocol title;
- A description of the event;
- The impact on subject safety (if any);
- The immediate action(s) taken to ensure subjects were not harmed;
- A corrective action plan to prevent re-occurrence;
- Non-compliance assertion;
- Timetable of events;
- Supporting information from other sources (e.g., Sponsor), if applicable.

Reports and allegations of non-compliance will be evaluated by the IRB and can result in an action up to and including suspension or termination of IRB approval. Any report of non-compliance determined by the IRB to be serious or continuing or determination to suspend or terminate IRB approval will be reported to the appropriate regulatory agency by Chesapeake IRB.
9.5. Continuing Review
Chesapeake IRB determines the frequency of continuing review for the Protocol and Principal Investigator/site’s conduct of the protocol at the time of initial approval. The frequency of continuing review may be changed at the discretion of the IRB; however, it shall be no greater than 12 months.

Notification of an upcoming continuing review and the information required for submission to the IRB (report on the progress of the research) is communicated to the submitting party and/or the Principal Investigator well in advance of the submission deadline. Every effort is made to notify the sponsor, and/or Principal Investigator that a continuing review report is due. Delays in providing the required documentation can jeopardize IRB approval. Without continuing review and approval, all study related activities must stop unless continued participation is approved by Chesapeake IRB to ensure subject safety.

Continuing review activities must continue as long as the research remains open to long-term follow-up of subjects, even when the research is permanently closed to new enrollment and all subjects have completed all research-related interventions, or when the remaining research activities are limited to the collection of private identifiable information.

For studies conducted under an FWA, continuing review activities must continue in accordance with the criteria stated above and until all data analysis of identifiable private information is complete.

9.6. FDA/OHRP or other Regulatory Audits
Principal Investigators and Sponsors under Chesapeake IRB’s oversight must notify Chesapeake IRB of any Inspection Reports, FDA Form 483s, Warning Letters, Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letters, or actions taken by any regulatory agency (e.g. local, state, or federal) including legal or medical actions that occur. This notification must occur promptly via the CIRBI website and no later than 2 weeks (10 business days) from the time of the event. If the Principal Investigator or site received an FDA Form 483 and/or Warning Letter, any responses to the FDA must be included with the notification. If the Principal Investigator or site did not respond to the FDA, the Principal Investigator must provide a written explanation to Chesapeake IRB of the corrective actions put into place at the site(s) to address any finding(s).

Inspections/Audits with no findings do not require submission to the IRB.

9.7. Massachusetts Sites
Sites located in the state of Massachusetts that are under an IND are required to be visited annually, per Massachusetts Department of Public Health requirements. Sites will be contacted to schedule these visits.

10. After Completion of the Research

10.1. Termination Notification
The federal regulations require that the IRB be notified of all changes in research activity. Study termination (close out) is considered a change in research activity which requires reporting to Chesapeake IRB. Principal Investigators and Sponsors must notify Chesapeake IRB when all research-related activities are complete and there are no active subjects participating in the research.
termination notification is required even if there were no subjects enrolled in the study. The termination submission includes questions about enrollment activities and problems encountered during the conduct of the study.

Chesapeake IRB will send the Principal Investigators and sponsors notification of study termination. Sponsors will not receive a notification of termination until all sites have submitted a termination report and received official notification from Chesapeake IRB. Chesapeake IRB considers a study closed (and archived) when all IRB-approved sites have been terminated and the sponsor has submitted a termination report and received an official notification of termination from Chesapeake IRB.

All terminated studies are archived in accordance with regulatory requirements.

10.2. Protocol and Site Expiration
If Chesapeake IRB has not reviewed and approved continuation of a research study and/or Principal Investigator by the expiration date, the research must stop unless Chesapeake IRB finds that it is in the best interest of individual subjects to continue participating in the research intervention(s) or interactions. Enrollment of new subjects cannot occur after expiration of IRB approval.

If the Principal Investigator wishes to continue to conduct a study for which IRB approval has expired, the following documentation must be submitted within 30 days of expiration:

- Complete Continuing Review Information;
- Supporting documentation, as appropriate;
- Rationale for not providing complete information to Chesapeake IRB in a timely manner; and
- Corrective steps in place to prevent future delays.

If received within 30 days of expiration, Chesapeake IRB reviews the Continuing Review for the referenced protocol and/or Principal Investigator. Research activities may not resume until Chesapeake IRB approval documentation is issued.

If the required continuing review documentation is not received within 30 days of study expiration, Chesapeake IRB requires a complete protocol and/or Principal Investigator re-submission for review.

10.3. Final Reports after Study Completion
Based on applicable regulatory requirements, the investigator should provide the IRB and applicable regulatory authority with a summary of the study’s outcome and any required reports upon completion of the study.